

### Letter

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## Gold(I)-Catalyzed Highly Enantioselective [4+2]-Annulations of Cyclopentadienes with Nitrosoarenes via Nitroso-Povarov versus Oxidative Nitroso-Povarov Reactions

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KEYWORDS: nitrosoarenes, cyclopentadienes, gold, enantioselections, nitroso-povarov.

**ABSTRACT:** This work reports gold-catalyzed highly enantioselective nitroso-Povarov reactions between cyclopentadienes and nitrosoarenes in cold dichloroethane, in which nitrosoarenes serve as  $4\pi$ -electron donors and cyclopentadienes as  $2\pi$ donors. High enantioselectivity has been achieved for substrates over a wide scope. With the same chiral catalyst, nitroso-4fluorobenzenes in these reactions under DCM/THF/water/air led to oxidative nitroso-Povarov reactions also with high enantioselectivity. We performed <sup>18</sup>O-labeling experiments to confirm that both water and O<sub>2</sub> participate in the reactions; these data support a mechanism involving nitrosoarenes as nucleophiles and gold- $\pi$ -dienes as electrophiles.

Nitrosoarenes<sup>[1]</sup> are versatile building blocks to undergo catalytic cycloadditions with alkynes,<sup>[2]</sup> allenes<sup>[3]</sup> and 1,3dienes.<sup>[4]</sup> Catalytic cycloadditions of 1,3-dienes with nitrosoarenes proceed exclusively through hetreo-Diels-Alder reactions:<sup>[5]</sup> their asymmetric versions have been extensively studied because of their widespread applications in the synthesis of drug intermediates, natural products or bioactive molecules.<sup>[5-7]</sup> Excellent enatioselectivity has been achieved for electron-rich 1,3dienes bearing an amino or alkoxy group,<sup>[6]</sup> which can react satisfactorily with nitrosoarenes over a broad scope (eq 1). For unfunctionalized 1,3-dienes, high enantioselectivity is known only for cyclopentadienes and 2-nitrosopyridines using chiral Cu catalysts (eq 2).<sup>[7]</sup>

The advent of gold catalysis has inspired new functionalizations of alkynes with weak nucleophiles,[8] but the development of gold catalysis on electrophilic activations of 1,3-dienes has not progressed, showing no examples in asymmetric reactions.<sup>[9]</sup> We recently reported<sup>[10a]</sup> gold catalyzed [4+2] reactions between nitrsoarenes and 1,3-dienes, in which dienes work as reactive alkenes and nitrosoarenes serve as  $4\pi$ -donors like *N*-arylimines in Povarov reactions<sup>[11]</sup> (eqs 3-4). We thus named the reactions as nitroso-Povarov reactions. To highlight the utility of this new catalysis, this work reports the first success of their enantioselective versions with ee up to 99%. We also discover that the same cyclopentadienes are also reactive toward nitroso-4fluorobenzenes in DCM/THF/water under air, leading to 54 novel oxidative nitroso-Povarov reactions with high 55 enantioselectivity. The occurrence of two asymmetric 56 processes confirms a mechanism involving gold- $\pi$ -dienes (I) 57 as electrophiles and nitrosoarenes as nucleophiles; the 58 other process involving gold-bound nitroso species as elec-59 trophiles is unlikely to occur. 60









As cyclopentadiene derivatives readily undergo self dimerizations, we employed 1-allenyl-4-ene 1a as the precursor of cyclopentadiene 1a';[10] theses precursors can be stored at room temperature for a few days. This one-pot operation gave the desired product **3a** in better yields. In a standard operation, initial species 1a was treated with a gold catalyst in DCE (25 °C) for 5 min to ensure a complete formation of cyclopentadienes 1a' before treatment with nitrosobenzene 2a. We examined various cationic gold(I) catalysts Ln(AuCl)<sub>2</sub>/AgX bearing chiral bisphosphine ligands Ln (n=1-5, Table 1, entries 1-12). The use of  $L_1(AuCl)_2/AgNTf_2$  ( $L_1 = (R)-3,5-t-Bu-4-MeO-MeOBIPHEP$ ) in DCE (25 °C, 10 min) afforded the desired product (+)-3a in 78% yield and 61% ee (entry 1). Cooling the reaction at 0 °C greatly improved the enantiopurity of (+)-3a to 87% ee (entry 2). To our pleasure, the reaction in DCE (-30 °C, 9 h)

