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Chemoselective Asymmetric Intramolecular Dearomatization of Phenols with α-Diazoacetamides Catalyzed by Silver Phosphate

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Supporting Information Placeholder

ABSTRACT: We report an asymmetric dearomatization of phenols using Ag carbenoids generated from α-diazoacetamides. The Ag catalyst preferentially promoted an intramolecular dearomatization of phenols, while a Rh or Cu catalyst caused a C–H insertion and a Büchner reaction. Experimental and computational studies indicated the Ag carbenoids have a carbocation-like character, making their behavior and properties quite unique. Highly enantioselective transformations using Ag carbenoids have not yet been reported. We achieved a Ag carbenoid-mediated chemo- and highly enantioselective phenol dearomatization with broad substrate generality for the first time.

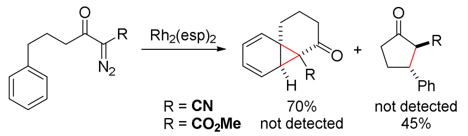
Achieving a high level of chemoselectivity enhances synthetic efficiency by reducing the number of steps needed to protect the functional groups and minimize undesired byproducts, which contributes to step and atom economy. Notably, controlling the chemoselectivity in divergent reactions promoted by extremely reactive chemical species is a rewarding challenge in modern organic chemistry.

Metal carbenoids are highly active carbon species with divergent reactivity.[1] Recently, several groups succeeded in controlling the chemoselectivity of metal carbenoid-mediated reactions against arenes. Reisman developed a substrate-controlled arene cyclopropanation (Scheme 1a).[2] Using α-diazo-β-ketonitriles as substrates,[3] the cyclopropanation was preferentially promoted over the C–H insertion. The development of catalyst-controlled chemoselective reactions of metal carbenoids and their mechanistic studies is also reported. Che developed Ru-catalyzed intramolecular primary (1°) C–H insertion in contrast to a Rh-catalyzed reaction preferring secondary (2°) C–H insertion or a Büchner reaction (Scheme 1b).[4,5] Liu, Zhang and Lan, Shi independently reported chemo- and site-selective alkylations of phenols using a Au catalyst with a phosphite ligand (Scheme 1c).[6,7] While methods to control the reactivity of metal carbenoids continue to be developed,[8,9] the development of chemo- and highly enantioselective reactions of arenes with metal carbenoids has remained an unsolved challenge.

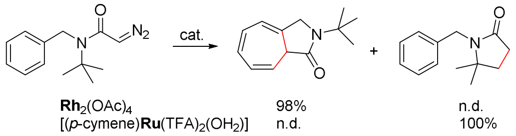
Catalytic asymmetric dearomatization (CADA)[10] reactions of phenols are particularly powerful strategies for assembling versatile three-dimensional cyclic architectures from widely available aromatic feedstocks. Chiral hypervalent iodine catalysts were utilized for CADA reactions of phenols to construct chiral *ortho*-spirolactone structures.[11] Enantiocontrol at the *para*-position in these reactions remains difficult, however, due to the remote distance from the chiral environment created by O-bound iodine(III).[12] In sharp contrast, *para*-substituted phenols can directly react with chirally modified electrophiles at the *ipso*-position to construct the chiral center at the *para*-position. Extensive efforts recently focused on the development of the CADA processes based on this strategy.[13,14,15] The presence of substituents at the *meta*-position of phenols, however, was prerequisite to achieve efficient enantiodiscrimination of the Re/Si face of the carbon at the *para*-position.

