# Oxidant-Free Au(I)-Catalyzed Halide Exchange and C$_{sp2}$−O Bond Forming Reactions

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Ⓢ *Supporting Information*

ABSTRACT: Au has been demonstrated to mediate a number of organic transformations through the utilization of its π Lewis acid character, Au(I)/Au(III) redox properties or a combination of both. As a result of the high oxidation potential of the Au(I)/Au(III) couple, redox catalysis involving Au typically requires the use of a strong external oxidant. This study demonstrates unusual external oxidant-free Au(I)-catalyzed halide exchange (including fluorination) and C$_{sp2}$−O bond formation reactions utilizing a model aryl halide macrocyclic substrate. Additionally, the halide exchange and C$_{sp2}$−O coupling reactivity could also be extrapolated to substrates bearing a single chelating group, providing further insight into the reaction mechanism. This work provides the first examples of external oxidant-free Au(I)-catalyzed carbon−heteroatom cross-coupling reactions.
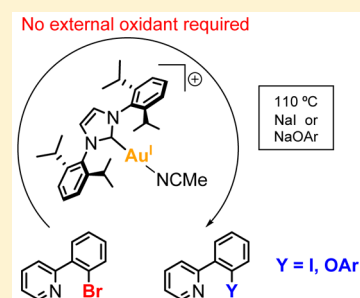
INTRODUCTION

Metal-mediated transformations in organic synthesis have revolutionized the design of retro-synthetic strategies for the preparation of new organic compounds.[1,2] Among these strategies, carbon−carbon (C−C) and carbon−heteroatom (C−X) forming cross-coupling reactions mediated by Pd and Cu have become the most established options.[3−12] Nevertheless, the discovery of new methodologies involving other transition metals with the possibility of providing new selectivities is highly desirable. Recently, during screening of the redox chemistry of coinage metals with a model aryl macrocyclic ligand, we have provided experimental evidence regarding the unexpected feasibility of Ag(I)/Ag(III) two-electron redox cycles in C−C and C−heteroatom cross-coupling catalysis,[13] operating analogously to Cu(I)/Cu(III) catalysis (Scheme 1).[14,15] In contrast

Scheme 1. Previously Reported M(I) (M = Cu or Ag) Catalyzed Halide Exchange Reactions in Model Aryl Halide Macrocyclic Substrates
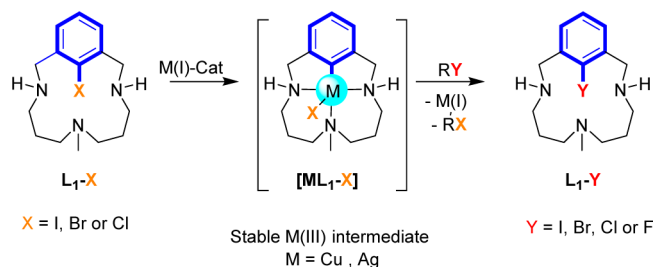
to the other coinage metals, Au-catalyzed cross-coupling catalysis has only been observed in the presence of external oxidants.[16−20] This difference in reactivity is due to the high

oxidation potential of the Au(I)/Au(III) redox couple (E_0 = +1.41 V in water),[21] and, as a result, Au(I)-catalyzed C−C bond forming reactions utilizing the π Lewis acid properties of Au are more common.[22−29]

The engagement of Au(I) catalysis in aryl halide oxidative addition has been a matter of controversy over the past few years. In 2007 Corma and co-workers reported what they considered to be the first example of Au(I)-catalyzed Sonogashira couplings using aryl iodides without the need for an external oxidant,[30] but in 2010, Espinet, Echavarren and co-workers provided evidence on the unlikelihood that these Au(I)-catalyzed Sonogashira coupling reactions proceeded in the absence of Pd impurities.[31,32] Around the same time, Lambert and co-workers provided further evidence that the activity observed in these Au-catalyzed Sonogashira couplings was a consequence of the presence of Au nanoparticles.[33] The latter observation was also later reported by Corma and co-workers in 2011.[34]

The viability of the oxidative addition of aryl halides at Au(I) has recently attracted renewed interest, particularly in work reported by Bourissou and co-workers whereby the crystal structures of aryl-Au(III)-I oxidative addition products have been reported.[35] These compounds are reported to be extremely stable and no further reactivity was observed. In addition, Toste recently reported Au(I) oxidative addition using biphenylene to obtain [IPrAu(III)(biphenyl)]$^+$, where its Lewis acid properties are further exploited.[36] Reductive elimination from Au(III) for C−C bond formation has long been known, particularly from the groups of Kochi, Tobias and Vincent, reporting reductive eliminations from dialkyl−Au(III) complexes, although not in a

Table 1. Catalytic Halide Exchange Reactions with L₁−X in CD₃CN under N₂[a]
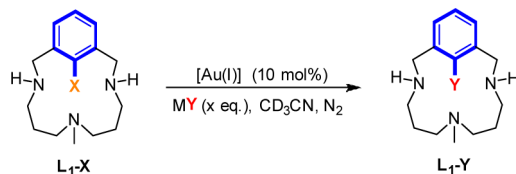
entry	L₁−X	MY (equiv)	Au(I) (10 mol %)	T (°C)	t (h)	yield L₁−Y (%)[b]
1	**L₁−I**	Bu₄N−Cl (2)	AuCl(PPh₃)	40	48	>99
2			Au(NTf₂)PPh₃	40	48	97
3			[Au(NCMe)IPr]⁺	40	6	>99[c]
4			-	40	48	2
5		NaBr (10)	AuCl(PPh₃)	40	48	5 (94)[d]
6			Au(NTf₂)PPh₃	40	48	9 (96)[d]
7			[Au(NCMe)IPr]⁺	40	30	15 (97)[d]
8			-	40	48	0 (36)[d]
9	**L₁−Br**	Bu₄N−Cl (2)	AuCl(PPh₃)	40	60	98
10			Au(NTf₂)PPh₃	40	60	99
11			[Au(NCMe)IPr]⁺	40	12	99
12			-	40	60	trace
13		NaI (10)	AuCl(PPh₃)	70	18	95
14			Au(NTf₂)PPh₃	70	8	92
15			[Au(NCMe)IPr]⁺	70	4	94
16			-	70	18	23
17	**L₁−Cl**	NaBr (10)	AuCl(PPh₃)	70	72	30 (56)[e]
18			Au(NTf₂)PPh₃	70	72	34
19			[Au(NCMe)IPr]⁺	70	72	46 (59)[e]
20			-	70	72	trace
21		NaI (10)	AuCl(PPh₃)	70	100	42 (64)[f]
22			Au(NTf₂)PPh₃	70	100	48
23			[Au(NCMe)IPr]⁺	70	48	67
24			-	70	100	16

