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Silver-Catalyzed Asymmetric Insertion into Phenolic O–H Bonds using Aryl Diazoacetates and Theoretical Mechanistic Studies

Shingo Harada,*[a] Koki Tanikawa,[a] Haruka Homma,[a] Chigaya Sakai,[a] Tsubasa Ito,[a] and Tetsuhiro Nemoto*[a,b]

Abstract: An enantioselective insertion reaction of silver carbenes generated from donor-acceptor-substituted diazo compounds into the O–H bond of phenols was developed. A homobinuclear silver complex with a chiral phosphorous ligand was created in situ from $AgNTf_2$ and (*S*)-XylylBINAP (a 2-to-1 mole ratio). Detailed mechanistic studies using combined experimental and computational techniques revealed that one silver atom center of the catalyst forms a silver carbene and another one works as a Lewis acid for the nucleophilic addition of a phenol. Two counteranions, two water molecules, and two silver atoms cooperatively mediate the subsequent protonation event to lower the activation energy and control enantioselectivity, affording an array of valuable α-aryl-α-aryloxy esters.

α-Aryl-α-aryloxy-carbonyl functionalities are biologically fascinating molecular structures and a useful platform in organic synthesis. The class of molecules containing the functional group system and their variants possess an array of bioactivities, as represented by MBX and Cymbalta (duloxetine) shown in Figure 1.[1,2] Commonly applied approaches for the asymmetric synthesis of these valuable scaffolds, however, require multistep processes based on chiral pool synthesis or the utilization of chiral auxiliaries.[3] Therefore, the development of efficient synthetic methods for the molecular architecture is desirable.

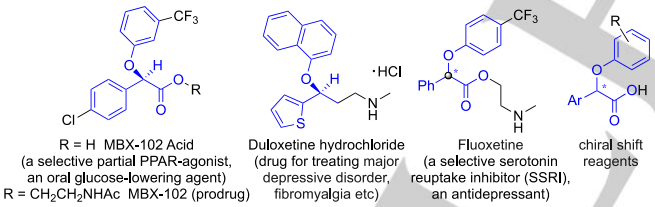
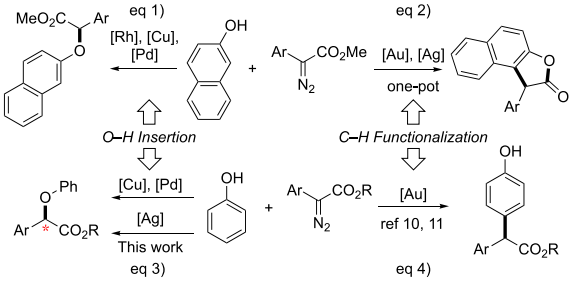


Figure 1. Bioactive and useful compounds possessing α-aryl-α-aryloxy-carbonyl group and their derivatives.

A transition metal-promoted O–H insertion reaction[4,5,6] into phenols[7,8] with α-aryl-α-diazoacetates is a straightforward method for asymmetric synthesis of α-aryl-α-aryloxyacetates. In this field, much effort has been dedicated to developing chiral metal catalysis for synthesizing these molecules in an enantioenriched form.[4-9] In 2006, Fu achieved a chiral copper complex-catalyzed O–H insertion reaction of aliphatic alcohols, but the insertion reaction into the phenolic hydroxy group proceeded with only 11% enantiomeric excess (eq 3, Scheme 1).[6a] Although other attempts using copper catalysis with chiral ligands continue to improve the enantioselectivity, the results were unsatisfactory (7%[8b], 10% ee[8a]). In 2014, palladium complexes with chiral spirobisoxazoline ligands were found to be effective for a highly enantioselective O–H insertion of α-aryl-α-diazo methyl ester into phenols reported by Zhu and Zhou group,[8d] while Lan, Shi[10] and Liu, Zhang[11] groups independently reported that a gold catalyst chemoselectively caused the C–H bond functionalization of phenols.[12,13] The development of an insertion reaction into the O–H bond of phenols with stereocontrol, however, remains a challenge.[6h] Whereas chiral rhodium, copper, and palladium catalysts have been employed for carbene-transfer reactions,[14] silver-carbene reactions[15] are quite rare and there remains room for improvement in terms of their stereoselectivities.[16] Our group has developed a series of metal-carbene reactions[17] and recently achieved an asymmetric intramolecular dearomatization reaction of phenols with α-diazoamides using chiral silver phosphate.[18] In the course of our studies, an intermolecular reaction of naphthols with gold- or silver-carbenes chemoselectively provided C–H functionalized products (eq 2),[19] whereas silver-carbene reactions with phenols gave O–H insertion products (eq 3). We anticipated that an asymmetric O–H insertion reaction using a silver complex could