Scheme 1. Chemoselective reactions of arenes with metal carbenoids

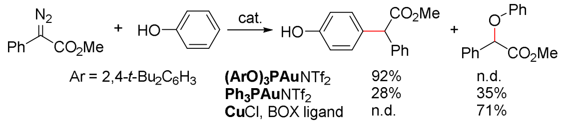
(a) Substrate-controlled chemoselective arene cyclopropanation over C–H insertion



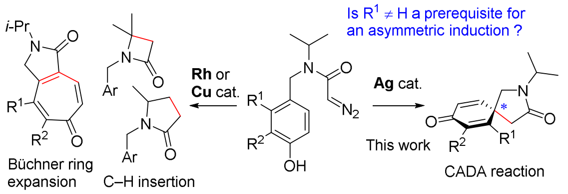
(b) Metal-controlled 1° C–H insertion over Büchner reaction or 2° C–H insertion



(c) Metal- and ligand- controlled site-selective alkylation of phenols over O–H insertion



(d) Metal- and ligand- controlled chemoselective asymmetric dearomatization

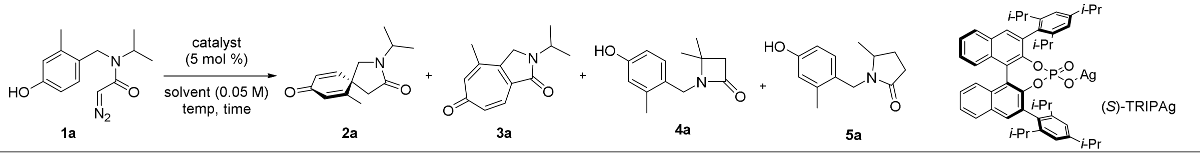


esp is α,α,α',α'-tetramethyl-1,3-benzenedipropanoate. n.d. is not described.

We envisioned that chemoselective dearomatization reactions of phenols could be realized using an electrophilic metal carbenoid if the competing Büchner reaction or the C–H insertion could be controlled by the appropriate selection of metal and ligands. Herein, we report intramolecular CADA reactions using chiral Ag phosphate, and describe the first successful examples of discrimination of the enantiotopic face of the carbon at the *para*-position on the phenolic ring without a substituent at the *meta*-position.

To assess the chemoselectivity in divergent reactions, we began our studies using α-diazoamide **1a** as a model substrate possessing 1°, 2°, and 3° C–H bonds as well as a phenol unit (Table 1). The reaction of **1a** in the presence of 5 mol % $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature gave tropone **3a** through a Büchner reaction and 1° and 3° C–H insertion products **4a** and **5a** in 26%, 15%, and 17% yield, respectively (entry 1). Using $Cu(NCMe)_4PF_6$ as a catalyst, azaspiro[4.5]decane derivative **2a** was obtained in only 6% yield (entry 2). The reaction with $(2,4\text{-}t\text{-}Bu_2C_6H_3O)_3PAuCl$ and $AgSbF_6$, utilized by Liu and Zhang[6a] provided **2a** in 52% yield (entry 3). To expand the asymmetric reaction,[16] a catalyst system using $(2,4\text{-}t\text{-}Bu_2C_6H_3O)_3PAuCl$ and (*S*)-TRIPAg for generation of the chiral counteranion[17] in situ was examined, furnishing **2a** with enantiomeric ratio (er) of 28:72 (entry 4). The absolute configuration of the major enantiomer of **2a** was determined to be *S* by Mosher's ester analysis after some transformations.[16] To investigate the effect of Ag salt, the reaction was performed using only (*S*)-TRIPAg as a catalyst. Interestingly, it proceeded smoothly to produce the opposite enantiomer of **2a** as a major product without a significant loss of chemoselectivity (51% yield, 81:19 er, entry 5).[18] To confirm the effect of Ag metal without phosphate, $AgSbF_6$ was utilized, which exhibited a different chemoselectivity from those obtained using a Rh or Cu catalyst (entries 1 and 2 vs 6). In addition, to eliminate the possibility of Brønsted acid catalysis, 2,6-di-*tert*-butylpyridine was used as an additive in the reaction conditions of entries 5 and 6, and similar results were observed (entries 5 vs 7, 6 vs 8). These results indicate that the Ag catalyst promoted the dearomatization process preferentially. Examples of Ag carbenoids used in synthetic organic chemistry and its mechanistic investigations are quite limited, despite the known unique reactivities of Ag carbenoids compared with other metals.[19] Moreover, no highly enantioselective reactions with Ag carbenoid have been reported,[19] leading us to conduct the study using a (*S*)-TRIPAg catalyst. Next, solvent screening revealed that a polar solvent was appropriate for the reaction system; the yield increased to 61% in 2-butanone (entry 14) while no further improvement was observed in other solvents (entries 9-13). Comprehensive examination of additives revealed that benzoic acid effectively increased the yield to 89% without decreasing the er (entry 15).