[a]Conditions: 15.3 μmol **L₁−X**, 10 mol % Au(I), MY, 0.5 mL CD₃CN, N₂; see Au(I) catalyst structures in Scheme 2. [b]Yields calculated using ¹H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. [c]Quantitative yield after 30 h using 5 mol % of Au(I) cat. [d]In parentheses, experiments at 70 °C. [e]In parentheses, LiBr (10 equiv) as bromide source. [f]In parentheses, yield after 350 h.

catalytic fashion.[37−40] More recently, Toste and co-workers have also described an extremely fast reductive elimination from Au(III) complexes forming biaryl compounds.[41] These oxidative addition and reductive elimination steps have been combined in a stepwise stoichiometric intramolecular Au-mediated allylation of arylboronic acids proceeding through an isolable Au(III) intermediate indicating the feasibility of these conversions.[36,42,43]

Inspired by these reports, we decided to investigate the possibility of external oxidant-free Au(I)-catalyzed cross-coupling reactions using our model systems and to study the intrinsic differences of Au reactivity compared to the previously reported two-electron redox catalysis with Ag and Cu.[8,13,15]

RESULTS AND DISCUSSION

Au(I)-Catalyzed Halide Exchange in Aryl−X Model Substrates (X = Cl, Br, I). In analogy to our previous works on Ag and Cu based halide exchange reactions, we first attempted a stoichiometric reaction by adding 1 equiv of a Au(I) source, [AuCl(SMe₂)], to a CD₃CN solution of **L₁−Br** (1 equiv) in which we observed the immediate formation of a precipitate as well as a change in the color of the solution to pale violet, indicating the decomposition of the Au(I) precursor to Au(0) in the form of Au nanoparticles. This result suggested that the soft nature of the Au(I) cation could not be stabilized by the secondary and tertiary amines of the model aryl halide macrocycle in contrast to our previous examples using Cu and Ag.

Also, we realized that Au(I) was prone to disproportionation to form metallic Au; therefore, a strongly coordinating ligand should be used to stabilize Au(I) in solution to avoid this detrimental side reaction.

We decided to first investigate the potential for catalytic halide exchange in the aryl halide macrocycle mediated by [AuCl(PPh₃)]. Initially, we focused on **L₁−I** in the presence of a catalytic amount of [AuCl(PPh₃)] (10 mol %) and 2 equiv of tetrabutylammonium chloride (nBu₄N−Cl) in CD₃CN, and we were pleased to observe clean and quantitative conversion to the halide exchanged product, **L₁−Cl** in 48 h at 40 °C (Table 1, entry 1). Importantly, in the absence of Au(I), only traces of halide exchange product were observed, confirming the role of Au(I) as catalyst (Table 1, entry 4). Conversion of **L₁−I** to **L₁−Br** was also cleanly achieved, although the optimization process rendered improved results using slightly higher temperatures (70 °C; Table 1, entries 5−8). Subsequently, the study was extended to the bromide containing aryl macrocycle, **L₁−Br**. This conversion is analogous to the well-known Cu-catalyzed Buchwald transformation of aryl−bromides to the corresponding aryl−iodides,[44] and again it was possible to cleanly realize the Cl and I exchanged products (Table 1, entries 9−16). As can be seen in a ¹H NMR monitoring experiment (Scheme 2), the reactions proceeded cleanly and showed no presence of intermediates during the catalytic transformation of **L₁−Br** to **L₁−I**. Halide exchange reactions

Scheme 2. ^{1}H NMR Spectra of the Evolution of the Benzylic Region during the Halide Exchange Reaction from L_1−Br to L_1−I (Table 1, entry 13) in CD$_3$CN^a
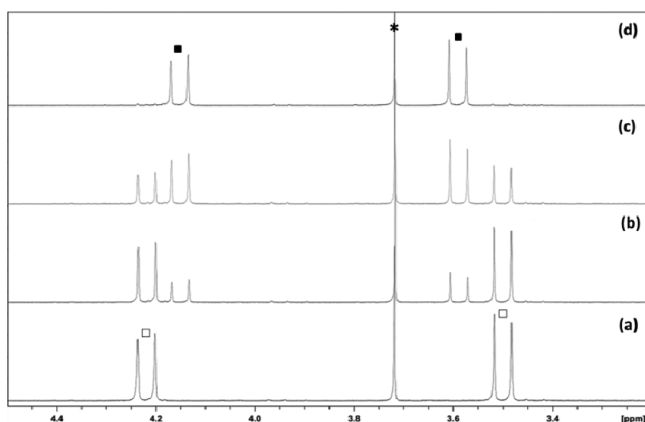

^{a}(a) $t = 0$ h, (b) $t = 2$ h, (c) $t = 8$ h and (d) $t = 18$ h. □ L_1−I, ■ L_1−Br, and * 1,3,5-trimethoxybenzene (internal standard).

starting from L_1−Cl (Table 1, entries 17−24) proved to be significantly more challenging than those with L_1−I and L_1−Br, likely as a result of the stronger Ar−X bond (Ar−Cl = 97.3 kcal·mol^{-1}, Ar−Br = 82.7 kcal·mol^{-1} and Ar−I = 66.9 kcal·mol^{-1}).[45] With respect to the iodination of L_1−Cl, even after prolonged reaction times of up to 350 h (Table 1, entry 21), we were unable to realize quantitative conversions. The low conversion of L_1−Cl to L_1−Br using NaBr (30% yield, Table 1, entry 17) may be also attributed to the low solubility of the initial halide salt in acetonitrile. The use of more soluble LiBr improved the yield of L_1−Br to 56% (Table 1, entry 17). The precipitation of the sodium salts (NaCl and NaBr) from the CD$_3$CN solution may be key to understanding the catalytic cycle turnover towards heavier halide products;[14] no halide exchange reaction is observed in the exchange of aryl chloride toward aryl bromide or aryl iodide when using soluble nBu$_4$NBr or nBu$_4$NI, respectively.

