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Enantioselective Carbene Insertion into O−H of Phenols with Chiral Palladium/2,2′-Biimidazole Complexes

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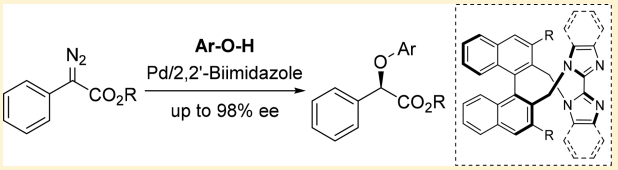
Supporting Information

ABSTRACT: A highly enantioselective insertion of α-aryl-α-diazoacetates into the O−H bonds of phenols has been successfully developed by employing palladium/2,2′-biimidazole complexes as catalysts, furnishing the chiral α-aryl-α-aryloxyacetates with up to 98% ee and 97% yield. Furthermore, these chiral palladium/2,2′-biimidazole complexes have also exhibited a good performance in the asymmetric insertion of α-aryl-α-diazoacetates into the N−H bonds of carbazoles. It was noted that these protocols also represent the successful application of palladium complexes of axially chiral 2,2′-biimidazole ligands in asymmetric catalysis.

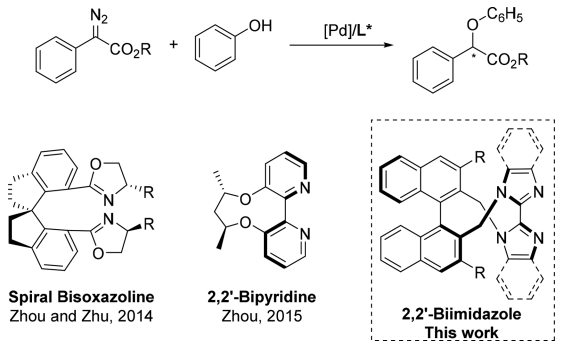


The chiral α-aryl-α-aryloxyacetates are ubiquitous structural motifs in many naturally occurring compounds and active pharmaceutical ingredients.[1] For instance, MBX-102 exhibits full therapeutic activity and acts as an oral glucose-lowering agent for the treatment of type 2 diabetes in clinical development.[2] The benzisoxazolone-substituted α-aryloxyphenylacetic acids as selective partial agonists of peroxisome proliferator activated receptor (PPAR)-γ show potent antihyperglycemic efficacy and hypolipidemic activity.[3] Considering the remarkable significance of this framework, the methodologies for enantioselective synthesis of this motif have attracted considerable attention.

Over the past few decades, the chiral α-aryl-α-aryloxyacetates could be obtained by multistep transformations with chiral auxiliaries such as chiral lactamides and chiral alcohols.[1,4] However, the lower atomic economy restricts their wide application in light of the increasing demand for green chemistry. In recent years, transition-metal-catalyzed carbene transfer reactions have attracted much attention in asymmetric catalysis.[5] In particular, the catalytic asymmetric insertion reactions of metal carbenoid from α-diazocarbonyl compounds into X−H have provided an efficient way to construct the chiral compounds.[6] To date, many catalytic systems based on copper, rhodium, and palladium have been developed and successfully applied in asymmetric insertion of α-aryl-α-diazoacetates into the O−H bonds of phenols to access the chiral α-aryl-α-aryloxyacetates.[7]

Palladium catalysts and reagents are indispensable and versatile in modern organic synthesis.[8] Recently, palladium-catalyzed asymmetric insertion of α-aryl-α-diazoacetates into the O−H bonds of phenols has received considerable attention (Scheme 1). In 2014, Zhou and Zhu reported a palladium-catalyzed O−H insertion reaction between phenols and α-aryl-α-diazoacetates by using chiral spirobisoxazoline ligands,

Scheme 1. Palladium-Catalyzed Enantioselective O−H Insertion of Phenols



providing the products in good yields and excellent enantioselectivities.[9] In 2015, the palladium-catalyzed enantioselective insertion of α-aryl-α-diazoacetates into the O−H bonds of phenols was developed by our group with the aid of axially chiral bipyridine ligands (Cn-ACBP), providing the corresponding α-aryl-α-aryloxyacetates with up to 99% ee.[10] Although tremendous advances have been obtained, the development of efficient catalytic systems to access the optically active α-aryl-α-aryloxyacetates is still highly desirable.

