Enantioselective Au(I)/Au(III) Redox Catalysis Enabled by Rationally Designed Chiral (P,N)-Ligands

Chetan C. Chintawar,† Vivek W. Bhojare,‡ Manoj V. Mane,†§ and Nitin T. Patil*†

†Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal 462 066, India
‡Physical Chemistry Division, CSIR – National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India
§Academy of Scientific and Innovative Research (AcSIR), New Delhi 110 025, India

Abstract: We report, for the first time, the concept of enantioselective Au(I)/Au(III) redox catalysis, enabled by the newly designed hemilabile chiral (P,N)-ligands – ChetPhos. The potential of this concept has been demonstrated by the development of enantioselective 1,2-oxarylation and 1,2-aminocaulration of alkenes which provided direct access to the medicinally relevant 3-oxo- and 3-aminochromans (up to 88% yield and 99% ee). DFT studies were carried out to underpin the enantioinduction model, which revealed that the greater trans-influence of phosphorus allows precise positioning of the substrate in the C2-symmetric chiral environment present around nitrogen, imparting a high level of enantioselectivity.

Over the last 15 years, enantioselective gold catalysis has evolved as one of the most dynamic areas of research. In general, these reactions rely on the attack of a nucleophile on gold-coordinated C-C multiple bonds followed by proto-dearomatization. In the past decade, Au(I)/Au(III) redox catalysis has emerged as a new technique, opening up avenues for the cross-coupling of 1,2-difunctionalization reactions of C-C multiple bonds that were previously inaccessible with Au(I) or Au(III) catalysis (Scheme 1a). The pioneering work by Zhang and Toste group revealed the role of external oxidants to overcome the high redox potential of Au(I)/Au(III) couple (E0 = +1.41 V) and to facilitate two-electron redox cycle in gold catalysis. Later, Gouris group introduced the merged gold/photoredox strategy to circumvent the need for a stoichiometric amount of oxidants in these processes. To access redox gold catalysis, our group and others introduced ethynylbenziodoxolones which served a dual role as an oxidant and an alkene surrogate. Clearly, the field of Au(I)/Au(III) redox catalysis has grown tremendously and has already begun to have an impact in organic synthesis. Despite of these remarkable advancements, to date, there is no method available to achieve enantioselective Au(I)/Au(III) redox catalysis.

The main challenge in realizing enantioselective Au(I)/Au(III) redox catalysis is to tackle the typical geometrical restrictions and distinct coordination behaviour of Au(I) and Au(III) species. The Au(I) complexes are generally dicoordinated and linear; while Au(III) complexes prefer tetracoordinate square-planar geometry. Therefore, in order to achieve enantioselective Au(I)/Au(III) redox catalysis, it is necessary to control four-coordination sites of in situ generated Au(III) intermediate by a single modular ligand (L) present on LAuX. Further, the linear geometry favored by Au(I) complexes prevents the use of chiral bidentate ligands, which are required to impart structural rigidity to the in situ generated Au(III) complexes. Consequently, the tetracoordinated Au(III) intermediate generated in the presence of oxidant or photocatalyst remains structurally non-rigid and holds multiple substrate binding possibilities, making the enantio-induction highly challenging (Scheme 1a, LHS).

Recently, Bourissou, our group, and Hammond/Lu showed the potential of hemilabile (P,N)-ligand, MeDalPhos, to access catalytic C-C, C-N, C-S, and C-Se cross-coupling reactions (Scheme 1a, RHS) by facilitating the bottleneck oxidative addition of organohalides to Au(I) catalyst. Integrating this cross-coupling reactivity with the π-activation chemistry, we developed redox-neutral interplay mode to achieve gold-catalyzed 1,2-difunctionalization of C-C multiple bonds. Bourissou and Shi further utilized this concept to achieve 1,2-heteroaarylation of alkenes. Inspired by the success of (P,N)-ligands in Au(I)/Au(III) redox catalysis, we envisioned the design of a new class of

