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

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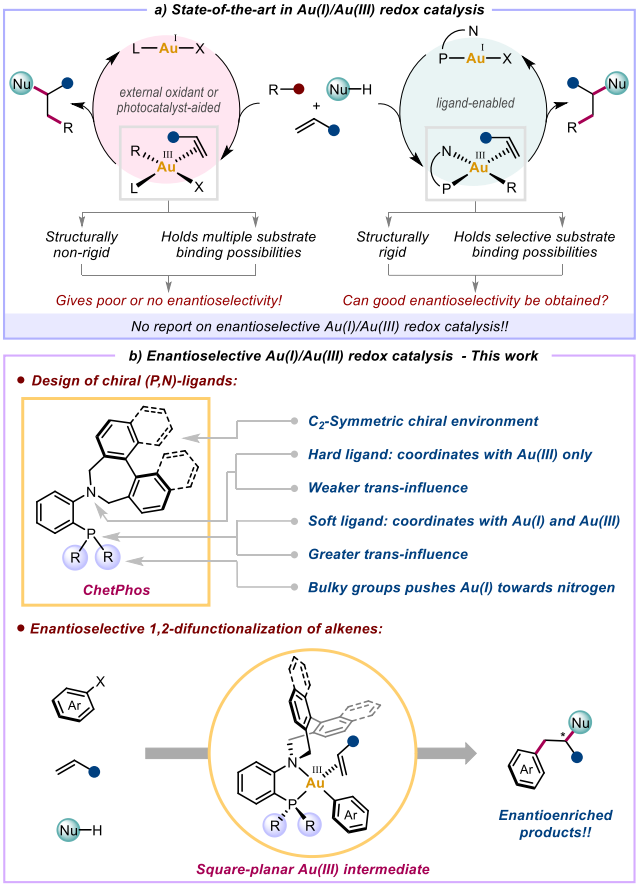
ABSTRACT: We report, for the first time, the concept of enantioselective Au(I)/Au(III) redox catalysis, enabled by the newly designed hemilabile chiral (P,N)-ligands – ChetPhos. The potential of this concept has been demonstrated by the development of enantioselective 1,2-oxyarylation and 1,2-aminoarylation of alkenes which provided direct access to the medicinally relevant 3-oxy- 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 C_2-symmetric chiral environment present around nitrogen, imparting a high level of enantioselectivity.