Scheme 1. Reactions of naphthols and phenols with various metal-carbenes.

be established if the chiral environment of the catalyst could be appropriately designed and created. The conditions using a silver catalyst would provide complementary functional group compatibility with already-known methods. For instance, an aryl iodide, a versatile synthetic fragment for carbon–carbon bond-forming reactions in coupling chemistry, is potentially reactive under transition metal catalysis. In fact, substrate examples with these functionalities have not been described.[4-7] Another concern is that O–H insertion products are easily racemizable

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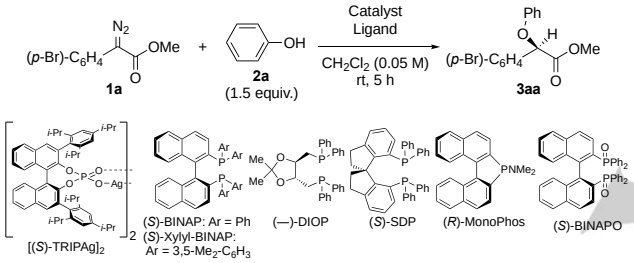
chiral methyl acetates under basic conditions, and thus harsh acidic conditions (HCl in dioxane under reflux) are required for hydrolysis of the ester to avoid the issue.[8d]

Herein, we describe the development of a carbene insertion reaction into phenols with donor-acceptor-substituted diazo compounds using a silver catalyst. Synthesized ester could be transformed under mild conditions without any racemization. Combined experimental and theoretical analyses were also executed to clarify the reaction mechanism and the origin of enantioinduction in chiral silver catalysis.

We commenced our experimental studies using phenol (**2a**) and methyl 2-(4-bromophenyl)-2-diazoacetate (**1a**) as model substrates in the presence of a [(*S*)-TRIPAg] dimer catalyst (Table 1).[18b] The attempted insertion reaction in dichloromethane solvent at room temperature proceeded smoothly, affording the desired O–H insertion product (**3aa**) in good yield with 71:29 *er* (entry 1). A similar level of stereocontrol was observed when

Table 1: Optimization of reaction conditions for the O–H insertion.[a]



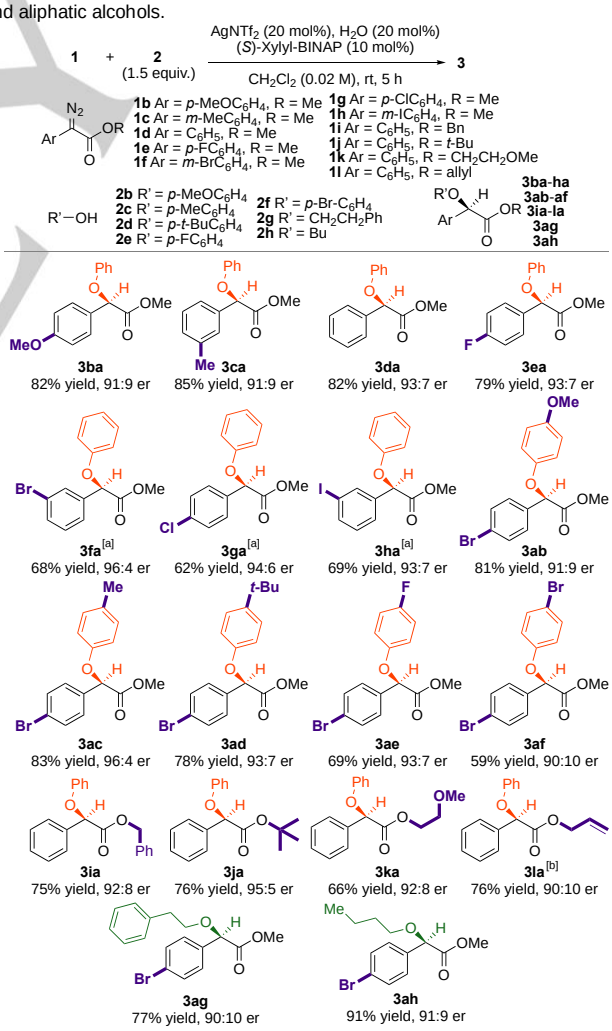
entry	Catalyst/Ligand (mol%)	Yield (%)	*er* (*R*:*S*)
1	[(*S*)-TRIPAg]$_2$/none(10/0)	80	71:29
2	AgNTf$_2$/(*S*)-BINAP (20/20)	22	69:31
3	AgNTf$_2$/(*S*)-BINAP(20/15)	37	85:15
4	AgNTf$_2$/(*S*)-BINAP(20/10)	62	91:9
5	AgNTf$_2$/(*S*)-BINAP(20/7.5)	65	67:33
6[b]	AgNTf$_2$/(*S*)-BINAP(10/20)	13	55:45
7	CuOTf/(*S*)-BINAP(20/10)	25	64:36
8	[AllylPdCl]$_2$/(*S*)-BINAP(10/10)	35	50:50
9	AgNTf$_2$/(–)-DIOP(20/10)	52	44:56
10	AgNTf$_2$/(*S*)-SDP(20/10)	37	50:50
11	AgNTf$_2$/(*R*)-MonoPhos(10/10)	50	50:50
12	AgNTf$_2$/(*S*)-BINAPO(20/10)	58	42:58
13	AgNTf$_2$/(*S*)-XylylBINAP(20/10)	72	92:8
14[c]	AgNTf$_2$/(*S*)-XylylBINAP(20/10)	74	93:7
15[c,d]	AgNTf$_2$/(*S*)-XylylBINAP(20/10)	69	84:16
16[c,e]	AgNTf$_2$/(*S*)-XylylBINAP(20/10)	81	95:5