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#### Table 1. Optimization of [4+3]-Annulation



Entry	Ligand (L*)	х	Solvent	Temp./Time (°C/h)	<b>(+)-3a</b> Yield/ee (%) <sup>¢</sup>	
1	$L_1$	$NTf_2$	DCE	25/10 min	78/61	
2	L <sub>1</sub>	$NTf_2$	DCE	0/1.5	77/87	
3	L <sub>1</sub>	NTf <sub>2</sub>	DCE	-30/9	76/96	
4	L <sub>1</sub>	SbF6	DCE	-30/9	74/92	
5	L <sub>1</sub>	OTf	DCE	-30/9	71/91	
6	L <sub>1</sub>	$NTf_2$	DCM	-30/9	72/94	
7	L <sub>1</sub>	$NTf_2$	toluene	-30/9	75/95	
8	L <sub>2</sub>	$NTf_2$	DCE	-30/9	75/58	
9	L <sub>3</sub>	$NTf_2$	DCE	-30/9	74/62	
10	$L_4$	$NTf_2$	DCE	-30/9	75/88	
11	$L_5$	$NTf_2$	DCE	-30/9	75/92	
12	L <sub>6</sub>	NTf <sub>2</sub>	DCE	-30/9	74/96	

<sup>*a*</sup>[**1a**] = 0.2 M. <sup>*b*</sup>Product yields are obtained after purification from a silica column. <sup>*c*</sup>The ee values were determined by chiral HPLC analysis on a chiral stationary phase.



further increased the ee up to 96% (entry 3). We varied silver salts with AgSbF<sub>6</sub> and AgOTf to afford (+)-3a in 91-92% ee (entries 4-5). For  $L_1(AuCl)_2/AgNTf_2$ , the ee values were 94% in DCM and 95% in toluene, both at -30 °C (entries 6-7). For a less bulky catalyst like  $L_2(AuCl)_2/AgNTf_2$  (L<sub>2</sub> = (*R*)-(+)-MeO-BIPHEP) in DCE (-30 °C, 9 h), compound (+)-3a was obtained with 58% ee and 75% yield (entry 8). We switched to  $L_3(AuCl)_2/AgNTf_2$  ( $L_3 = (R)-3,5-Xyl-$ MeOBIPHEP), further delivering (+)-3a with 62% ee and 74% yield (entry 9). The use of  $L_4(AuCl)_2/AgNTf_2(L_4 = (R))$ -3,5-*t*-Bu-MeOBIPHEP) gave (+)-3a with 88% ee (entry 10). For  $L_5 = (R)$ -SEGPHOS, its catalytic annulation (-30 °C, 9 h) afforded (+)-3a with 92% ee (entry 11), but its substituted form L<sub>6</sub> increased the ee value to 96%. The absolute configuration of (+)-3a was inferred from its bromo-containing relatives (+)-3d.

Under these optimized conditions, we assessed these new enantioselective reactions with various vinylallenes (Table 2). All resulting products **3** arose from the

regioselective annulations of nitrosoarenes with the more substituted alkenes of cyclopentadienes 1'. We first tested the reactions on C1-aryl-substituted vinylallenes **1b-1g** (X = Me, OMe, Br, Cl, CO<sub>2</sub>Me and OTBS), affording the annulation products (+)-3b-3g in 63-84% yields with excellent ee values (88-99%, entries 1-6). The absolute configurations of bromo-containing product (+)-3d was determined by an X-ray diffreaction.<sup>[12]</sup> These annulations were amenable to their 3- and 2-substituted phenyl derivatives 1h-j (R<sup>1</sup>= 3- $XC_6H_4$ , X = Me, Cl; R<sup>1</sup> = 2-MeC<sub>6</sub>H<sub>4</sub>), yielding desired (+)-**3h-j** in 58-78% yields with 88-91% ee (entries 7-9). For species **1k**, bearing  $R^1$  = 2-naphthyl, its resulting product (-)-**3k** was obtained in 81% yield with 87% ee (entry 10). C(1)heteroaryl substituted vinylallenes 1l and 1m (R<sup>1</sup> = 2- and 3-thienyl) were also suitable to these enantioselective annulations, furnishing (+)-3l and (+)-3m in 73-77% yield with 83% and 96% ee respectively (entries 11-12). With R<sup>1</sup> = phenyl, we varied the R<sup>2</sup> or R<sup>3</sup> substituents of vinylallenes, **1n-1o** with one butyl group; the resulting products (+)-3n and (+)-30 were also produced in 65%-67% yields, together with 81% and 71% ee (entries 13-14). But for vinylallenes bearing a  $R^2$  phenyl group [ $R^3$  = Me (1p) and  $R^3 = H_1(1q)$ , compounds (+)-3p and (-)-3q were obtained in 60-65% with 94% ee (entry 15-16). We aslo prepared all-alkyl-substituted allenylene 1r that could not be converted to the desired annulation product 3r with this chiral gold catalyst (entry 17).