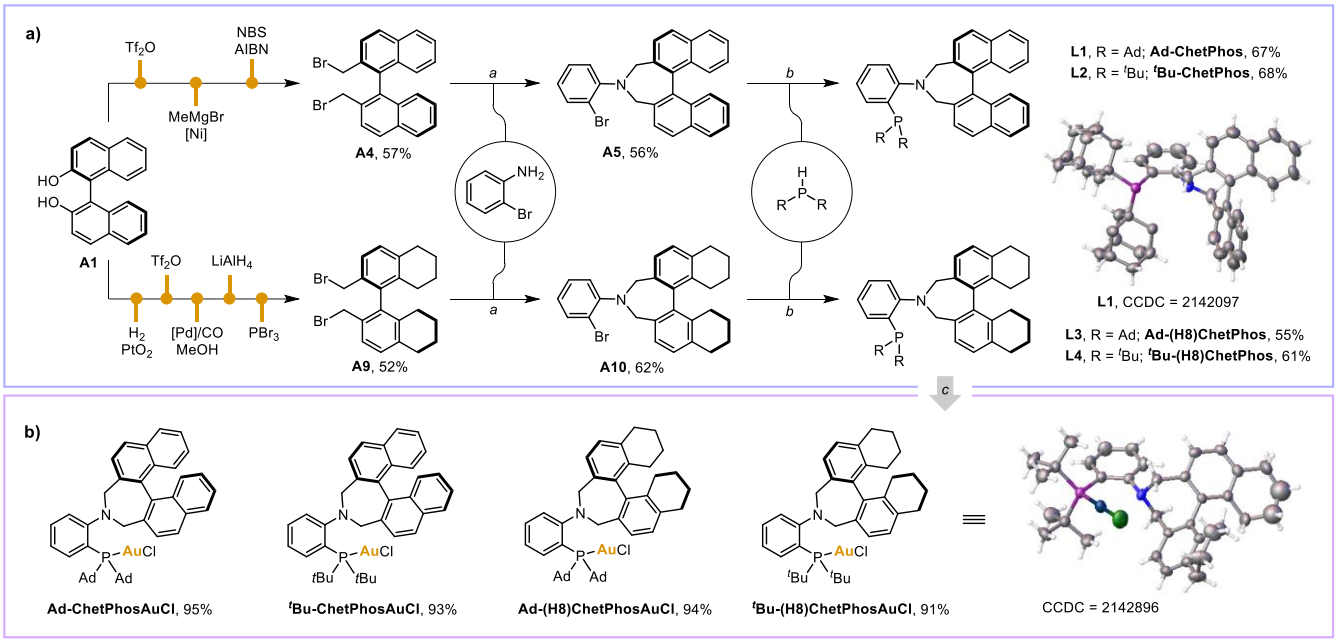
Over the last 15 years, enantioselective gold catalysis has evolved as one of the most dynamic areas of research.[1] In general, these reactions rely on the attack of a nucleophile on gold-coordinated C-C multiple bonds followed by proto-deauration. In the past decade, Au(I)/Au(III) redox catalysis has emerged as a new technique, opening up avenues for the cross-coupling and 1,2-difunctioalization reactions of C-C multiple bonds that were previously inaccessible with Au(I) or Au(III) catalysis (Scheme 1a).[2] The pioneering work by Zhang[3] and Toste[4] group revealed the role of external oxidants to overcome the high redox potential of Au(I)/Au(III) couple (E^0 = +1.41 V) and to facilitate two-electron redox cycle in gold catalysis.[2a-d,g,j] Later, Glorius group[5] introduced the merged gold/photoredox strategy to circumvent the need for a stoichiometric amount of oxidants in these processes.[2e,f,i,k] To access redox gold catalysis, our group[6] and others[7] introduced ethynylbenziodoxolones which served a dual role as an oxidant and an alkyne surrogate.[2h] Clearly, the field of Au(I)/Au(III) redox catalysis has grown tremendously and has already began to have an impact in organic synthesis.[2] 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 realising 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.[8] The Au(I) complexes are generally dicoordinated and linear; while Au(III) complexes prefer tetracoordinated square-planar geometry.[9] 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 modulatory ligand (L) present on LAuX. Further, the linear geometry favored by Au(I) complexes prevents the use of chiral bidentate ligands,[10] 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).[11]

Recently, Bourissou,[12] our group,[13] and Hammond/Lu[14] showcased the potential of hemilabile (P,N)-ligand, MeDalPhos,[15] 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.[16] Bourissou[17] and Shi[18] further utilized this concept to achieve 1,2-heteroarylation 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





Conditions: a) 1 equiv. **S4** or **S9**, 3 equiv. 2-bromoaniline, 20 mol% NaI, 4 equiv. K_2CO_3, MeCN, reflux, 36 h; b) 1 equiv. **S5** or **S10**, 1.1 equiv. R_2PH, 5 mol% $Pd(OAc)_2$, 6 mol% dippf, 1.2 equiv. NaO^tBu, toluene, 110 °C, 24 h; c) 1 equiv. **L**, 1 equiv. Me_2SAuCl, DCM, rt, 10 h

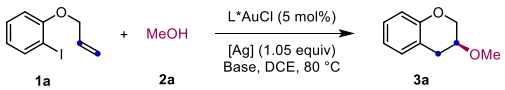
Figure 1. Synthetic route to new chiral (P,N)-ligands and their gold(I) complexes.

