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SERRA, Jordi, WHITEOAK, Christopher, ACUÑA-PARÉS, Ferran, FONT, Marc, LUIS, Josep M., LLORET-FILLOL, Julio and RIBAS, Xavi (2015). Oxidant-Free Au(I)-Catalyzed Halide Exchange and Csp2–O Bond Forming Reactions. Journal of the American Chemical Society, 137 (41), 13389-13397.

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# Oxidant-Free Au(I)-Catalyzed Halide Exchange and $Csp^2$-O Bond Forming Reactions

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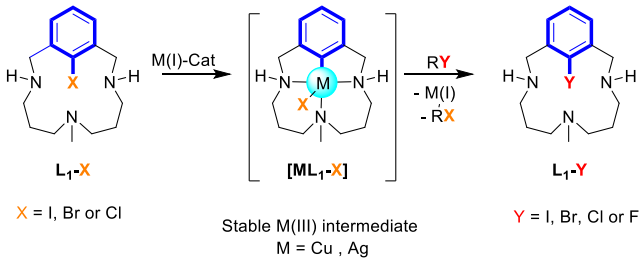
**ABSTRACT:** Au has been demonstrated to mediate a number of organic transformations through the utilization of its π Lewis acid character, Au(I)/Au(III) redox properties or a combination of both. As a result of the high oxidation potential of the Au(I)/Au(III) couple, redox catalysis involving Au typically 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] Amongst 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.[3-8,9-12] 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 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]




**Scheme 1**. Previously reported M(I) (M = Cu or Ag) catalyzed halide exchange reactions in model aryl halide macrocyclic substrates.

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 after 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 catalytic fashion.[37,38,39,40] 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

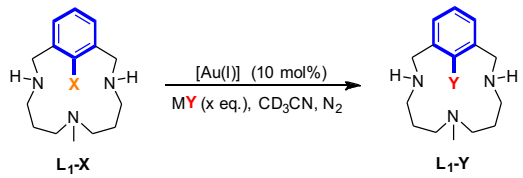
differences of Au reactivity compared to the previously reported two-electron redox catalysis with Ag and Cu.[8, 13, 15]

## 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 one equivalent of a Au(I) source, [AuCl(SMe$_2$)], to a $CD_3CN$ solution of **L$_1$-Br** (1 equiv) in, whereby 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 as with 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(PPh$_3$)]. Initially we focused on **L$_1$-I** in the presence of a catalytic amount of [AuCl(PPh$_3$)] (10 mol%) and 2 equivalents of tetrabutylammonium chloride (*n*Bu$_4$N-Cl) in $CD_3CN$ and we were pleased to observe clean and quantitative conversion to the halide exchanged product, **L$_1$-Cl** in 48 hours 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 **L$_1$-I** to **L$_1$-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, **L$_1$-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 and 16). As can be seen in a $^1$H NMR monitoring experiment (Scheme 2), the reactions proceeded cleanly and showed no presence of intermediates during the catalytic transformation of **L$_1$-Br** to **L$_1$-I**. Halide exchange reactions starting from **L$_1$-Cl** (Table 1, entries 17 and 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 $CD_3CN$ 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 towards aryl bromide or aryl iodide when using soluble *n*Bu$_4$NBr or *n*Bu$_4$NI, respectively.

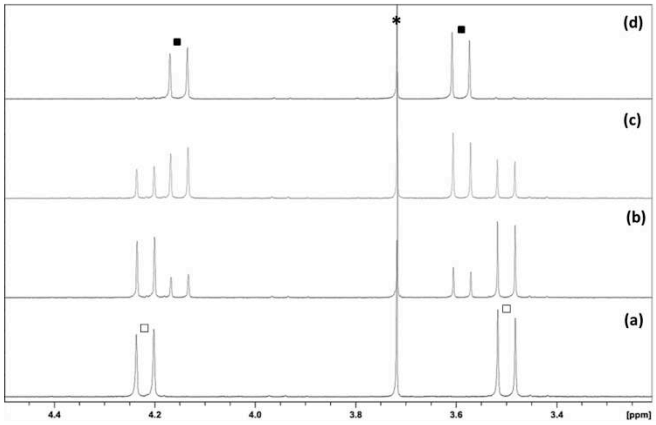
**Table 1.** Catalytic halide exchange reactions with **L$_1$-X** in $CD_3CN$ under $N_2$.[a]