## Table 2. Enantioselective nitroso-Povarov reaction wth various vinylallenes



<sup>*a*</sup>**[1a]** = 0.2 M. <sup>*b*</sup>Product yields are obtained after purification from a silica column. <sup>*c*</sup>The ee values were determined by chiral HPLC analysis on a chiral stationary phase.

We next examined these enantioselective annulations with various nitrosoarenes **2** to assess the reaction generality (Table 3). For nitrosoarenes **2b-2h** bearing electrondonating group (CH<sub>3</sub>, *i*-Pr) or an electron withdrawing group (Cl, Br, F, NO<sub>2</sub>, or CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) at the para-phenyl positions, their enantioselective annulations afforded desired products (+)-**4b-4f** and (-)-**4g-4h** in 71-79% yields with ee levels ca. 86-98% (entries 1-7). Among them, small 4-chloro derivative **4d** was achieved with the best enantioselectivity 1

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ca. 98% ee. For *meta*-phenyl nitroso species **2i** and **2j** (R<sup>2</sup> = Cl and Br), their resulting products (+)-**4i** and (+)-**4j** were obtained with 97% and 92% ee, respectively (entries 8 and 9). Again, the chloro-containing product (+)-**4i** was efficient to achieve high enantioselectivity. Alkenes such as styrenes, cyclopentene, acrylate were unreactive toward nitrosoarenes. Furans, indoles, benzofurans were inapplicable substrates.<sup>[13]</sup> Cyclohexadienes reacted with nitrosoarenes to give nitroso-Diels-Alder products.<sup>[14]</sup>

In Table 3, we obtained one minor product (-)-**5***a* in 13% yield using nitroso-4-fluorobenzene **2e** (entry 5). To our pleasure, we developed also novel oxidative nitroso-Povarov reactions when vinylallene **1a**, fluoro-containing nitroso **2f**, water and air were treated with chiral gold catalysts. Other nitrosoarenes like nitrosobenzene **2a** and 4-chlorophenyl derivative **2d** were inapplicable substrates although nitroso species **2d** was found reactive with acyclic dienes in such oxidative nitroso-Povarovreactions.<sup>[10a]</sup>

# Table 3. Enantioselective nitroso-Povarov reaction wth various nitrosoarenes



a[1a] = 0.2 M. bProduct yields are obtained after purification from a silica column. cThe ee values were determined by chiral HPLC analysis on a chiral stationary phase. dan oxidative annulation product (-)-5a was obtained in 13% yield and 95.0% ee

We conducted this reaction involving chiral catalyst  $L_1(AuCl)_2/AgNTf_2$  ( $L_1 = (R)$ -3,5-*t*-Bu-4-MeO-MeOBIPHEP) to run the reaction in DCM/THF/H<sub>2</sub>O under air at -20 °C, the yield of our target (-)-**5a** was 62% with the ee up to 95% ee (eq 5). The absolute configuration of compound (-)-**5a** was inferred from X-ray diffraction of its bromo derivative (-)-**5c** (vide infra). With the same chiral  $L_1(AuCl)_2/AgNTf_2$ , oxidized form (-)-**5a** and its non-oxidized form (+)-**4f** have the same configurations at one tertiary carbon and one-tertiary O-carbon. Notably, our new target (-)-**5a** was not accessible from the non-oxidized form (+)-**4f** with gold catalyst under DCM/THF/H<sub>2</sub>O/air (eq 5).