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;[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;[12a,16a] 3) the chelation of (P,N)-ligand with 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_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).[19] The dibromo compounds **A4**[20] and **A9**[21] were derived from (*S*)-BINOL by following the literature known procedures. These compounds were then treated with 2-bromoaniline to afford dinaphthoazipine 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 (**L1**–**L4**).[22] The reaction of these ligands with Me_2SAuCl 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 ^{t}Bu-(H8)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 alkene **1a** as a substrate and methanol **2a** as a nucleophilic partner in the presence of $AgSbF_6$, K_3PO_4 and DCE at 80 °C (Table 1). [19] To our delight, all variants of ChetPhos ligated Au(I)-complexes catalyzed the desired1,2-oxyarylation

Table 1. Optimization of Reaction Conditions[a]

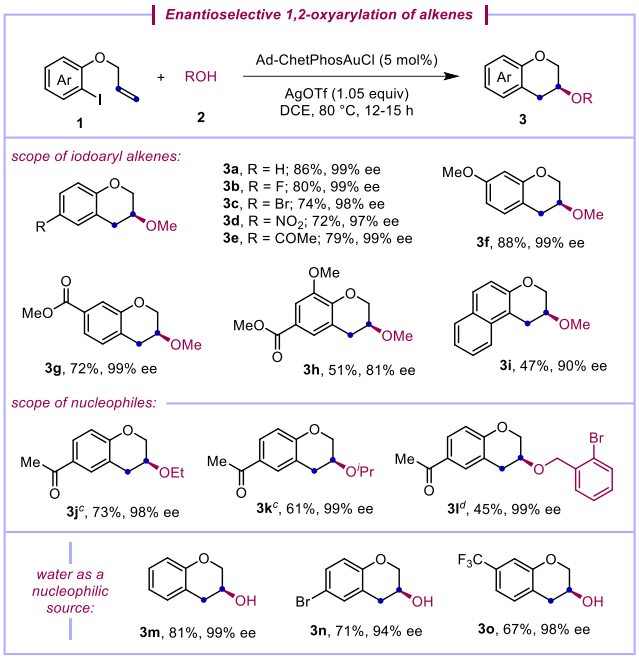


1a 2a 3a

Entry	L*	[Ag]	Base	Yield[b] (%)	ee (%)
1	Ad-ChetPhos	$AgSbF_6$	K_3PO_4	64	97
2	^{t}Bu-ChetPhos	$AgSbF_6$	K_3PO_4	61	96
3	Ad-(H8)ChetPhos	$AgSbF_6$	K_3PO_4	55	94
4	^{t}Bu-(H8)ChetPhos	$AgSbF_6$	K_3PO_4	52	94
5	Ad-ChetPhos	$AgBF_4$	K_3PO_4	61	97
6	Ad-ChetPhos	AgOTf	K_3PO_4	78	98
7	Ad-ChetPhos	$AgNTf_2$	K_3PO_4	59	97
8	Ad-ChetPhos	AgOTs	K_3PO_4	27	96
9	Ad-ChetPhos	AgOTf	K_2CO_3	67	97
10	Ad-ChetPhos	AgOTf	DTBP	42	98
11[c]	Ad-ChetPhos	AgOTf	K_3PO_4	81	99
12[d]	Ad-ChetPhos	AgOTf	K_3PO_4	86	99
13	**Ad-ChetPhos**	**AgOTf**	**None**	**86**	**99**

[a]Conditions: 0.1 mmol **1a**, 1.0 mmol **2a**, 0.005 mmol L*AuCl, 0.105 mmol [Ag], 0.05 mmol base, DCE (0.1 M), 80 °C. [b]Isolated yields. [c]0.03 mmol K_3PO_4, [d]0.01 mmol K_3PO_4.

Scheme 2. Scope of 1,2-Oxyarylation of Alkenes[a,b]



[a]Conditions: 0.2 mmol **1**, 2 mmol **2**, 0.01 mmol Ad-ChetPhosAuCl, 0.21 mmol AgOTf, DCE (0.1 M), 80 °C, 12–15 h. [b]Isolated yields. [c]1 mmol alcohol was added. [d]0.6 mmol 2-bromobenzyl acohol was added.

reaction in moderate yield and excellent enantiomeric 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.[19] 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 K_3PO_4 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 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, *iso*-propanol, and 2-bromobenzylacohol 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.