In general, although the halide exchange reactions catalyzed by [AuCl(PPh$_3$)] were effective, in some cases they struggled to reach completion after extended periods of time (days). To tackle the poor reactivity of AuCl(PPh$_3$), we hypothesized that the availability of the coordination site on the Au(I) center might have an important effect on the reaction outcome. Recently, theoretical calculations have suggested that a putative oxidative addition of aryl halides to Au(I) would be much easier when employing [Au(I)L]$^+$ complexes.[46] Although these kind of cationic Au(I) complexes have proven very unstable, the use of a weakly coordinating counterion can prevent such decomposition. In view of this, we tested the efficiency of [Au(NTf$_2$)PPh$_3$] (NTf$_2$ = bis(trifluoromethanesulfonyl)imidate) as Au(I) catalyst in the previously described halide exchange transformations (Scheme 3).[47,48] The results obtained were comparable to those using [AuCl(PPh$_3$)] (see Table 1), except for the iodination of L_1−Br, which was accomplished in the same excellent yields in only 8 h (Table 1, entry 14). We also attempted the chloride abstraction from AuCl(PPh$_3$) by silver salts with an accompanying noncoordinating anion, such as BF$_4^-$ or SbF$_6^-$ in acetonitrile solution, to occupy the vacant coordination site by a labile solvent molecule.[49,50] [Au(NCMe)PPh$_3$]SbF$_6$ was synthesized, but its use as a catalyst proved unsuccessful due to rapid decomposition into [Ph$_3$P−Au−PPh$_3$]$^+$ species and Au(0) in solution at temperatures above 25 °C.

Scheme 3. Au(I) Catalysts Used in This Work

[AuCl(PPh$_3$)]   [Au(NTf$_2$)(PPh$_3$)]

[Au(NCMe)IPr](SbF$_6$)
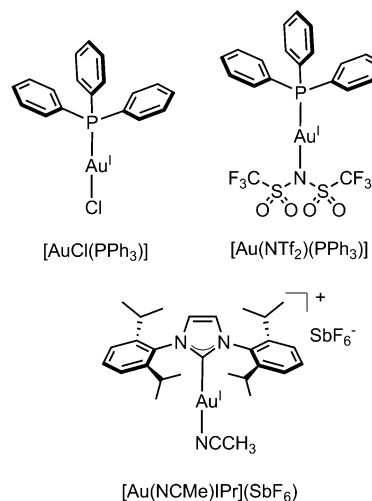
In view of the difficulties in isolating an alternative triphenylphosphine-based Au complex that shows improved reactivity, we sought another ancillary ligand. Over the past few years, Nolan and co-workers have prepared a range of complexes with N-heterocyclic donor ligands (NHC) replacing the common phosphines.[49−52] This type of ligand has been reported to stabilize cationic Au(I) much more effectively than PPh$_3$, while maintaining its catalytic properties. Hence, we prepared [Au(NCMe)IPr]SbF$_6$ (IPr = 1,3-bis(di-isopropylphenyl)-imidazol-2-ylidene) starting from commercially available AuCl-(IPr) (Scheme 3). Subsequently, we tested its catalytic efficacy towards halide exchange reactions within the aryl halide macrocyclic substrates (Table 1). To our delight, good to excellent yields were also attained employing significantly shorter reaction times, especially for the chlorination of L_1−I and L_1−Br (Table 1, entries 3 and 11) and the iodination of L_1−Br and L_1−Cl (Table 1, entries 15 and 23). For comparison, in some reactions AuCl(IPr) or AuBr(IPr) were used instead of [Au-(NCMe)IPr](SbF$_6$) and the same results were obtained (see Table S3). This is an important indication that the catalytic activity of a Au(I) complex, namely [AuX(L)], is predominantly governed by the nature of the ancillary ligand L rather than the counteranion X.

Au(I)-Catalyzed C−F Bond Forming Reactions with Model Macrocyclic Substrates. Since catalytic halide exchange reactions mediated by Au(I) were shown to be successful with the combination of any pair of L_1−X and MY (where X, Y = Cl, Br, I), we then sought to investigate the possibility of halide exchange for the realization of fluorination products using AuCl(PPh$_3$), Au(NTf$_2$)(PPh$_3$) or [Au(NCMe)IPr](SbF$_6$) as catalysts. Initially, we tested Bu$_4$NF as fluoride source, but we found it to be completely ineffective. In contrast, addition of 2 equiv of AgF, a typical fluoride source for catalytic fluorination reactions,[53] to a solution of ligand L_1−Cl and 10 mol % of AuCl(PPh$_3$) or Au(NTf$_2$)(PPh$_3$) at 70 °C afforded the desired fluorination product, L_1−F (Table 2, entries 1−2), albeit in low but encouraging 32% and 36% yields, respectively. Changing L_1−Cl for L_1−Br or L_1−I as starting substrate provided improved yields in shorter reaction times (Table 2, entries 10 and 19), although the background reaction (blank experiments, Table 2 entries 4, 9, 13, 18, 20) becomes more significant than when using L_1−Cl, which can be explained by the previously demonstrated Ag-mediated fluorination catalysis operating with the intermediacy of an aryl−Ag(III) species.[13] The permethylated

Table 2. Catalytic Fluorination Reactions with L_1–X and L_5–X in CD_3CN under N_2[a]