We assessed the substrate scope of these new oxidative annulations using various vinylallenes 1 and nitroso-4-fluorobenzenes 2f, 2k-2o; these asymmetric reactions were

performed with  $L_1(AuCl)_2/AgNTf_2$  (5/10 mol %). As shown in Table 4, various para-pheny-substituted vinylallenes 1b-**1d**, **1s** and **1h** (X = Cl. Br, Me and CF<sub>3</sub>) became appropriate substrates to react well with nitroso-4-fluorobenzene 2f, further yielding products (-)-**5b**-**5f** in good yields (61-67%) and excellent ee levels (90-97%, entries 1-5). The absolute configuration of the bromo-containing product (-)-5c was determined by X-ray analysis.<sup>[12]</sup> 2-Thienyl derived substrate 1l gave the corresponding product (-)-5g in 59% yields and 80% ee. For 2- and 3-phenyl-substituted vinylallenes 1j and 1i, their annulation products (-)-5h and (-)-5i were produced in 61-62% yields and 80% and 96% ee values. We tested the reactions on various 3-substituted-4flurophenylnitroso 2k-n, further providing the corresponding products (-)-5j-5m in 65-73% yields and 87-97% ee (entries 9-12). With nitroso-2,4-difluorobenzene 20, the desired product (-)-5n was obtained in 68% yield and 55% ee (entry 13).

#### Table 4. The Scope of [5+1]-Annulations





We further examined this asymmetric annulation for an acyclic diene **6a** using the same chiral catalyst; its resulting product **6b** via an oxidative annulation was obtained in only 14% ee, possibly due to its flexible conformation to render the enantioselectivity ineffective (eq 6). For an ethyl-derived acyclic diene **6c** (E/Z = 1.9:1), its asymmetric reaction gave **6d** as two diastereomers in racemic forms. Large alkyl group is not favorable for the enantioselectivity. This trend is consistent



with our observations for cyclopentadienes as shown by vinylallenes **1n** and **1o** (entries 13-14, Table 2). We performed gram-scale reactions on the two enatioselective annulations.

In CH<sub>2</sub>Cl<sub>2</sub>/THF/water, the transformation of vinylallene **1a** into (-)-**5a** in air was achieved with 57% yield and 95% ee under standard conditions (eq 7). The reductive cleavage of enantiopure (-)-**5a** (95% ee) with zinc powder in MeOH/H<sub>2</sub>O/AcOH produced the desired products (-)-**8a** to retain their initial enantiopurities (eq 7). As depicted in Scheme 1, vinylallene **1a** (5.88 mmol) delivered product (+)-**3a** in 72% yield (1.17 g) and 94% ee. A reductive cleavage of this product with Zn in MeOH/H<sub>2</sub>O/AcOH afforded (+)-**7a** with 94% ee and 88% yield. The

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Scheme 1. Chemical functionalizations of the cyclic nitroxyl product (+)-3a



compound (+)-**7a** was protected with 1,1'carbonyldiimidazole (CDI) to yield a conformationally rigid product (+)-**7b** with 94% ee and 92% yield, which was elaborated stereoselectively into the compound (+)-**7c** with *m*-CPBA epoxidation.

We performed <sup>18</sup>O-labeling experiments involving <sup>\*</sup>O<sub>2</sub> and  $H_2^*0$  (\*0 = 99% <sup>18</sup>0) respectively (eq 8). Treatment of cyclopentadiene 1a' with nitroso-4-fluorobenzene 2f and  $LAuCl/AgNTf_2$  (L = P(t-Bu)<sub>2</sub>(o-biphenyl, 10/20 mol %) in DCM/THF/H<sub>2</sub><sup>18</sup>O under O<sub>2</sub> afforded compound **5a** bearing high  ${}^{18}$ O content ( ${}^{16}$ O: ${}^{18}$ O = 1:1.3). In contrast, the same reaction under <sup>18</sup>O<sub>2</sub>/H<sub>2</sub>O yielded <sup>18</sup>O-containg product \*O-5a bearing 20% <sup>18</sup>O content. Both H<sub>2</sub>O and O<sub>2</sub> thus proved to be the oxygen sources for the ketone groups of compound **5a**. Herein, we did not observe an <sup>18</sup>O-exchange between compound **5a** and H<sub>2</sub><sup>18</sup>O in the presence of gold catalyst. Interestingly, N-hydroxy aniline also enabled this [4+2]annulation, but in a very slow process. We performed its asymmetric version using chiral L<sub>1</sub>(AuCl)<sub>2</sub>/AgNTf<sub>2</sub> (2.5/5 mol %) in DCE (25 °C, 10 h), but the resulting product 3a was completely racemic with only 22% yield (eq 9). In contrast, nitrosobenzene 2a afforded the product (+)-3a in 61% ee within 10 min (Table 1, entry 1). Accordingly, formation of compound **3a** relies on an attack of *N*-hydroxy aniline at gold- $\pi$ -diene, irrelevant to its oxidized form 2a (eq 9).