[a] The diazo compound **1a**, dissolved in CH_2Cl_2, was added drop-wise over 90 min. [b] **1a** recovered (36%). [c] Reaction was performed in 0.02 M solvent. [d] MS 5A (1 g/mmol) was used. [e] 20 mol% of water was used.

using 20 mol% of AgNTf$_2$ and (*S*)-BINAP, giving **3aa**, albeit in lower yield (22%, entry 2). The mole ratio of Ag salt to the ligand significantly affected the yield and enantioselectivity, and a 2-to-1 ratio was determined to be optimal (entries 2-6).[20] Although other metal salts such as Cu or Pd catalyst and chiral phosphorous ligands or phosphine oxide did not improve the *enantiomeric ratio* of **3aa** (entries 7-12), the use of (*S*)-XylylBINAP was effective for the O–H insertion reaction (92:8 *er*, entry 13). Further comprehensive examination of the reaction conditions revealed that the addition of 20 mol% of water gave a satisfactory result (entries 15-16).

With the optimal conditions for the Ag-catalyzed O–H insertion reaction in hand (Table 1, entry 16), we evaluated the scope of the method (Table 2). α-Aryl-α-diazoacetates **1b** and **1c** with electron-donating substituents were applicable in this O–H insertion, affording the corresponding products **3ba**, **3ca** in 81% yields with high enantioselectivities (94:6, 91:9 *er*, respectively). Reactions of α -diazoacetates **1e**-**1h** possessing electron-deficient aryl substituents also proceeded with a high level of enantiocontrol (**3ea**-**3ha**, 93:7 to 95:5 *er*). In addition, electron-abundant and deficient phenols were usable in the O–H insertion, furnishing the functionalized methyl esters (**3ab**-**3af**). Other enantioenriched esters such as benzyl, *tert*-butyl, 2-methoxyethyl, and allyl ester variants were obtained in moderate to good yields (**3ia**-**3la**, 66-76% yield, 90:10 to 95:5 *er*). Although the method under palladium catalysis produced decent results (74% yield, 86:14 *er*) when using aliphatic alcohol such as butanol,[8d] this silver catalysis furnished **3ah** in high yield with high selectivity (91% yield, 91:9 *er*).[21]

Table 2*:* Substrate scope of asymmetric insertions into O–H bond of phenols and aliphatic alcohols.



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[a] 3 equivalent of PhOH was used. [b] Reaction was performed in 0.012 M solvent.