Scheme 1. Background and Synopsis of Present Work

a) State-of-the-art in Au(I)/Au(III) redox catalysis

b) Enantioselective Au(I)/Au(III) redox catalysis - This work

- Design of chiral (P,N)-ligands:
  - C2-Symmetric chiral environment
  - Hard ligand: coordinates with Au(III) only
  - Soft ligand: coordinates with Au(I) and Au(III)
  - Greater trans-influence
  - Bulky groups push Au(I) towards nitrogen

- Enantioselective 1,2-difunctionalization of alkenes:
  - Enantioenriched products!
hemilabile chiral (P,N)-ligands, namely ChetPhos, to access highly elusive enantioselective Au(I)/Au(III) redox catalysis (Scheme 1b). Following assumptions were taken into consideration for designing the chiral ligand: 1) the soft phosphorus center of the ligand should coordinate with the soft Au(I) species to form a linear LAuX complex; while the hard nitrogen center should coordinate with the in situ generated high valent Au(III) species;\textsuperscript{12a,16a} 2) the phosphorus center must bear the bulky alkyl groups in order to push the Au(I) center towards nitrogen, which is necessary to expedite the oxidative addition process by allowing nitrogen coordination;\textsuperscript{12a,16a} 3) the chelation of (P,N)-ligand in situ generated Au(III) species should offer the desired structural rigidity required for efficient enantio-induction; 4) the greater trans-influence of phosphorus in a square-planar Au(III) intermediate should allow the precise positioning of substrate in the C\textsubscript{2}-symmetric chiral environment present around the nitrogen center. The successful realization of this concept would open up a gateway for enantioselective Au(I)/Au(III) redox catalysis. Herein, we disclose the synthesis of new chiral (P,N)-ligands and their successful implementation in developing the first enantioselective 1,2-heteroarylation of alkenes under Au(I)/Au(III) redox catalysis.

We commenced our study by undertaking the synthesis of proposed chiral (P,N)-ligands (Figure 1a).\textsuperscript{19} The dibromo compounds A\textsubscript{4} and A9\textsuperscript{21} were derived from (S)-BINOL by following the literature known procedures. These compounds were then treated with 2-bromoaniline to afford diphenazepine derivatives A5 and A10, which were then subjected to the palladium-catalyzed C-P coupling with di-adamantyl or di-tert-butylphosphines to access the desired (P,N)-ligands (L\textsubscript{1}–L\textsubscript{4}).\textsuperscript{22} The reaction of these ligands with MesS\textsubscript{AuCl} afforded the respective gold(I) complexes (Figure 1b). The structures of these ligands and gold(I) complexes were unambiguously confirmed by obtaining the X-ray crystallographic data for Ad-ChetPhos and 'Bu-(H)ChetPhosAuCl.

With these newly synthesized chiral gold(I) complexes in hand, we set out to explore their catalytic activities. At the outset, we chose iodoaryl alkenes 1\textsubscript{a} as a substrate and methanol 2\textsubscript{a} as a nucleophilic partner in the presence of AgSbF\textsubscript{6}, K\textsubscript{3}PO\textsubscript{4} and DCE at 80 °C (Table 1).\textsuperscript{19} To our delight, all variants of ChetPhos ligated Au(I)-complexes catalyzed the desired 1,2-oxyarylation.