Very recently, we have developed a series of axially chiral 2,2′-biimidazole ligands, which have been successfully applied in the copper- or iron-catalyzed N−H insertion reaction of α-diazoacetates with carbazole compounds, providing the chiral

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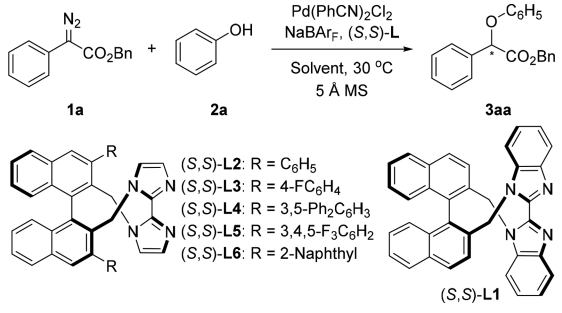
N-substituted carbazoles in high yields and up to 96% ee.[11] As an extension to our efforts in the application of axially chiral 2,2′-diimidazole ligands in asymmetric catalysis, herein we report the enantioselective O−H bond insertion between phenols and α-aryl-α-diazoacetates with a palladium/axially chiral 2,2′-biimidazole complex as a catalyst, giving the corresponding products with up to 98% ee and 97% yield.

At the outset of our study, we selected the phenol **2a** and α-phenyl-α-diazoacetate **1a** as model substrates to optimize the reaction conditions (Table 1). First, with the axially chiral 2,2′-biimidazole (*S*,*S*)-**L1** as ligand and $NaBAr_F$ as additive, the reaction proceeded smoothly under the catalysis of $Pd(PhCN)_2Cl_2$ in CH_2Cl_2 with 72% ee and 82% yield (entry 1). Subsequently, the effect of solvents was screened with $Pd(PhCN)_2Cl_2$ as a precursor. The reaction exhibited a high reactivity and moderate enantioselectivity in $CHCl_3$ (entry 2). It was noted that the enantioselectivity was increased to 90% when the reaction was carried out in toluene (entry 3). However, the reaction conducted in THF had poor reactivity (entry 5). On the basis of the results of entries 2 and 3, we reasoned that a solvent mixture of $CHCl_3$ and toluene would have a better effect on this reaction. As predicted, 95% ee and 91% yield were obtained when a solvent mixture of $CHCl_3$ and toluene in a ratio of 1:1 was used (entry 6). In order to further improve the yield of the reaction, the amount of phenol **2a** was increased to 3 equiv; full conversion and 94% yield could be obtained (entry 7).

Subsequently, different chiral 2,2′-biimidazole ligands were evaluated; we were pleased to find that all of the 2,2′-biimidazole ligands exhibited good yields and moderate to high enantioselectivities. It was found that (*S*,*S*)-**L2**, (*S*,*S*)-**L3**, and (*S*,*S*)-**L6** gave the desired product **3aa** in good activities and up to 95% ee (entries 8, 9, and 12). When (*S*,*S*)-**L4** and (*S*,*S*)-**L5** were used as ligands, the enantioselectivities decreased to 72% (entry 10) and 76% (entry 11) due to the steric hindrance of the aryl substituent on the 3,3′-positions of the binaphthyl moiety. (*S*,*S*)-**L1** was proved to be beneficial for this reaction, furnishing the desired product in 96% ee and 94% yield when the scale of the reaction was increased to 0.2 mmol (entry 13). Thus, the optimized reaction conditions were established: $Pd(PhCN)_2Cl_2$ (5.0 mol %), (*S*,*S*)-**L1** (5.0 mol %), $NaBAr_F$ (12 mol %), 5 Å MS (200 mg), $CHCl_3$/toluene (1/1), 30 °C.

With the optimized conditions in hand, we next investigated the substrate scope by carrying out reactions of various α-aryl-α-diazoacetates **1** with phenol **2a** (entries 1−9, Table 2).