| Entry | **L$_1$-X** | MY (eq.) | Au(I) (10 mol%) | T (°C) | t (h) | Yield **L$_1$-Y** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **L$_1$-I** | Bu$_4$N-Cl (2) | AuCl(PPh$_3$) | 40 | 48 | >99 |
| 2 | | | Au(NTf$_2$)PPh$_3$ | 40 | 48 | 97 |
| 3 | | | [Au(NCMe)IPr]$^+$ | 40 | 6 | >99[c] |
| 4 | | | - | 40 | 48 | 2 |
| 5 | | NaBr (10) | AuCl(PPh$_3$) | 40 | 48 | 5 (94)[d] |
| 6 | | | Au(NTf$_2$)PPh$_3$ | 40 | 48 | 9 (96)[d] |
| 7 | | | [Au(NCMe)IPr]$^+$ | 40 | 30 | 15 (97)[d] |
| 8 | | | - | 40 | 48 | 0 (36)[d] |
| 9 | **L$_1$-Br** | Bu$_4$N-Cl (2) | AuCl(PPh$_3$) | 40 | 60 | 98 |
| 10 | | | Au(NTf$_2$)PPh$_3$ | 40 | 60 | 99 |
| 11 | | | [Au(NCMe)IPr]$^+$ | 40 | 12 | 99 |
| 12 | | | - | 40 | 60 | trace |
| 13 | | NaI (10) | AuCl(PPh$_3$) | 70 | 18 | 95 |
| 14 | | | Au(NTf$_2$)PPh$_3$ | 70 | 8 | 92 |
| 15 | | | [Au(NCMe)IPr]$^+$ | 70 | 4 | 94 |
| 16 | | | - | 70 | 18 | 23 |
| 17 | **L$_1$-Cl** | NaBr (10) | AuCl(PPh$_3$) | 70 | 72 | 30 (56)[e] |
| 18 | | | Au(NTf$_2$)PPh$_3$ | 70 | 72 | 34 |
| 19 | | | [Au(NCMe)IPr]$^+$ | 70 | 72 | 46 (59)[e] |
| 20 | | | - | 70 | 72 | trace |
| 21 | | NaI (10) | AuCl(PPh$_3$) | 70 | 100 | 42 (64)[f] |
| 22 | | | Au(NTf$_2$)PPh$_3$ | 70 | 100 | 48 |
| 23 | | | [Au(NCMe)IPr]$^+$ | 70 | 48 | 67 |
| 24 | | | - | 70 | 100 | 16 |

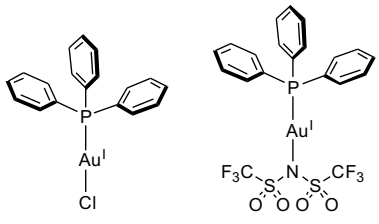
[a]Conditions: 15.3 µmol **L$_1$-X**, 10 mol% Au(I), MY, 0.5 mL $CD_3CN$, $N_2$; see Au(I) catalyst structures in Scheme 2. [b]Yields calculated using $^1$H NMR spectra, with 1,3,5-trimethoxybenzene as internal standard. [c] Quantitative yield after 30 h using 5 mol% of Au(I) cat. [d] In parenthesis, experiments at 70 °C. [e] In parenthesis, LiBr (10 eq.) as bromide source. [f] In parenthesis, yield after 350 h.

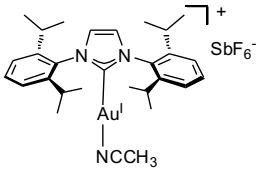
In general, although the halide exchange reactions catalyzed by [AuCl(PPh$_3$)] were effective, in some cases they struggled to reach completion after extended periods of time (days). To tackle the poor reactivity of AuCl(PPh$_3$), we hypothesized that the availability of the coordination site on the 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 non-coordinating 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(MeCN)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 ºC.




**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 $CD_3CN$: (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).