Hydrogenation of **3ia** with Pd/C at room temperature quantitatively furnished the corresponding carboxylic acid with no loss of enantiopurity relative to the starting material.[22]

While detailed mechanisms of the asymmetric carbene insertion into O–H bond of water have been investigated,[23] the reaction process of an asymmetric insertion into phenol has not been studied.[24] Therefore, the following experiments were performed to obtain mechanistic information. Reaction in the presence of alkyne **4**, instead of using phenol, gave a cyclopropene **5** (eq 5), which generated the Ag-carbene species in situ.[25] No nonlinear effect between the enantioselectivity values of **3aa** and catalyst was observed (figure 2), indicating an involvement of a single catalyst in the enantiodetermining process. In addition, water molecule(s) would participate in the enantiodetermining step, in view of the results of entries 12, 14 and 15 in Table 1 and some previous studies of metal-carbene mediated insertion reactions.[23,26] This reaction exhibited a kinetic isotope effect (k_H/k_D=3.17, eq 6)[27], thereby supporting the notion that O–H bond cleavage or C–H bond formation is the rate-determining step.

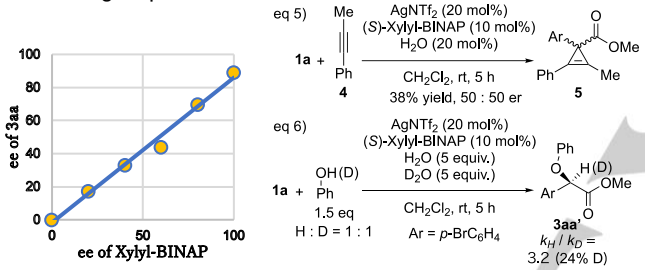
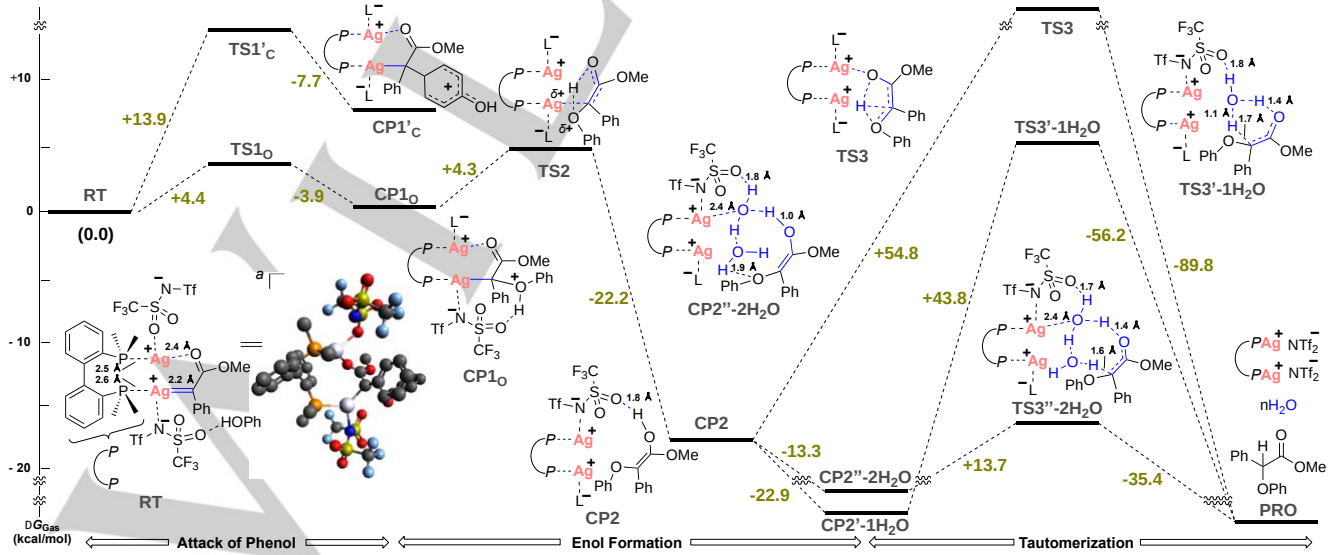


Figure 2. No chiral amplification.