R = H; L_1-X　　　　　　　　R = H; L_1-F
R = Me; L_5-X　　　　　　　R = Me; L_5-F
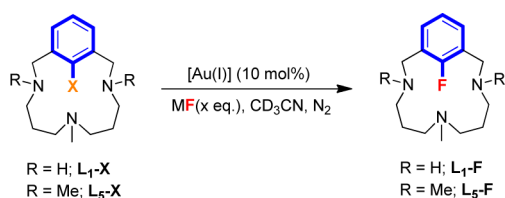
entry	L_n–X	MF (equiv)	Au(I) (10 mol %)	T (°C)	t (h)	yield L_n–F (%)[b]
1	L_1–Cl	AgF (2)	AuCl(PPh$_3$)	70	72	32[c]
2		AgF (2)	Au(NTf$_2$)PPh$_3$	70	72	36[c]
3		AgF (2)	[Au(NCMe)IPr]$^+$	70	24	64[d]
4		AgF (2)	-	70	72	6
5	L_5–Cl	KF (5)	[Au(NCMe)IPr]$^+$	70	72	14[e]
6		AgF (2)	AuCl(PPh$_3$)	70	72	51
7		AgF (2)	Au(NTf$_2$)PPh$_3$	70	72	50
8		AgF (2)	[Au(NCMe)IPr]$^+$	70	12	98
9		AgF (2)	-	70	72	4
10	L_1–Br	AgF (2)	AuCl(PPh$_3$)	40	48	49[f]
11		AgF (2)	Au(NTf$_2$)PPh$_3$	40	48	54[g]
12		AgF (2)	[Au(NCMe)IPr]$^+$	40	48	68[h]
13		AgF (2)	-	40	48	42
14	L_5–Br	KF (5)	[Au(NCMe)IPr]$^+$	70	48	23[e]
15		AgF (2)	AuCl(PPh$_3$)	40	48	100
16		AgF (2)	Au(NTf$_2$)PPh$_3$	40	48	100
17		AgF (2)	[Au(NCMe)IPr]$^+$	40	6	100
18		AgF (2)	-	40	48	100
19	L_1–I	AgF (2)	AuCl(PPh$_3$)	40	24	56[i]
20		AgF (2)	-	40	24	54

[a]Conditions: 15.3 μmol L_1–X or L_5–X, 10 mol % Au(I), MF, 0.5 mL CD_3CN, N_2. [b]Yields calculated using ^{1}H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. [c]6% of L_1–N-intra observed. [d]5% of L_1–N-intra observed. [e]0% yield when Au(I) source is absent. [f]7% of L_1–N-intra observed. [g]9% of L_1–N-intra observed. [h]8% of L_1–N-intra observed. [i]5% of L_1–N-intra observed.

macrocyclic substrates, L_5–X (X= Cl, Br), exhibited significantly enhanced fluorination yields when compared to their L_1–X analogues (Table 2, entries 5−9 and 14−18), which suggested that the strong basicity of the F$^-$ anion directly affected the secondary amines in the reactions using L_1–X. It is known that the secondary amines of the macrocyclic L_1–X ligand are relatively easily deprotonated upon formation of aryl−Cu(III) and aryl−Ag(III) species,[13,54] triggering the formation of side-products such as intramolecular C−N coupling products. The presence of L_1–N-intra compound[13,14,55] as a byproduct (Table 2) may suggest the formation of an organometallic Au−C$_{ayrl}$ bond (see Mechanistic Insight section for discussion). In the case of L_1–Cl and L_5–Cl, only residual fluorination is observed if Au(I) is excluded (Table 2, entries 4 and 9), thus demonstrating a distinctive genuine reactivity for Au catalysis compared to Ag-mediated transformations. Interestingly, 14% and 23% of L_5–F were obtained using KF as the fluoride source when fluorinating L_5–Cl and L_5–Br, respectively (Table 2, entries 5 and 14), suggesting that Au has a central role in this fluorination catalysis.

Au(I)-Catalyzed C−O Bond Forming Reactions Using Phenols with Model Macrocyclic Substrates. To the best of our knowledge, there are no reported examples of Au-catalyzed Ullmann-type coupling reactions, and therefore, to further expand the substrate scope and applicability of the

catalyst system, we decided to investigate the potential for C−O and C−S bond formation using a range of substituted phenols and thiophenol. We were pleased to observe that with the phenolic substrates it was possible to form the desired coupling products (Table 3, entries 2−8). We found it

**Table 3. Catalytic C−O Bond Forming Reactions with L_1–Br and L_5–Br in CD_3CN under N_2[a]**

L_1-Br　　　HXPh(R)　　　　　　　　L_1-XPh(R)
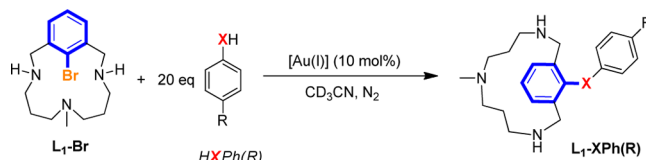
Entry	X	R	Au(I) (10 mol%)	Yield L_1-XPh(R) (%)[b] 25 °C	40°C	70 °C
1	O	H	AuCl(PPh$_3$)	-	-	34[c]
2		H	Au(NTf$_2$)PPh$_3$	-	51	75
3		Me	Au(NTf$_2$)PPh$_3$	-	41	71
4		OMe	Au(NTf$_2$)PPh$_3$	-	45[d]	89[e]
5		OMe	[Au(NCMe)IPr]$^+$	-	44[f]	87[g]
6		NO$_2$	Au(NTf$_2$)PPh$_3$	-	15	35
7		CF$_3$	Au(NTf$_2$)PPh$_3$	-	32	56
8		Cl	Au(NTf$_2$)PPh$_3$	29	52	79 (61)[h]
9		Cl	[Au(NCMe)IPr]$^+$	42	61	84 (83)[h]
10		Cl	-	<1	15	45
11	S	H	Au(NTf$_2$)PPh$_3$	-	0	0

[a]Conditions: 15.3 μmol L_1–Br or L_5–Br, 10 mol % Au(I), nucleophile, 0.5 mL CD_3CN, N_2, 24 h. [b]Yields calculated using ^{1}H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. [c]10% L_1–Cl observed in addition to C−O coupling product. [d]2% of L_1–H observed. [e]9% of L_1–H observed. [f]4% of L_1–H observed. [g]10% of L_1–H observed. [h]Yield after 8 h in parentheses.