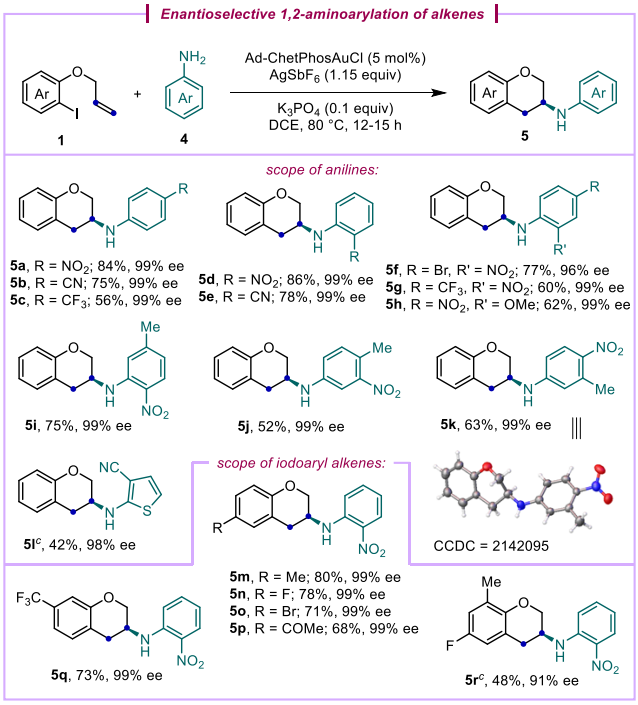
With the success in 1,2-oxyarylation reaction, we wondered whether amines could be used as nucleophilic partners to obtain 3-aminochromane derivatives. Be noted that 3-aminochromans represent the core structure of several marketed drug molecules.[23] However, conventional approaches to obtain these compounds in enantiopure form largely rely on chiral resolution.[24] To explore the feasibility of enantioselective 1,2-aminoarylation of alkenes, we used iodoaryl alkene **1a** and 4-nitroaniline as amine source. After brief optimization studies[19] 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. $AgSbF_6$, and 0.1 equiv. K_3PO_4 were used in 0.1 M DCE.

In general, a wide array of anilines reacted smoothly with iodoaryl alkene **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 anilines 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**.

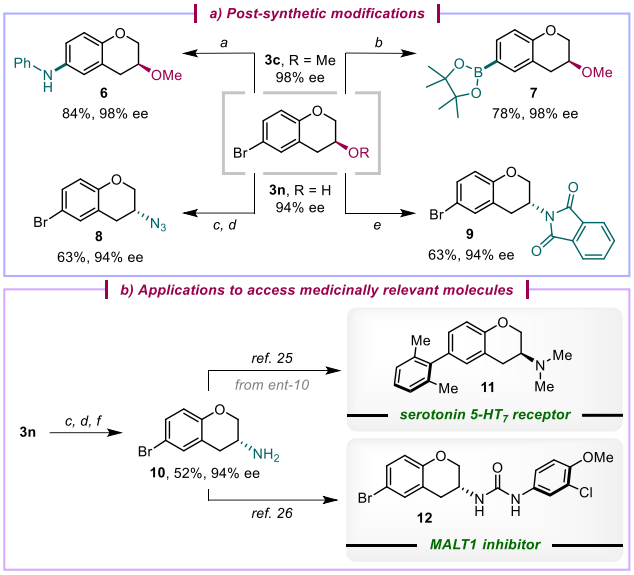
Next, the scope of iodoaryl alkene **1** was verified against 2-nitroaniline. Interestingly, all the desired 3-aminochromanes were obtained in 99% ee (68–80% yield) when variously substituted iodoaryl alkenes (**5m**–**5q**) were used as substrates. However, a little drop in yield and ee was noticed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

The synthetic utility was demonstrated by performing the post-synthetic modifications of 3-oxychromans (Figure 2a). The C-N and C-B coupling with **3c** was performed under Pd catalysis

Scheme 3. Scope of 1,2-Aminoarylation of Alkenes[a,b]



[a]Conditions: 0.22 mmol 1, 0.2 mmol 4, 0.01 mmol Ad-ChetPhosAuCl, 0.23 mmol $AgSbF_6$, DCE (0.1 M), 80 °C, 12–15 h. [b]Isolated yields. [c]Reaction was stirred for 20 h.