To further elucidate the reaction mechanism, we performed computational studies based on quantum chemical calculations (Scheme 2).[22] A structurally simplified achiral ligand was used to clear the whole course of the reaction. The fact that the mole ratio of Ag salt/ligand (1/2) was quite critical for the reaction efficiency suggests that each Ag atom center could have a single phosphine functionality as a ligand in the in situ-generated catalyst complex.[20] Because computational analyses of the generation of Ag-carbene from diazo compounds were previously performed,[28] we initiated our calculation from Ag-carbene **RT**, where carbonyl oxygen coordinated to the other cationic Ag atom, making the carbene more electrophilic. Nucleophilic attack of a phenol oxygen on the Ag-carbene proceeded smoothly with a low activation energy of +4.4 kcal/mol *via* **TS1$_O$**, generating a formally C-bound and O-bound Ag_2-enolate **CP1$_O$**. On the other hand, reaction at the *para*-position of phenol was kinetically and thermodynamically unfavorable, likely due to the steric repulsion and/or dearomatization[29] of phenol, contrary to the Au-carbene reaction.[10,11,19,26] Enol formation to **CP2** from **CP1$_O$** also occurred with a reasonably low energy barrier, but the following key tautomerization of **CP2** to the final product (**PRO**) was calculated to be an impractical process with excessive activation energy ($\Delta\Delta G^{\ddagger}$ = +54.8 kcal/mol, **TS3**). **PRO** was also found to be accessible with $\Delta\Delta G^{\ddagger}$ = +13.7 kcal/mol *via* **CP2''-2H$_2$O** and **TS3''-2H$_2$O**, where two water molecules assist in the proton transfer. A proton shuttle catalysis through hydrogen-bonding network would be operative,[30] accounting for the water-sensitivity of the Ag-catalysed reaction.

To shed light on the origin of the asymmetric induction, the protonation process was studied in more detail by depicting a chiral ligand in CH_2Cl_2 solvent. In the **TS$_R$-2H$_2$O** model, providing (*R*)-product, cooperative attractive interactions[31] were working between two Ag centers, counteranions, and the substrate, as well as two water molecules in the chiral environment. Notably, the dual Ag···O interactions would generate the reactive proton donor to the enolate (bond length of the O–H (violet): 1.24 Å), positively affecting the total Gibbs Energy of the asymmetric protonation. On the other hand, a single and longer Ag···O interaction (2.5 Å) and analogous kind of hydrogen network were working in **TS$_S$-2H$_2$O**. These factors would make a critical difference to the activation energy ($\Delta\Delta\Delta G^{\ddagger}$ = 1.78 kcal/mol) for the enantiodiscrimination of the enols, which corresponds to 95:5 selectivity, supporting the experimental results.



Scheme 2. Reaction coordinate diagram and calculated key structures for the O–H insertion reaction (L=NTf_2). Optimal geometries and frequencies were computed at the rB3LYP/6-31G* (for H, C, N, O) and LanL2DZ (Ag) levels of theory. [a] Hydrogen atoms have been omitted for the sake of clarity.

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In conclusion, we developed a silver-catalyzed asymmetric insertion reaction into the O–H bond of phenols and aliphatic alcohols with donor-acceptor-substituted diazo compounds. The reaction proceeded under mild conditions at room temperature, furnishing α-aryl-α-aryloxy esters in enantioenriched form. We proposed water- and counter anion-mediated asymmetric protonation of silver-enol complex based on computational argumentations. Further methodology development using a chiral homobinuclear silver catalyst is ongoing in our laboratory.

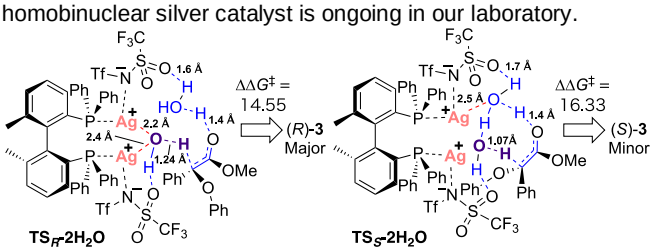

Figure 3. Enantiodetermining transition state structures in CH_2Cl_2 calculated at the rB3LYP/6-31G** and LANL2DZ level of theory (*G*: in kcal/mol).

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Keywords: bimetallic • carbenes • silver • insertion • density functional calculations

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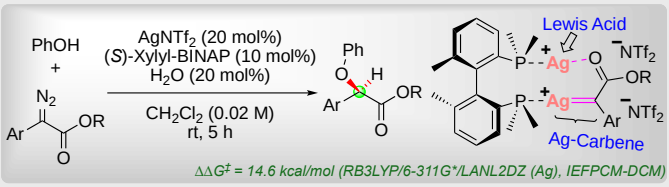

A chiral homobinuclear silver complex-catalyzed carbene insertion into O-H bonds of phenols was developed. The catalyst was created in situ from $AgNTf_2$ and (*S*)-XylylBINAP (a 2-to-1 mole ratio). Theoretical studies revealed that water- and counter anion-mediated asymmetric protonation of silver-enol complex is the enantiodetermining step for the synthesis of α-aryl-α-aryloxy esters in an enantioenriched form.

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