Table 1. Optimization of the reaction conditions



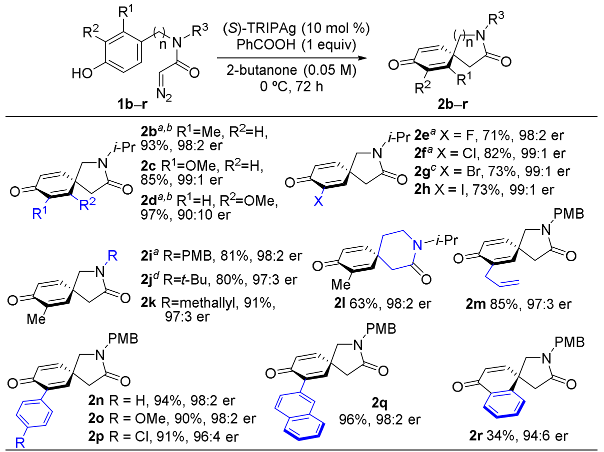
entry	catalyst	additive	solvent	temp (°C)	time (h)	yield (%)[a]				er of **2a** (*R*:*S*)
						2a	**3a**	**4a**	**5a**	
1	$Rh_2(OAc)_4$	–	CH_2Cl_2	rt	16	0	26	15	17	–
2	$Cu(NCMe)_4PF_6$	–	CH_2Cl_2	rt	6	6	20	25	16	–
3	$(ArO)_3PAuCl/AgSbF_6$	–	CH_2Cl_2	rt	16	52	0	0	0	–
4	$(ArO)_3PAuCl$/(*S*)-TRIPAg	–	CH_2Cl_2	rt	16	84	0	0	0	28:72
5	(*S*)-TRIPAg	–	CH_2Cl_2	rt	1	51	15	0	0	81:19
6	$AgSbF_6$	–	CH_2Cl_2	rt	22	30	7	5	0	–
7	(*S*)-TRIPAg	$2,6\text{-}t\text{-}Bu_2py$[b]	CH_2Cl_2	rt	16	45	5	0	0	80:20
8	$AgSbF_6$	$2,6\text{-}t\text{-}Bu_2py$[b]	CH_2Cl_2	rt	22	28	3	2	0	–
9	(*S*)-TRIPAg	–	CH_2Cl_2	0	3	49	15	0	0	88:12
10	(*S*)-TRIPAg	–	toluene	0	24	57	3	0	0	69:31
11	(*S*)-TRIPAg	–	THF	0	24	44	13	0	0	93:7
12	(*S*)-TRIPAg	–	EtOAc	0	24	48	5	0	0	90:10
13	(*S*)-TRIPAg	–	acetone	0	20	55	7	0	0	95:5
14	(*S*)-TRIPAg	–	2-butanone	0	21	61	8	0	0	95:5
15	(*S*)-TRIPAg	Benzoic acid[c]	2-butanone	0	48	89[d]	0	0	0	95:5

[a] Determined by ^{1}H-NMR analysis of the crude mixture. [b] 10 mol % of $2,6\text{-}t\text{-}Bu_2py$ was used. [c] 1 equiv. [d] Isolated yield. Ar is $2,4\text{-}t\text{-}Bu_2C_6H_3$.