With chiral L<sub>1</sub>(AuCl)<sub>2</sub>/AgNTf<sub>2</sub>, two enantioselective cyclization products (+)-**4f** and (-)-**5a** bear the same (*3S*, *9S*)-

configurations and high enantiopurity; this information indicate that they have a common intermediate. As shown in Scheme 2, we postulate that this bulky chiral catalyst preferably coordinates selectively with only one face of the less substituted C(1,2)-olefin to form Au- $\pi$ -diene A. This argument is inferred by an experiment using N-hydroxy aniline that serves only as a nucleophile (eq 9). In this proposed mechanism, an oxygen-attack of nitroso species 2f at this  $\pi$ -diene **A** proceeds *trans* to gold catalyst, yielding allylgold species **B** bearing a nitrosonium moiety. Different ee values of products (-)-5a and (+)-4f indicates this A-B transformation is reversible. A ring closure of intermediate **B** affords *cis*-fused bicyclic species **C**, further yielding the observed product (+)-4f. Alternatively, intermediate B can be trapped with water to generate intermediates **D** and **E** sequentially before a ring closure. A final step is the O<sub>2</sub>oxidative aromatization of resulting cyclization species **F** to form compound (-)-5a and water. This process rationalizes our <sup>18</sup>O-labeling results (eq 8) that both  $O_2$  and  $H_2O$  serve as the oxygen sources in the products. Here, HF became produced, but its weak acidity rendered fluoride less dissociative, to allow the existence of active  $L_1Au^+$  catalyst. In the presence of water, only 9% HF is dissociative but free fluoride anion will react with HF again to yield HF<sub>2</sub><sup>-</sup> anion.<sup>[15]</sup>

An alternative pathway is an addition of nitrosoarene at gold coordinated-olefin; this pathway might be likely to occur. But it will also lead to a competitive 1,4-addition to give nitroso Diels-Alder product as shown in eqs 1-2. In contrast, the mechanism in Scheme 2 will not have a side reaction.

# Scheme 2. Postulated mechanisms for the two asymmetric reactions



Before this work, asymmetric functionalization of 1,3dienes as a 2- $\pi$ -donor has no examples in gold catalysis.<sup>[17]</sup> This work reports the first gold(I)-catalyzed enantioselective nitroso-Povarov reactions between substituted cyclopentadienes and commonly used nitrosoarenes<sup>[16]</sup> over a wide scope. Most of these [4+2]annulations were obtained in satisfactory yields with high ee levels. With the same chiral gold catalyst, the same cyclopentadienes reacted well with nitroso-4-fluorobenzenes in DCM/THF/H<sub>2</sub>O under air, yielding oxidative nitroso-Povarov products with excellent enantioselectivity. We performed <sup>18</sup>O-labeling experiments to confirm that both water and O<sub>2</sub> are the oxygen sources for the ketone group of re1

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sulting products. Our experimental data indicate an initial attack of nitrosoarenes at gold- $\pi$ -dienes to induce high enantioselectivity. The use of gold- $\pi$ -diene intermediates in asymmetric catalysis is a viable tool to access enantiopure compounds.<sup>[13-14, 17]</sup>

### ASSOCIATED CONTENT

#### Supporting Information

Experimental procedures, characterization data, crystallography data, and <sup>1</sup>H NMR and <sup>13</sup>C NMR for representative compounds (PDF)

This material is available free of charge via the Internet at http://pubs.acs.org..

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- (13) As stated in our previous report (ref 10a), common alkenes such as styrenes, cyclopentene, acrylate were unreactive toward nitroarenes. Furans, indoles, benzofurans were inapplicable substrates because they do not form  $\pi$ -complex with Au complex.
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