necessary to use Au(NTf$_2$)PPh$_3$ as Au(I) source for this study, as during experiments using AuCl(PPh$_3$) we observed rapid formation of the Cl-exchanged product. The amount of L_1–Cl formed did not exceed 10% yield, confirming that the chloride source was the Au(I) salt, and thus strongly suggesting that C−Br bond activation mediated by Au had occurred (Table 3, entry 1, and Figure S17 in Supporting Information). On the other hand, it can be seen that variation of the electronic properties of the phenol has an important effect on the yield, with electron-donating substituents typically giving higher yields (e.g., *p*-methoxylphenol = 89%, Table 3, entry 4) compared with phenols with strongly electron-withdrawing groups (e.g., *p*-nitrophenol = 35%, Table 3, entry 6). Finally, we found that the nature of the Au(I) catalyst has a clear impact on the yields and temperatures where reactions can be conducted. When [Au(NCMe)IPr](SbF$_6$) was used as catalyst, coupling with *p*-chlorophenol could be achieved in moderate yields at room temperature, conditions where the background reaction is absent (Table 3, entries 9−10). When using thiophenol, we were unable to detect any C−S coupling product (Table 3, entry 11), probably due to the affinity of thiols to coordinate to Au(I), thus blocking the catalyst. It is also interesting to highlight the presence of a small amount of L_1–H byproduct in some of the C−O catalysis in Table 3, which again suggests the intermediacy of an Au−C$_{ayrl}$ bond.

Au(I)-Catalyzed Halide Exchange and C−O Bond Forming Reactions with Nonmacrocyclic Substrates. Following these successful studies, we attempted to transfer

Scheme 4. Screening of *ortho*-Chelating Groups (Yields for Blank Experiments without Au Catalyst in Parentheses) for (a) Bromide to Iodide Exchange (Yields Calculated by GC Analysis) and (b) C−O Coupling with Sodium *p*-Chlorophenolate (Yields Calculated by ¹H NMR)
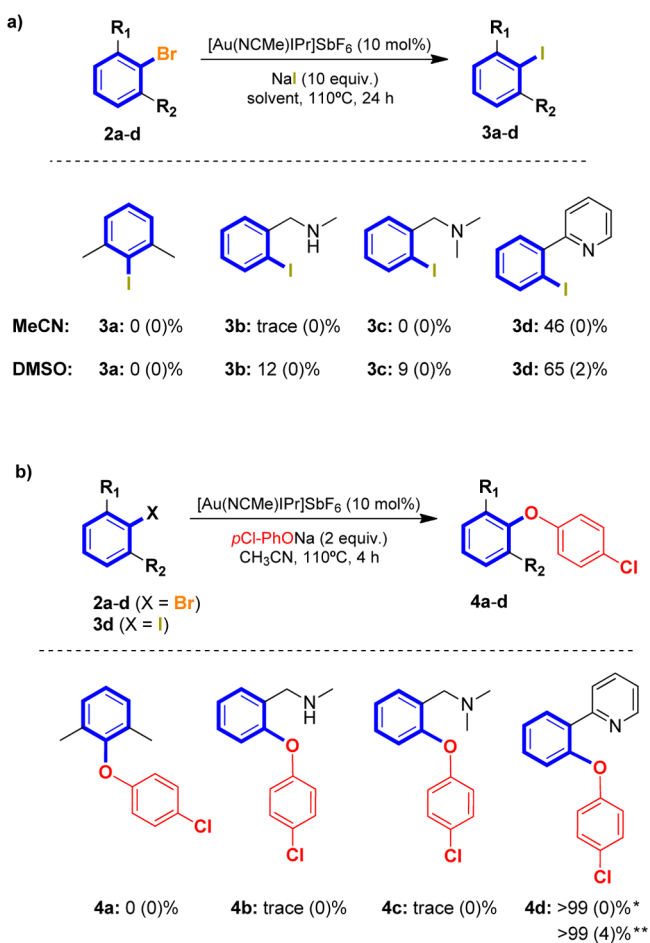
*X = Br, 65% yield after 24 h at 90 °C; **X = I, yield at 90 °C.

the reactivity from the aryl halide macrocyclic model substrates to other compounds in order to gain further insight into the mechanism and also demonstrate further reactivity (Scheme 4). Since the strongly coordinating ligands PPh$_3$ and IPr required to achieve the catalysis shown above are likely to remain coordinated to the Au center throughout the course of the reaction, we wondered if the macrocyclic triamine chain was necessary for the reaction to proceed. Therefore, we explored the representative catalytic performance of halide exchange and C−O coupling with three different aryl halide substrates containing a single chelation site (N atom) and one without (2a−d, Scheme 4). Among the different Au(I) sources used previously, the cationic [Au(NCMe)IPr]SbF$_6$ complex was selected for this study as it allowed vastly improved results. Attempts towards bromide to iodide exchange with 2-bromo-1,3-dimethylbenzene (3a) afforded no product, suggesting that Au is not catalyzing the halide exchange reactions through its Lewis acid character and that a chelating group is crucial for catalysis to occur. Subsequently, aliphatic amine chelating groups (both secondary and tertiary amines in analogy to the aryl halide macrocycles L$_1$−Br and L$_5$−Br, respectively) were introduced and again little or no halide exchange was observed when acetonitrile was employed as solvent (Scheme 4a, 3b and 3c).

Upon replacement of the aliphatic amine moieties with a pyridyl chelating group, we were pleased to observe 46% of the halide exchanged product (Scheme 4a, 3d). Importantly, 0% conversion was obtained in the absence of Au. The pyridyl chelating groups are significantly different in terms of their electronic properties to amine chelating groups. However, we propose that the higher activity observed with the pyridyl group is a consequence of the increased rigidity of the resulting chelate enabling the required disposition of the Au(I) reactive intermediate to activate the C-X bond of the substrate. These results demonstrate the importance of rigid chelation and highlight the beneficial nature of the rigid aryl halide macrocycle used in this study. Changing the solvent to DMSO provided increased yields of the halide exchanged products except in the case of the nonchelate containing substrate, 3a, (Scheme 4a), thus following a similar trend as in acetonitrile.