**Table 1. Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>L\textsuperscript{*}</th>
<th>[Ag]</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ad-ChetPhos</td>
<td>AgSbF\textsubscript{6}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>64</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>'Bu-ChetPhos</td>
<td>AgSbF\textsubscript{6}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>61</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Ad-(H)ChetPhos</td>
<td>AgSbF\textsubscript{6}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>55</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>'Bu-(H)ChetPhos</td>
<td>AgSbF\textsubscript{6}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>52</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Ad-ChetPhos</td>
<td>AgBF\textsubscript{4}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{f}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>78</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>Ad-ChetPhos</td>
<td>AgNT\textsubscript{f}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>59</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{s}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>27</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{f}</td>
<td>K\textsubscript{3}CO\textsubscript{3}</td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{f}</td>
<td>DTBP</td>
<td>42</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{f}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>81</td>
<td>99</td>
</tr>
<tr>
<td>12</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{f}</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>86</td>
<td>99</td>
</tr>
<tr>
<td>13</td>
<td>Ad-ChetPhos</td>
<td>AgOT\textsubscript{f}</td>
<td>None</td>
<td>86</td>
<td>99</td>
</tr>
</tbody>
</table>

\*Conditions: 0.1 mmol 1\textsubscript{a}, 1.0 mmol 2\textsubscript{a}, 0.005 mmol L\textsuperscript{*}AuCl, 0.105 mmol [Ag], 0.05 mmol base, DCE (0.1 M), 80 °C. \*Isolated yields. \*0.03 mmol K\textsubscript{3}PO\textsubscript{4}, 0.01 mmol K\textsubscript{3}PO\textsubscript{4}.

**Figure 1.** Synthetic route to new chiral (P,N)-ligands and their gold(I) complexes.
reaction in moderate yield and excellent enantioselective excess (entries 1-4). Among all chiral (P,N)-ligands, Ad-ChetPhos afforded 3-methoxychromane 3a with excellent enantioselectivity (97% ee, entry 1). In order to further optimize the reaction conditions, several halide scavengers, bases, and solvents were screened. For instance, when different silver salts were tested (entries 5-8), the use of AgOTf improved the yield of the reaction to 78% (98% ee). The variation of bases did not further improve the yield of the reaction (entries 9-10). However, lowering the amount of K2PO4 increased the yield of the reaction (entries 11-12). Interestingly, the desired 3-methoxychromane was isolated in the highest 86% yield and 99% ee when the reaction was performed in the absence of base.

Next, we turned our attention towards evaluating the generality of enantioselective 1,2-oxyarylation reaction (Scheme 2). To our delight, various derivatives of 3-methoxychromanes (3a-3i) were obtained in excellent enantiomeric excess (81-99% ee) and moderate to good yields (47-86%) when differently substituted iodoaryl alkenes (1a-1i) were subjected to standard reaction conditions. For instance, halo-, nitro-, and keto- substituted 3-methoxychromane 3b-3e were obtained in 72-80% yield with 97-99% ee. Further, substrates 1f and 1g also reacted smoothly to afford corresponding products (3f and 3g) in good yields with excellent enantioselectivity. However, considerable drop in yield and ee were observed in the case of 3h (51%, 81% ee) and 3i (47%, 90% ee). Other alcohols such as ethanol, isopropyl, and 2-bromobenzyl alcohol also reacted well with 1a to afford the desired products 3j-3l in excellent enantioselectivity (98-99% ee) and moderate to good yields (45-73%). Interestingly, when water was used as a nucleophile, the corresponding 3-hydroxychromans 3m-3o (67-81%, 94-99% ee) were readily obtained.

With the success in 1,2-oxyarylation reaction, we wondered whether amines could be used as nucleophilic partners to obtain 3-aminochromane derivatives. Be noted that 3-aminochromans represent the core structure of several marketed drug molecules. However, conventional approaches to obtain these compounds in enantiopure form largely rely on chiral resolution. To explore the feasibility of enantioselective 1,2-aminooarylation of alkenes, we used iodoaryl alkenes 1a and 4-nitroaniline as amine source. After brief optimization studies, we were delighted to find that the desired product 5a could be obtained in highest 84% yield and 99% ee when 5 mol% Ad-ChetPhosAuCl, 1.15 equiv. AgSbF6, and 0.1 equiv. K3PO4 were used in 0.1 M DCE.