Conditions: a) 1 equiv. **3c**, 1.1 equiv. $PhNH_2$, 3 mol% $Pd(OAc)_2$, 6 mol% XPhos, 1.5 equiv. K^{t}OBu, toluene, 90 °C, 12 h; b) 1 equiv. **3c**, 1 equiv. B_2Pin_2, 3 mol% $Pd(PPh_3)_2Cl_2$, 1.5 equiv. NaOAc, neat, 110 °C, 12 h; c) 1 equiv. **3n**, 2 equiv. Et_3N, 1.5 equiv. MsCl, DCM, 0 °C to rt, 8 h; d) 1 equiv. mesylate of **3n**, 5 equiv. NaN_3, DMF, 100 °C, 12 h; e) 1 equiv. **3n**, 2 equiv. phthalimide, 2 equiv. PPh_3, 2 equiv. DEAD, benzene, 0 °C to rt, 8 h; f) 1 equiv. **8**, 2 equiv. $LiAlH_4$, THF, 0 °C to rt, 4 h.

Figure 2. a) Post-synthetic modifications; b) Applications.

to obtain the functionalized 3-methoxychromans **6** (84%, 98% ee) and **7** (78%, 98% ee), respectively. Besides, the hydroxyl group of **3n** was converted to mesylate which after S_N2 displacement with azide afforded 3-azidochromane **8** (63%, 94% ee). Further, a Mitsunobu reaction was performed with **3n** and phthalimide to obtain the corresponding product **9** (63%, 94% ee). Our methodology provides efficient access to enantio-enriched 6-bromo-3-aminochromane **10** (Figure 2b) which is a precursor for the synthesis of serotonin 5-HT_7 receptor **11**[25] and MALT1 inhibitor **12**.[26]

To underpin the enantioinduction model, DFT calculations were performed with Guassian 09 programs using **1a** and 4-nitroaniline as model substrates (Figure 3).[19] The studies revealed that the coordination of alkene *trans* to phosphorus is energetically favoured giving the Au(III)-π complex **Int-A**. The subsequent

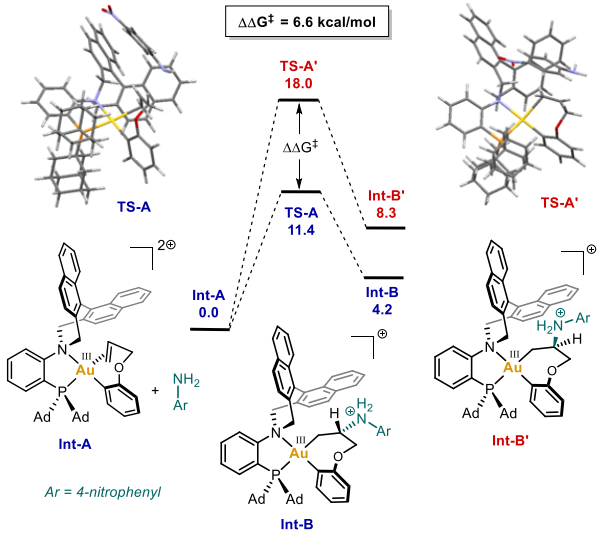


Figure 3. DFT calculations for enantio-determining step.

nucleophilic attack of 4-nitroaniline on the activated alkene in **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 – ChetPhos. The potential of this concept is demonstrated in gold-catalyzed 1,2-oxyarylation and 1,2-aminoarylation of alkenes leading to medicinally important 3-oxy- 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.

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