The C−O coupling reactions were also investigated with the nonmacrocyclic substrates and the same trend as for the halide exchange reaction was obtained. The more rigid 2-(2-bromophenyl)pyridine (2d) afford quantitative yields for the biaryl ether 4d, whereas minor or no conversion was achieved when using substrates 2a−c (Scheme 4b). It is worth noting that the reaction requires the presence of a base to achieve initial deprotonation of the phenol-derivative. Nevertheless, the use of the corresponding independently prepared sodium *p*-chlorophenolate proved more beneficial to the reaction outcome (Scheme 4b).

Thereafter, we explored the substrate scope to evaluate the potential of these transformations and to gain mechanistic insight. We expanded the scope of the nonmacrocyclic substrates, preparing 2da and 2db, which contain an electron-withdrawing group (*p*CF$_3$, 2da) or an electron-donating group (*p*OMe, 2db) in the *para*-position with respect to the bromine atom. Both substrates were tested in the Au(I)-catalyzed iodination of aryl bromides as well as the C−O bond formation to form the biaryl ether using *p*Cl-phenolate as nucleophile (Scheme 5a). The halide exchange reactions afforded similar yields of the iodinated product 3da and 3db under the same experimental conditions as when using 2d, and also excellent outcomes where found for the formation of the corresponding biaryl ether products 4da and 4db. Kinetic studies at the early stages of the C−O coupling reactions reveal higher yields for the *p*-trifluoromethyl substituted substrate (4da), although no unambiguous mechanistic information can be ascertained from the values obtained (Table 4). In addition, in order to explore the utility of this methodology towards the synthesis of other products, 2d was reacted with sodium methoxide as nucleophile, providing the aryl methyl ether 5d again in quantitative yields (Scheme 5b). These results suggest that other substrates, nucleophiles and reaction conditions might be found for a more general and applicable oxidant-free Au-catalyzed reaction that leads to the formation of new products of interest.

Mechanistic Insights. The results obtained permit some insights into the reaction mechanism although we have not been able to detect a putative aryl−Au(III) species analogous to the previously reported aryl−Cu(III) and aryl−Ag(III).[8,13,15] The difficulty in isolating this key intermediate is likely related to the challenge in avoiding Au(I) disproportionation when weak ligands are used to stabilize Au(I), i.e., AuCl(SMe$_2$) or bare AuI. The use of more stabilizing PPh$_3$ or IPr ligands enhance catalytic turnover but do not allow the detection of a putative square-planar aryl−Au(III), since PPh$_3$ or IPr ligands are likely not detached from Au(I) center during the catalytic cycle. The latter is in agreement with the fact that one chelating

Scheme 5. Substrate Scope of the Au(I)-Catalyzed C-Heteroatom Bond Forming Reactions (Conversions in Parentheses)
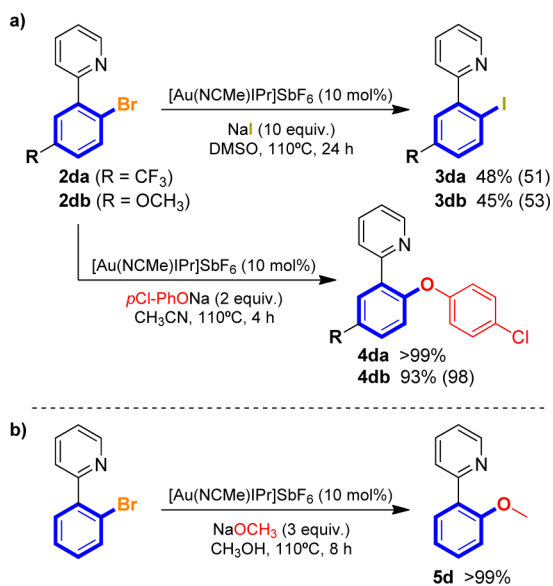

Table 4. Yields Obtained during the Initial Stages of the *p*Cl-Phenolate Coupling to 2d and Its *p*-Substituted Derivatives

|	yield (%)		
t (h)	R = H (**4d**)	R = CF$_3$ (**4da**)	R = OCH$_3$ (**4db**)
1	35	78	41
2	61	>99	73
4	>99	>99	93

group is sufficient to translate the catalytic performance from the macrocyclic substrate to the more simple substrates (Scheme 4). The coordination of the [Au(NCMe)IPr]SbF$_6$ to **L$_1$−Br** or **2d** can be observed experimentally by means of ^{1}H NMR and ESI-MS (see Supporting Information, Figures S28 and S29) However, a ^{1}H NMR monitoring experiment of the C−O coupling catalysis of *p*-chlorophenol and **2d** shows that under catalytic conditions, i.e., in the presence of excess of phenolate, [Au(OPh-*p*Cl)IPr] forms at room temperature as a catalytic intermediate (see Figures S29 and S32). The reaction only takes place upon heating, and once the catalysis has started, the bromide anion released from **2d** in the first catalytic cycle is immediately trapped by Au, forming [Au(Br)IPr] (see Figure S30). With the aim of evaluating if those species are indeed off-cycle intermediates of the reaction, independently prepared [Au(OPh-*p*Cl)IPr] and [Au(Br)IPr] were tested as catalysts in both the halide exchange and C−O bond forming reactions with the macrocyclic and nonmacrocyclic substrates, obtaining the same results as with [Au(NCMe)IPr]SbF$_6$ (see Table S3), which clearly supports their intermediacy in the reaction mechanism. ^{1}H NMR monitoring experiments do not prove that any of these Au species coordinate to the substrate, but the observation of reactivity in **2b−d** but not **2a** suggests that this is a requirement (see Figure S31). Indeed, under HRMS conditions, we can detect the in situ formation of [Au(**2d**)IPr]$^+$ by substitution of the coordinated phenolate or the bromide (Figures S33 and S34), thus providing experimental support to our proposal. Also, species [Au(**3d**)IPr]$^+$ and

[Au(**4d**)IPr]$^+$ are observed in the final crude reaction mixtures (Figures S10 and S30).