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-, 51-52] This type of ligand has been reported to stabilize cationic Au(I) much more efficiently than $PPh_3$, whilst maintaining its catalytic properties. Hence, we prepared [Au(NCMe)IPr]$SbF_6$ (IPr = 1,3-*bis*(diisopropylphenyl)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.

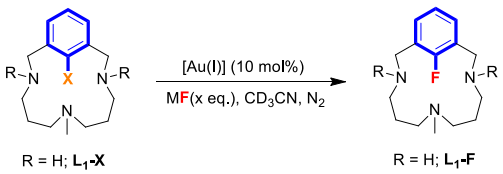



**Scheme 3**. Au(I) catalysts used in this work.

**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 $Bu_4NF$ as fluoride source, but we found it to be completely inefficient. In contrast, addition of two equivalents 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 70ºC 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 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 by-product (Table 2) may suggest the formation of an organometallic Au-C 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.

**Table 2**. Catalytic fluorination reactions with **$L_1$-X** and **$L_5$-X** in $CD_3CN$ under $N_2$.[a]



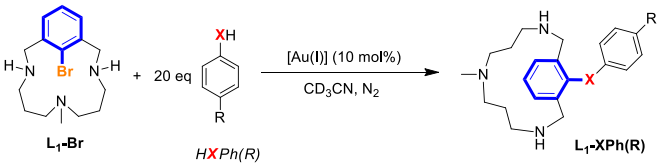

| Entry | **$L_n$-X** | MF (eq.) | Au(I) (10 mol%) | T (°C) | t (h) | Yield **$L_n$-F** (%)[b] |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| 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 $^1H$ 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.

**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). It was found to be 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 (eg. *p*-methoxylphenol = 89%, Table 3, entry 4) compared with phenols with strongly electron-withdrawing groups (eg. *p*-nitrophenol = 35%, Table 3, entry 6). Finally, we found that the nature of the Au(I) catalyst has a clear impact in the yields and temperature where reactions can be conducted. When $[Au(NCMe)IPr](SbF_6)$ was used as catalyst, coupling with *p*-chlorophenol can 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 aryl-Au bond.