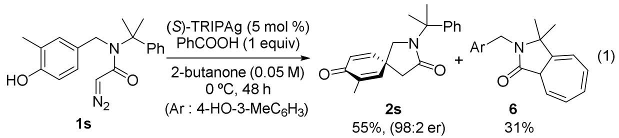
With the optimal reaction conditions in hand, we next investigated the substrate scope of this chemoselective CADA reaction using Ag catalysis (Table 2). We tested the reaction using phenols possessing a substituent at the *ortho*-position instead of at the *meta*-position. To our delight, when using **1b**, a high level of enantiocontrol as well as high chemoselectivity was observed, furnishing **2b** in 93% yield. Electron-deficient *ortho*-halophenols were also applicable to the CADA reaction with a larger amount of catalyst (7~10 mol %) for full conversion (**2e**-**2h**). In addition, α-diazoacetamides having removable substituents such as PMB on the amide nitrogen were applicable in a highly selective manner affording the products in good yield (**2i**, 81%).[20] The six-membered ring formation also proceeded with 10 mol % of the catalyst, producing azaspiro[5.5]undecane structure **2l**. Potentially reactive terminal alkene was tolerated in the CADA reaction without cyclopropanation (**2k** and **2m**). Substrates containing the biphenyl system **1n**-**q** were also effective for this reaction, affording the corresponding products **2n**-**q** in excellent yields and with high enantioselectivity. Naphthol derivative **1r** was also applied in this reaction, but there was room for improvement in the yield. It is worth emphasizing that the architecture of spirolactam bearing an all-carbon quaternary stereogenic center is ubiquitous in bioactive molecules.[21]

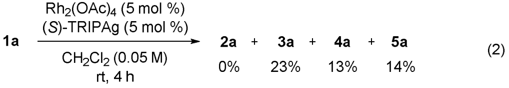
We next performed the following experiments to gain mechanistic insight into the developed CADA reaction. The reaction of **1s** bearing a dimethylphenylmethyl group on the amide under the optimum conditions using the Ag catalysis gave **2s** and cycloheptatriene **6** formed through Büchner reaction, which is specific to the carbene reaction[22] (eq 1), indicating the generation of Ag carbenoid. The production of tropone **3a** from **1a** also supports it (Table 1).

Table 2. Substrate scope



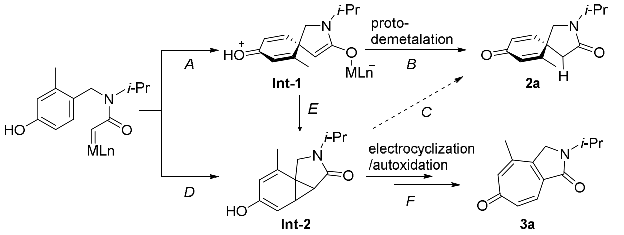
[a] 5 mol % of catalyst was used. [b] For 24 h. [c] 7 mol % of catalyst was used. [d] For 48 h.