The possibility that Au(0) colloids could be the active species responsible for this chemistry was also considered. To assess whether the catalyst is homogeneous or heterogeneous, we ran reactions under identical conditions except for the presence of a large excess of mercury (ca. ~500 equiv with respect to Au catalyst, under heavy stirring), which acts as a poison towards nanoparticles.[56,57] A quenching of reactivity would strongly suggest colloidal catalysis. However, when performing halide exchange catalysis and C−O coupling using both the aryl−Br macrocyclic model substrate (**L$_1$−Br**) and the bromoaryl-pyridine (**2d**), we did not detect a significant decrease in activities (see Table S2). Somewhat lower yields (10−30% lower) were observed at expense of the formation of side-products, but the previously observed halide exchange reactions and C−O couplings remained as the main transformations occurring in the solution. Notably, ^{1}H NMR analysis of the reaction crude at the end the catalysis indicates that the entire catalyst remains in solution in the form of [Au(Br)IPr], since authentic samples of free IPr and IPr·HOTf do not match the observed NHC signals, whereas an authentic sample of [Au(Br)IPr] does (Figure S35).

At present we cannot fully discard any mechanism, but as mentioned a Au(I) π-interaction with the aromatic ring is unlikely because only substrates with chelating groups give positive results. In fact, HRMS monitoring shows that [Au(OPh-*p*Cl)IPr] remains unaltered for 24 h under the catalytic conditions used for the reaction of **2a** with *p*-chlorophenol, with no conversion (Figure S31). Bourissou and co-workers have previously demonstrated that an oxidative addition step is significantly enhanced if nonlinearity is forced upon Au(I).[58] Given that one chelating group in the substrate is necessary (see Scheme 4), we hypothesize that this coordination may help in distorting the linearity of the Au(I) resting state, and allows for the reaction to occur upon heating (in the examples described here temperatures of 110 °C need to be applied to overcome the energy barrier). The observation of **L$_1$−N-intra** and **L$_1$−H** in C−F and C−O coupling catalysis is reminiscent of Cu(I)/Cu(III) and Ag(I)/Ag(III) catalysis when using the macrocyclic model substrates, also pointing towards the existence of a Au(I)/Au(III) catalytic cycle.

We also embarked on a DFT study to gain insight into the mechanism, and specifically we focused on the coupling of *p*Cl-PhO$^-$ with **3d** as the model reaction, using [Au(NCMe)IPr]$^+$ as the catalyst (see Supporting Information for computational details). First, we calculated the thermodynamic values of the replacement of a acetonitrile molecule in [Au(NCMe)IPr]$^+$ by the *p*Cl-PhO$^-$ group to form [Au(OPh-*p*Cl)Pr], finding that this is clearly an exergonic process (ΔG = −11.4 kcal·mol^{-1}). The free energy balances for the exchange of the coordinated *p*Cl-PhO$^-$ (ΔG = 2.5 kcal·mol^{-1}) or iodide (ΔG = −1.4 kcal·mol^{-1}) by **3d** allow the formation of [Au(**3d**)IPr]$^+$, and suggest that the generation of the analogous [Au(**2d**)IPr]$^+$ may be feasible under reaction conditions, thus in agreement with the HRMS experiments. Moreover, a complete reaction pathway for the C-halogen functionalization has been successfully computed at M06L level (Scheme 6), showing a transition state for the oxidative addition step (TSox) at 30.6 kcal/mol, and a TSred for the reductive elimination at 31.3 kcal/mol. Given the fact that reactions are conducted above 90 °C, these barriers are below the kinetic limit, thus in agreement with the experiments performed and the rather slow reactions. DFT calculations indicate that the reductive elimination step is rate limiting;

Scheme 6. DFT Reaction Profile for the Oxidative Addition/Reductive Elimination Steps of [Au(OPh-pCl)] over 3d Substrate[a]
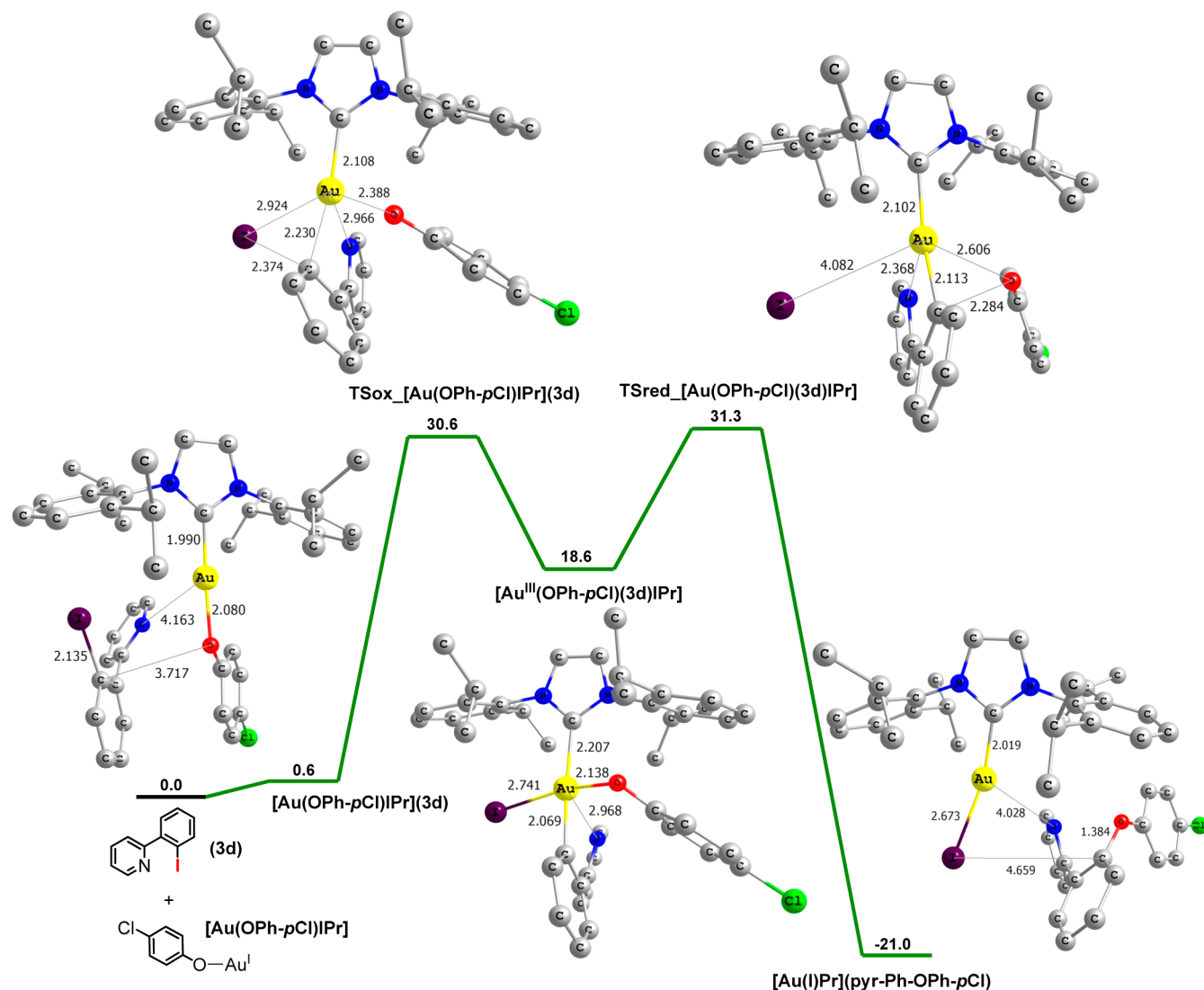
[a]Relative Gibbs energy values in acetonitrile solution are given in kcal·mol⁻¹ and selected bond distances in Å (H atoms are omitted for clarity).