**Table 3**. Catalytic fluorination reactions with **$L_1$-Br** and **$L_5$-Br** in $CD_3CN$ under $N_2$.[a]

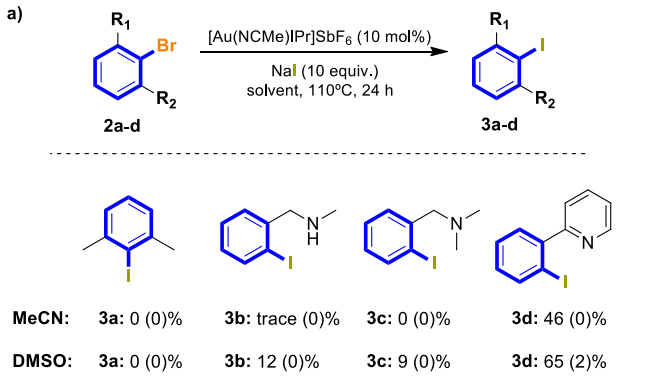


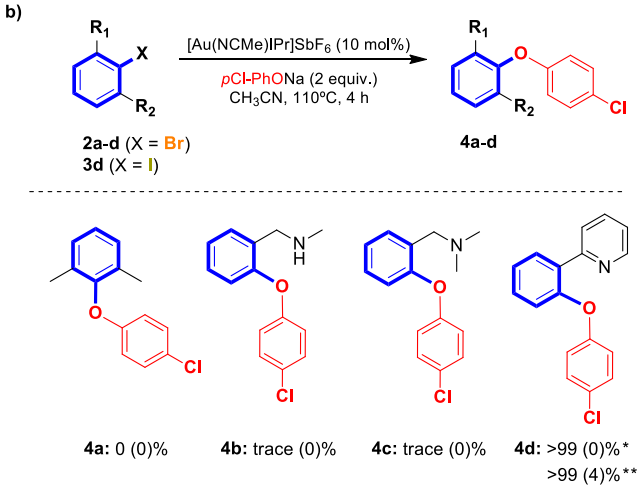

| Entry | X | R | Au(I) (10 mol%) | Yield **$L_1$-XPh(R)** (%)[b] | | |
|---|---|---|---|---|---|---|
| | | | | 25 ºC | 40ºC | 70 ºC |
| 1 | **O** | H | $AuCl(PPh_3)$ | - | - | 34[c] |
| 2 | | H | $Au(NTf_2)PPh_3$ | - | 51 | 75 |
| 3 | | Me | $Au(NTf_2)PPh_3$ | - | 41 | 71 |
| 4 | | OMe | $Au(NTf_2)PPh_3$ | - | 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 $CD_3CN$, $N_2$, 24h. [b]Yields calculated using $^1H$ 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 parenthesis.

**Au(I)-catalyzed Halide exchange and C-O bond forming reactions with non-macrocyclic substrates**. Following these successful studies we attempted to transfer 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 4, **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 4, **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 acti-

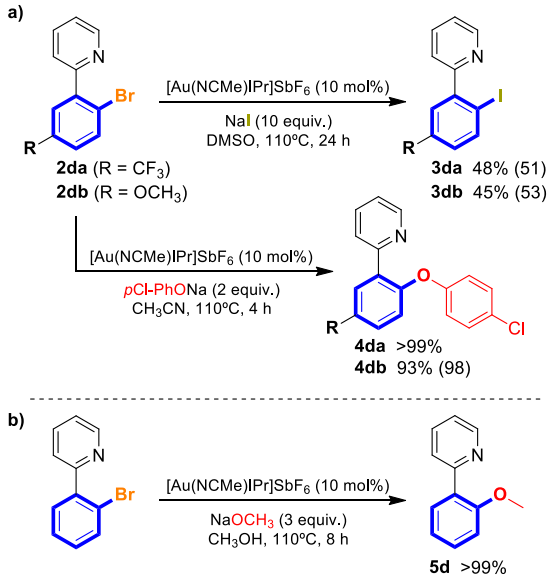
vate the C-X bond of the substrate. These results demonstrate the importance of rigid chelation and highlight the beneficial nature of the rigid aryl halide macrocycle used in this study. Changing the solvent to DMSO provided increased yields of the halide exchanged products except in the case of the non-chelate containing substrate, **3a**, (Scheme 4a), thus following a similar trend as in acetonitrile.




**Scheme 4.** Screening of *ortho*-chelating groups (yields for blank experiments without Au catalyst in parenthesis) for (a) bromide to iodide exchange (yields calculated by GC analysis) and (b) C-O coupling with sodium *p*-chlorophenolate (yields calculated by $^1$H-NMR).*X = Br, 65% yield after 24h at 90ºC; **X = I, yield at 90ºC.

The C-O coupling reactions were also investigated with the non-macrocyclic 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).




**Scheme 5.** Substrate scope of the Au(I)-catalyzed C-Heteroatom bond forming reactions (conversions in parenthesis).

**Table 4**. % yields obtained during the initial stages of the *p*Cl-phenolate coupling to **2d** and its *p*-substituted derivatives.

| t (h) | Yield (%) | | |
|---|---|---|---|
| | **R = H (4d)** | **R = $CF_3$ (4da)** | **R = $OCH_3$ (4db)** |
| 1 | 35 | 78 | 41 |
| 2 | 61 | >99 | 73 |
| 4 | >99 | >99 | 93 |

Thereafter we explored the substrate scope to evaluate the potential of these transformations and to gain mechanistic insight. We expanded the scope of the non-macrocyclic 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 unambigous 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.