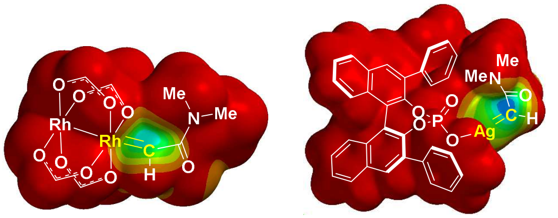


Plausible reaction pathways for this reaction are shown in Scheme 2. There are two possible pathways to form **2a**. One is electrophilic addition of the metal carbenoids to the *para*-position of phenol accompanied by dearomatization to generate **Int-1** (path A), followed by proto-demetalation (path B). The other is ring-opening of cyclopropane **Int-2** (path C), which could be formed through concerted arene cyclopropanation with a metal carbenoid (path D) or conjugate addition to enone from **Int-1** (path E). Tropone **3a** is formed by the Büchner reaction and subsequent autoxidation through path F, indicating that path F is more favorable than path C when using a Rh or Cu catalyst (Table 1, entries 1, 2). On the other hand, the Ag-catalyzed reaction produced **2a** preferentially. If the formation of **2a** from **Int-2** is postulated, (*S*)-TRIPAg must be an effective catalyst for path C. Thus, to test this hypothesis, we performed the reaction using a Rh$_2$(OAc)$_4$/(*S*)-TRIPAg mixed catalyst system, where **Int-2** generated by the Rh catalyst is expected to undergo ring-opening reaction to afford **2a** in the presence of the Ag catalyst. Under these conditions, **2a** was not isolated at all (eq 2). This result provides support that **2a** was formed through path B. The finding that benzoic acid improved the yield of **2a** by promoting path B while suppressing the production of **3a** also supports this mechanism (entries 14, 15). We therefore propose a stepwise mechanism based on the electrophilic addition of Ag carbenoid to phenol followed by proto-demetalation.

To elucidate the origin of the metal-dependent chemoselectivity, we performed a LUMO map[23] analysis based on DFT calculations at the M06 level with the 6-311G* basis set (LANL2TZ(f) basis set for Rh, Ag)[16] (Figure 1). The LUMO map clearly shows that Ag carbenoid has higher electrophilicity (deeper blue) than the Rh carbenoid. In addition, the Ag–carbene bond order is 0.29 lower than that of the Rh complex,[24] indicating weak back donation from Ag to the vacant carbene π-orbital. As a result, the longer distance[25] makes the Ag carbenoid carbon more carbocationic to facilitate the electrophilic addition to phenol (path A). These values of Ag carbenoid are very close to those of Au carbenoid,[26,27] rationalizing the observed similar chemoselectivity (entries 3, 4).



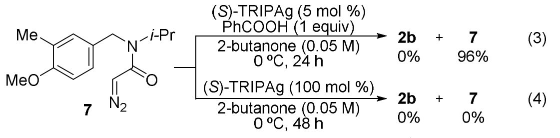
Scheme 2. Proposed reaction pathways



	M=C bond	
1.92	Length (Å)	2.14
1.17	Bond order	0.88

Figure 1. LUMO map for Rh and Ag carbenoids

We also studied an asymmetric induction of the CADA reaction. No nonlinear effects were observed when the enantiomeric excess of the (*S*)-TRIPAg was changed.[16] A kinetic study was also performed, and the reaction rate showed a first-order dependency on the catalyst.[16] These findings suggest the involvement of a single catalyst in the enantio- and rate-determining step. In addition, higher enantioselectivities were observed when phenols were substituted at the *ortho*-position compared with *meta*-substituted phenols (**2b** vs **2a**, **2c** vs **2d**). Furthermore, the anisole derivative **7** was not converted into the corresponding dearomatized product **2b** (eq 3, 4),[28] indicating that the interaction between the phenolic hydroxyl group and catalyst, and the CADA reaction proceed through a cyclophane-like transition state *via* hydrogen bonding[29] to realize the remote stereocontrol (Figure 2).



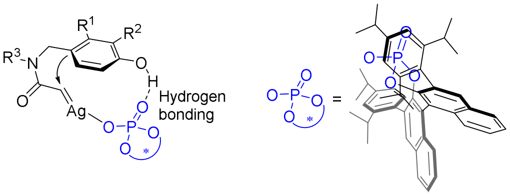


Figure 2. Plausible working model

In summary, we developed an asymmetric intramolecular dearomatization of phenol derivatives using Ag carbenoids. The methodology provides facile access to functionalized chiral spirolactams possessing an all-carbon quaternary stereogenic center with a high level of enantiocontrol regardless of the substituted position on the phenol ring. Experimental and theoretical studies indicated that the carbocation-like character facilitated the electrophilic addition of Ag carbenoid to phenol, realizing chemoselective promotion of the phenol dearomatization pathway. Further studies taking advantage of the specific properties of metal carbenoids are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interests.

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A graphic for the TOC