however, the fact that both TS are very close in energy suggests that subtle changes may favor switching to a rate limiting oxidative addition. The energetic similarity between both TS could justify the somewhat ambiguous trend among the electronically different *p*-substituted 2-(2-bromophenyl)pyridine substrates (Table 4). We have also determined the oxidative addition/reductive elimination Gibbs energy profile for another Au(I) isomer where the gold cation is coordinated to **3d** instead of *p*Cl-PhO⁻. However, the optimized oxidative addition TS (see Figure S37) is about 7 kcal/mol higher in energy than TSox and TSred described in Scheme 6.

Nucleophilic aromatic substitution was also explored computationally, where the cationic Au(I) would act as a Lewis acid to increase the reactivity of the aryl–I moiety. Remarkably, all the TS searches for the direct attack of the phenolate to **3d** actually converged to TSox (Scheme 6), thus driving the reaction through a Au(III) species and rendering the possibility of a direct nucleophilic attack on the aryl-carbon of **3d** unlikely.

This alternative mechanism was also studied experimentally. Having in hand the isolated methoxide insertion product **5d**, we studied the cationic Au(I)-mediated displacement of the

methoxy group in the presence of sodium *p*Cl-phenolate as nucleophile under the same reactions conditions described for **2d**. After sufficient time to allow any reaction to proceed, we quantitatively recovered the starting material. This is in contrast to a related nucleophilic aromatic substitution reported by Meyers and co-workers in the late 1970s describing a nucleophilic displacement of the *o*-methoxy group in comparable substrates to **2d** by organolithium and Grignard reagents. This suggests that our reported reaction indeed proceeds through a mechanism different to a Au-assisted nucleophilic aromatic substitution.[59]

A preliminary proposal for the Au(I) catalyzed C−O cross coupling based on the experimental and DFT study findings provided above is depicted in Scheme 7, involving the formation of the C−O product **4d** via the intermediacy of [Au(OPh-*p*Cl)IPr] and [Au(Br)IPr] resting state forms of the catalyst.

■ **CONCLUDING REMARKS**

In summary, to the best of our knowledge, we have described the first examples of oxidant-free Au(I)-catalyzed halide exchange and C−O cross coupling reactions. We have shown that a rigid

Scheme 7. Proposed Mechanism of [Au(NCMe)IPr]⁺ Catalyzed C−O Coupling Reaction with 2d and *p*-Chlorophenol
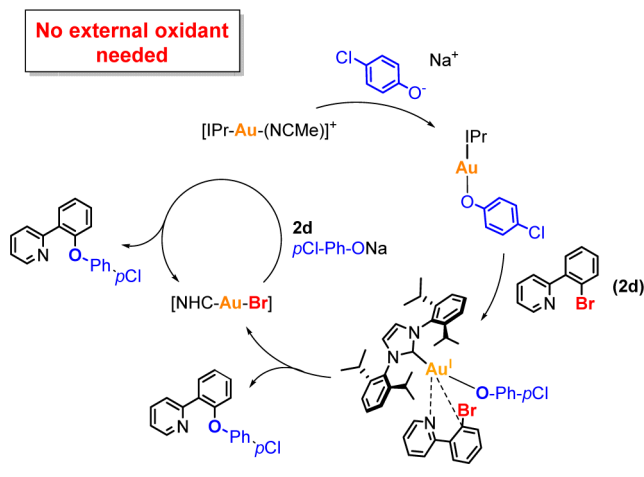
chelating group is highly beneficial for the catalysis, either using a triazamacrocyclic substrate (**L₁−X** or **L₅−X**) or 2-(2-bromophenyl)pyridine (**2d**). It has been shown that there are intrinsic differences compared to Cu and Ag analogous systems. Indeed, Au(I)-catalyzed fluorination reactions were possible for aryl chloride substrates, whereas Ag is inactive.[13] The mechanistic insight provided suggests catalysis involving two different resting states for the C−O coupling catalysis, both of which we have observed in situ under catalytic conditions. The halide exchange reactions are thought to proceed through a similar pathway, as the active catalysts should be formed in situ upon addition of excess of the halide. However, further investigations are needed to clarify the exact mechanism. This report is a proof of concept of the viability of oxidant-free Au(I)-catalyzed cross-coupling reactions and is envisioned to open new opportunities in Au catalysis.

ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08756.

> Chemical compound full characterization; HRMS and NMR monitoring experiments of the catalytic reactions; complete description of computational details; XYZ coordinates for all DFT calculated molecules (PDF)

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Notes
The authors declare no competing financial interest.

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