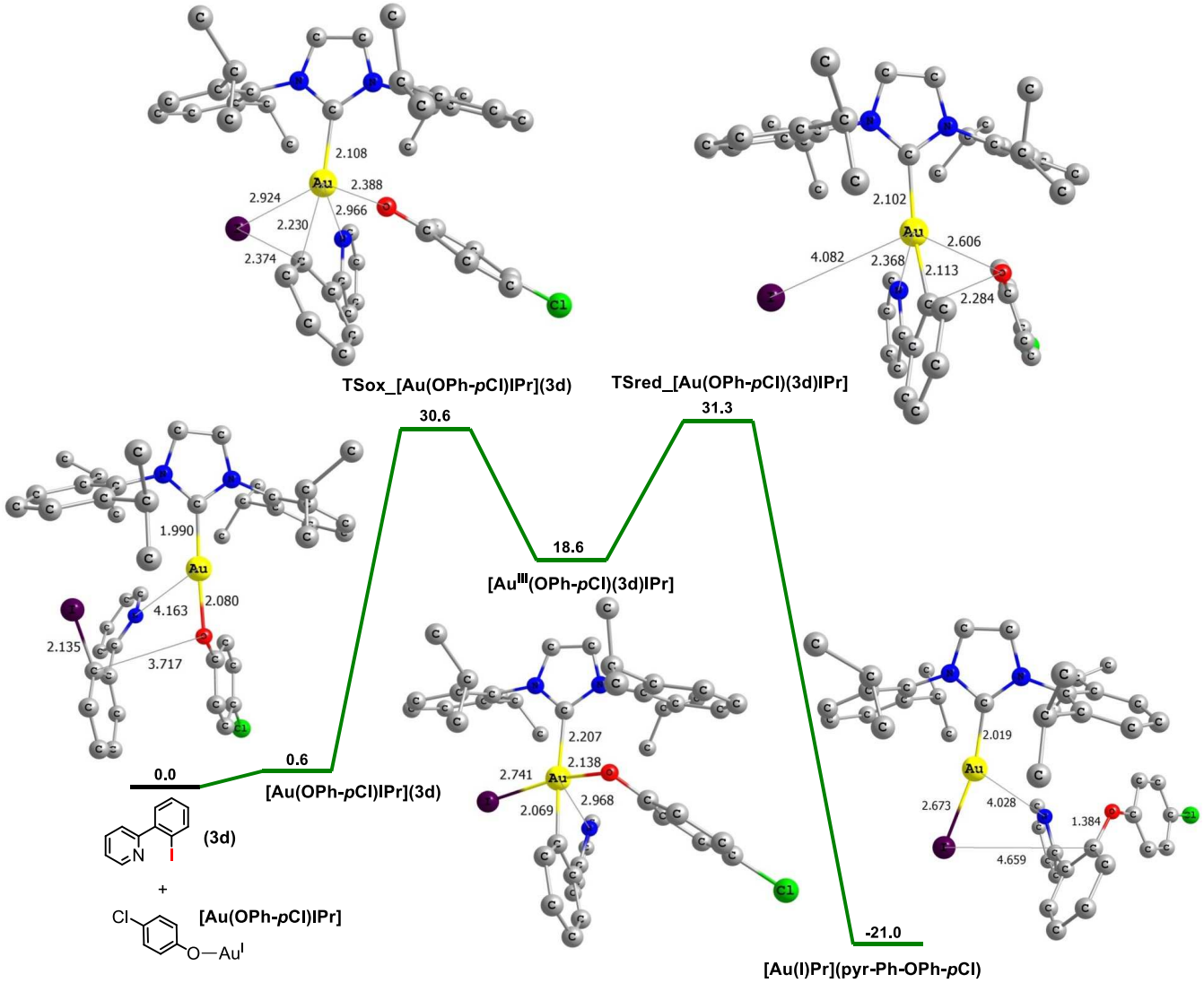
**Mechanistic insights.** The results obtained permit some insights into the reaction mechanism although we have not been able to detect a putative aryl-Au(III) species analogous to the previously reported aryl-Cu(III) and aryl-Ag(III).[8, 13, 15] The difficulty in isolating this key intermediate is 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 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 Figure 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-pCl)IPr] and [Au(Br)IPr] were tested as catalysts in both the halide exchange and C-O bond forming reactions with the macrocyclic and non-macrocyclic 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 $[Au(\mathbf{2d})IPr]^+$ by substitution of the coordinated phenolate or the bromide (Figures S33-S34), thus providing experimental support to our proposal. Also, species $[Au(\mathbf{3d})IPr]^+$ and $[Au(\mathbf{4d})IPr]^+$ 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. In order 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 eq 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 macrocylic 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 non-linearity 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 110ºC 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 of all, 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 ($\Delta G$ = -11.4 kcal·mol$^{-1}$). The free energy balances for the exchange of the coordinated *p*Cl-$PhO^-$ ($\Delta G$ = 2.5 kcal·mol$^{-1}$) or iodide ($\Delta G$ = -1.4 kcal·mol$^{-1}$) by **3d** allows the formation of $[Au(\mathbf{3d})IPr]^+$, and suggests that the generation of the analogous $[Au(\mathbf{2d})IPr]^+$ 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 90ºC, 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, 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.