In general, a wide array of amines reacted smoothly with iodoaryl alkenes 1a to furnish the desired 3-aminochromanes 5a-5l (Scheme 3) in moderate to good yield (42-86%) and excellent enantiomeric excess (96-99%). For instance, various substitutions at ortho and para position of aniline were well tolerated to afford the desired products 5a-5e in 56-86% yields. Interestingly, in all cases, 99% ee was obtained highlighting the excellent level of enantio-control offered by Ad-ChetPhos ligand. Moreover, various disubstituted amines bearing electron-donating and withdrawing groups as well as heteroaromatic amine also reacted well, giving products 5f-5l in 42-77% yield and 96-99% ee. The structure and absolute configuration of products were unambiguously confirmed by X-ray crystallographic analysis of 5k.

Next, the scope of iodoaryl alkenes 1 was verified against 2-nitroaniline. Interestingly, all the desired 3-aminochromanes were obtained in 99% ee (68-80% yield) when variously substituted iodoaryl alkenes (5m-5q) were used as substrates. However, a little drop in yield and ee was noticed (48%, 91% ee) when disubstituted iodoaryl alkenes 1r was used, clearly suggesting that the substituent ortho to alkoxy group hampers the reaction outcome (compare 5n and 5r).

The synthetic utility was demonstrated by performing the post-synthetic modifications of 3-oxochromans (Figure 2a). The C-N and C-B coupling with 3e was performed under Pd catalysis
nucleophilic attack of 4-nitroaniline on the activated alkene in \textbf{Int-A} is controlled by the C$_2$-symmetric chiral motif present on the adjacent nitrogen centre. The Si-face attack of a nucleophile (TA-A) has a barrier of 11.4 kcal/mol; while the Re-face attack (TS-A') demands 18.0 kcal/mol. Such a high energy difference (6.6 kcal/mol) clearly indicates that the newly developed ligand provides a powerful enantio-discrimination and rationalizes the excellent enantioselectivity observed in the present reaction.

In conclusion, we have developed the first example of enantioselective Au(I)/Au(III) redox catalysis, enabled by the newly designed hemilabile chiral (P,N)-ligands – ChemPhos. The potential of this concept is demonstrated in gold-catalyzed 1,2-oxynylation and 1,2-amination of alkenes leading to medicinally important 3-oxo- and 3-aminochromans with high yields and enantioselectivities. The greater trans-influence of phosphorus is the key to direct the alkene coordination adjacent to the nitrogen center; as a result, the nucleophilic attack on the alkene is governed by the C$_2$-symmetric chiral motif present around nitrogen. This concept of ligand-enabled enantioselective Au(I)/Au(III) redox catalysis should be applicable to a vast number of cross-coupling reactions and alkene difunctionalization reactions.\(^2\) Currently, we are focusing on the design and synthesis of new hemilabile chiral (P,N)-ligands and their applications in the Au(I)/Au(III) redox catalysis.

**AUTHOR INFORMATION**

**Corresponding Author**

Nitin T. Patil – Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhaouri, Bhopal 462 066, India; orcid.org/0000-0002-8372-2759; Email: npatil@iiserb.ac.in

**ACKNOWLEDGMENT**

Generous financial support by the Science and Engineering Research Board (SERB), New Delhi (File Nos. DIA/2018/000016 and EMR/2016/007177), is gratefully acknowledged. C.C.C. and V.W.B. thanks UGC and CSIR, respectively for the award of Senior Research Fellowship. We thank Abhik Paul from IISERB for his assistance with SC-XRD analysis.

**REFERENCES**


(19) For details, see Supplementary Information.


(22) Based on the substituents attached on the phosphorus and the nature of dimaphthoazipine skeleton the newly synthesized ligands have been named as: L1 = Ad-ChetPhos, L2 = Bu-ChetPhos, L3 = Ad-(H8)ChetPhos, and L4 = Bu-(H8)ChetPhos.