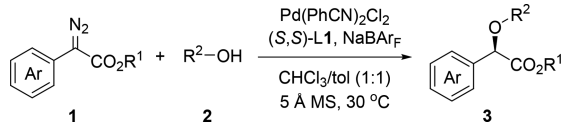
Table 1. Optimization of Conditions[a]



entry	solvent	(*S*,*S*)-**L**	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	(*S*,*S*)-**L1**	82	72
2	$CHCl_3$	(*S*,*S*)-**L1**	94	71
3	toluene (tol)	(*S*,*S*)-**L1**	82	90
4	benzene	(*S*,*S*)-**L1**	75	63
5	THF	(*S*,*S*)-**L1**	<5	nd
6	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L1**	91	95
7[d]	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L1**	94	94
8[d]	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L2**	85	95
9[d]	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L3**	88	93
10[d]	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L4**	85	72
11[d]	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L5**	88	76
12[d]	$CHCl_3$/tol (1/1)	(*S*,*S*)-**L6**	88	92
13[d,e]	$CHCl_3$/tol (1:1)	(*S*,*S*)-**L1**	94	96

[a]Reaction conditions unless specified otherwise: **1a** (0.1 mmol), **2a** (0.2 mmol), [M] (5.0 mol %), (*S*,*S*)-**L1** (5.0 mol %), $NaBAr_F$ (12 mol %), solvent (2.0 mL), 5 Å MS (200 mg), 3 h. [b]Isolated yields. [c]Determined by chiral HPLC. nd = not determined. [d]**1a**/**2a** = 1/3 (0.1 mmol/0.3 mmol). [e]The scale of the reaction was 0.2 mmol.

Table 2. Substrate Scope[a]



entry	Ar/R^1	R^2	yield (%)[b]	ee (%)[c]
1	C_6H_5/Bn	C_6H_5	94 (**3aa**)	96
2	C_6H_5/Et	C_6H_5	90 (**3ba**)	83
3	C_6H_5/^{i}Pr	C_6H_5	93 (**3ca**)	93
4	4-MeC_6H_4/Bn	C_6H_5	91 (**3da**)	97
5	4-PhC_6H_4/Bn	C_6H_5	95 (**3ea**)	94
6	4-FC_6H_4/Bn	C_6H_5	91 (**3fa**)	98
7	4-ClC_6H_4/Bn	C_6H_5	96 (**3ga**)	94
8	4-BrC_6H_4/Bn	C_6H_5	91 (**3ha**)	90
9	2-ClC_6H_4/Bn	C_6H_5	86 (**3ia**)	87
10	C_6H_5/Bn	4-MeC_6H_4	97 (**3ab**)	95
11	C_6H_5/Bn	4-$MeOC_6H_4$	93 (**3ac**)	97
12	C_6H_5/Bn	4-PhC_6H_4	92 (**3ad**)	92
13	C_6H_5/Bn	4-FC_6H_4	82 (**3ae**)	89
14	C_6H_5/Bn	4-ClC_6H_4	80 (**3af**)	88
15	C_6H_5/Bn	4-BrC_6H_4	87 (**3ag**)	84
16	C_6H_5/Bn	3-MeC_6H_4	93 (**3ah**)	95
17	C_6H_5/Bn	2-MeC_6H_4	83 (**3ai**)	92
18	C_6H_5/Bn	2-Naphthyl	97 (**3aj**)	94
19	C_6H_5/^{i}Pr	$C_6H_5CH_2$	47 (**3ck**)	76

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Pd(PhCN)_2Cl_2$ (5.0 mol %), (*S*,*S*)-**L1** (5.0 mol %), $NaBAr_F$ (12 mol %), $CHCl_3$/tol (1/1) (2.0 mL), 5 Å MS (200 mg), 30 °C, 3 h. [b]Isolated yields. [c]Determined by chiral HPLC.

Initially, the effect of the ester moiety of α-aryl-α-diazoacetates was examined. For the ethyl ester substituted **1b**, a slightly lower enantioselectivity was obtained (**3ba**). In the case of the isopropyl ester substituted **1c**, the reaction proceeded smoothly to produce **3ca** in high yield (93%) and enantioselectivity (93%). Next, a series of aryl-substituted diazoesters were also subjected to the standard conditions. Regardless of the electron-donating (Me) or electron-withdrawing (F, Cl, Br) nature of the para substituent on the phenyl moiety of the diazo esters, all of the substrates performed very well under the standard conditions, delivering the corresponding products in up to 96% yield and up to 98% ee (**3da**−**ha**). These results indicated that the electronic properties of the substituents on the phenyl ring had a marginal effect on the activity and enantioselectivity. With respect to the sterically hindered substrate **1i** with an *o*-