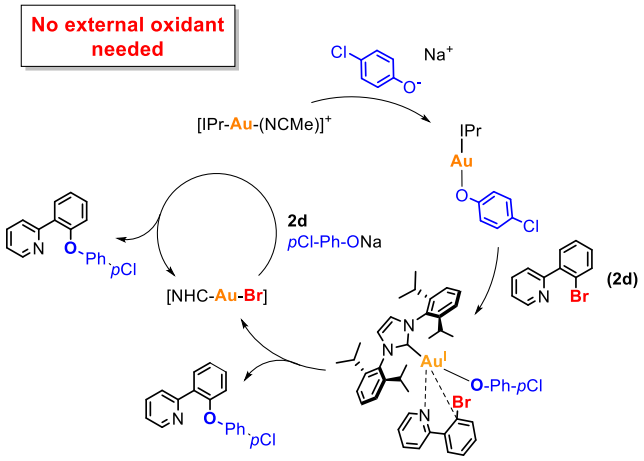



**Scheme 6.** DFT reaction profile for the oxidative addition / reductive elimination steps of [Au(OPh-*p*Cl)] over **3d** substrate. Relative Gibbs energy values in acetonitrile solution are given in kcal·mol$^{-1}$ and selected bond distances in Å (H atoms are omitted for clarity).

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 1970's 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.




**Scheme 7**. Proposed mechanism of $[Au(NCMe)IPr]^+$ catalyzed C-O coupling reaction with **2d** and *p*-chlorophenol.

**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 chelating group is highly beneficial for the catalysis, either using a triazamacrocyclic substrate (**$L_1$-X or $L_5$-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.

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

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## ACKNOWLEDGMENT

This work was supported by grants from the European Research Council (Starting Grant Project ERC-2011-StG-277801), the Spanish MINECO (CTQ2013-43012-P, Consolider-Ingenio CSD2010-00065, INNPLANTA project INP-2011-0059-PCT-420000-ACT1) and the Catalan DIUE of the Generalitat de Catalunya (2009SGR637). F. A.-P. thanks Universitat de Girona for a predoctoral grant. M.F and J.L.-F. thank a PhD grant and a RyC contract from Spanish MINECO, respectively. X.R. also thanks ICREA-Acadèmia award. J.S. thanks UdG for a PhD grant. J. S. also wants to thank his father for everything he has done.

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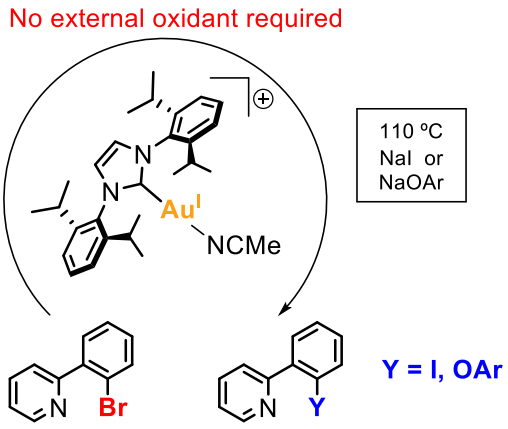


Here we report the development towards the first examples of oxidant-free Au(I)-catalyzed halide exchange and C-O bond-forming reactions. These reactions are only operative for substrates bearing an *ortho*-chelating group with enhanced rigidity, and using strong binding ligands (IPr, $PPh_3$) for the Au(I) catalysts. Mechanistic data points towards an organometallic pathway and experimental evidence regarding the coordination of the $[Au(IPr)]^+$ catalyst to the substrate is provided.