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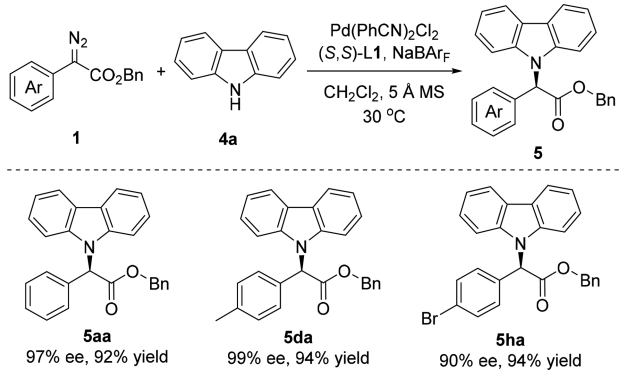
chloride group, the ee value of **3ia** was slightly decreased to 87%.

To further determine the substrate generality of this protocol, various phenols were evaluated in this protocol (entries 10−18, Table 2). First, a range of 4-subsitituted phenols were subjected to the standard conditions, substrates with electron-donating groups were examined, and high yields and enantioselectivities were obtained (**3ab**,**ac**). However, substrates with various electron-withdrawing groups afforded the corresponding products with slightly lower yields and enantioselectivities (**3ae**−**ag**) presumably due to electronic effects. In addition, a methyl substituent at different positions of the phenyl moiety of the phenol had little effect on the enantioselectivity of the reaction, and the desired products (**3ah**,**ai**) were obtained with high enantioselectivities (92−95%). When a methyl substituent was at the ortho position of the phenol, the yield was slightly decreased to 83%. It was noted that 2-naphthylphenol could also perform smoothly, giving the corresponding product (**3aj**) with 94% ee and 97% yield. In addition, benzyl alcohol **2k** and isopropyl α-phenyl-α-diazoacetate **1c** were employed as substrates to study the asymmetric O−H bond insertion under the standard conditions. The reaction was complicated, giving the desired product in 47% yield and 76% ee (**3ck**).

In addition, the chiral palladium/2,2′-biimidazole complexes also exhibited good performance in the asymmetric insertion of α-aryl-α-diazoacetates into the N−H bonds of carbazoles.[12] Several substrates were briefly examined for N−H insertion (Scheme 2). When benzyl α-phenyl-α-diazoacetate **1a** and 9*H*-carbazole **4a** were selected as the substrates, the reaction proceeded smoothly and provided the corresponding product in 97% ee and 92% yield (**5aa**). It was noted that excellent enantioselectivity was obtained when the **4b** with a *p*-methyl group as a substrate (**5da**). A bromo group instead of a methyl group at the para position led to slight erosion of the ee, but the yield was still maintained at a high level (**5ha**).

Scheme 2. Pd-Catalyzed Asymmetric Insertion of α-Aryl-α-diazoacetates into the N−H Bonds of Carbazoles[a]



[a]Reaction conditions: **4a** (0.1 mmol), **5a** (0.15 mmol), Pd(PhCN)$_2$Cl$_2$ (5.0 mol %), (*S*,*S*)-**L1** (5.0 mol %), NaBAr$_F$ (12 mol %), CH$_2$Cl$_2$ (2.0 mL), 5 Å MS (200 mg), 30 °C, 2 h.

In conclusion, a highly enantioselective insertion of α-aryl-α-diazoacetates into the O−H bonds of phenols has been successfully developed by using chiral palladium/2,2′-biimidazole complexes as catalysts, giving the chiral α-aryl-α-aryloxyacetates with up to 98% ee and 97% yield under mild conditions. This methodology further complements the studies of O−H bond insertion of α-diazoacetates. Moreover, the chiral palladium/2,2′-biimidazole complex catalyzed asymmetric insertion of α-aryl-α-diazoacetates into the N−H bonds of carbazoles has also been realized with up to 99% ee. These protocols represent the successful application of the axially chiral 2,2′-biimidazole ligands in palladium catalytic reactions. Further applications of these chiral 2,2′-biimidazole ligands in other catalytic asymmetric reactions are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00219.

General procedures and NMR spectra of obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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