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Au(I)/Au(III)-Catalyzed C–N Coupling

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Abstract: Cycling between Au(I) and Au(III) is challenging so that gold-catalyzed cross-couplings are rare. The (MeDalphos)AuCl complex, which we showed prone to undergo oxidative addition, is reported here to efficiently catalyze the C–N coupling of aryl iodides and amines. The transformation does not require external oxidant nor directing group. It is robust and works with a wide scope of aryl iodides and N-nucleophiles under mild conditions. Mechanistic studies, including the NMR and MS characterization of a key aryl amido Au(III) complex, strongly support a 2e redox cycle in which oxidative addition precedes transmetalation and reductive elimination is the rate-determining step.

Gold(III) chemistry has grown spectacularly during the last decade,¹ but applications in catalysis are still rare, mainly due to the difficulty to access the +III oxidation state. Nevertheless, some C–C and C–X (X = N, O...) cross-coupling reactions proceeding *via* Au(I)/Au(III) catalytic cycles have been reported recently, in particular arylation reactions.^{2,3} Most of these transformations make use of a strong external oxidant or a diazonium salt as electrophile, which limits the scope of compatible coupling partners and functional groups.⁴ Our group is exploring a complementary strategy based on “ancillary” ligands that emulate otherwise disfavoured reactivity at gold, such as oxidative addition.^{5,6} In this respect, the (P,N) ligand MeDalphos [Ad₂P(*o*-C₆H₄)NMe₂] was recently shown to readily promote oxidative addition of aryl iodides to gold and to enable catalytic C–C cross-coupling reactions under mild conditions without the need for an external oxidant.^{7,8} The (MeDalphos)AuCl complex was later reported by Spokoyny and coworkers to be very efficient for the stoichiometric arylation (C–S coupling) of unprotected peptides and proteins, as well as for the construction of hybrid nanoclusters.⁹

C–N cross-coupling is undoubtedly the most straightforward and general route to prepare aryl-amines. Palladium (Buchwald-Hartwig amination)¹⁰ and copper (Ullmann and Chan-Lam couplings)¹¹ occupy forefront positions in transition metal-catalyzed C–N cross-coupling. Gold-catalyzed methodologies are very interesting to develop as the specific properties of gold may enable to achieve transformations which are challenging or limited in scope with the other transition metals, but gold has been very rarely reported to promote C–N bond formation and C–N reductive elimination from Au(III) complexes actually remains very scarce.

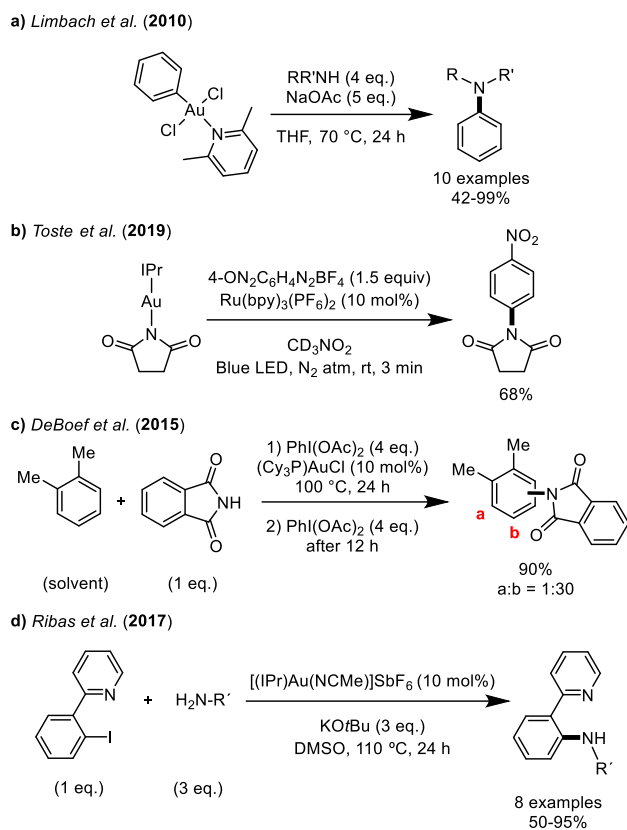
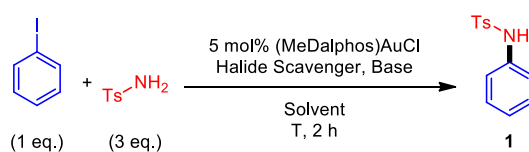


Figure 1. Stoichiometric and catalytic C–N coupling reactions mediated by gold complexes.

As summarized in Figure 1, a few arylation reactions of *N*-nucleophiles mediated by gold(III) have been reported over the last decade.^{12–16} Limbach and coworkers provided in 2010 the first examples of stoichiometric C–N reductive elimination of aryl gold(III) complexes by reacting well-defined 2,6-lutidine aryl gold(III) complexes with *N*-nucleophiles (Figure 1a).¹² Very recently, Toste *et al* described C–N coupling between an aryldiazonium salt and succinimide mediated by gold under photoredox conditions and detailed mechanistic studies were performed (Figure 1b).¹³ To the best of our knowledge, gold-catalyzed C–N couplings have only been reported twice so far. Direct and regioselective arylation of phtalimide (oxidative C–N coupling with arenes) has been achieved in 2015 by DeBoef and coworkers using phosphine gold(I) complexes and PhI(OAc)₂ as external oxidant.¹⁴ More recently, in 2017, Ribas *et al.* described the first oxidant-free Au-catalyzed C–N coupling involving aryl iodides (Figure 1d).¹⁵ Despite these significant advances, the reaction conditions (temperature $\geq 100^\circ\text{C}$, catalytic loading = 10 mol%) and the requirement of an external oxidant or a preinstalled directing group limit the scope and practical interest of the transformation.

With the aim to advance further this chemistry, we have investigated the possibility to catalyze C–N coupling with the (MeDalphos)AuCl complex, taking advantage of the faculty of this gold(I) complex to readily activate aryl iodides. Our results are reported hereafter. The scope and mechanism of the transformation are discussed.¹⁷

To start with, the coupling of *p*-toluenesulfonamide and iodobenzene was used as benchmark reaction. The influence of different reaction parameters (ratio of the coupling partners, T, halide scavenger, base, solvent) was studied (Table 1).¹⁹ The coupling product **1** was obtained in 99% yield using the conditions as given in entry 1. All other conditions resulted in lower yields, such as the use of K₃PO₄ or NaOAc^F as base, or other halide scavengers such as AgSbF₆ or AgBF₄ (entries 2–5). The highest yield was obtained using *o*-DCB/MeOH 50:1 as solvent (entries 6 and 7). Increasing further the temperature was not beneficial (entry 8).

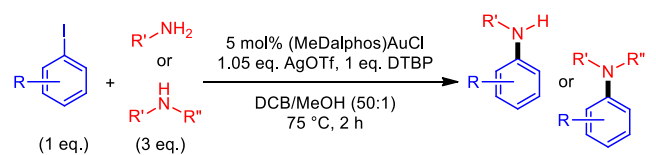


Entry	T	Halide Scavenger	Base	Solvent ^a	Yield
1	75 °C	AgOTf	DTBP	DCB/MeOH	99%
2	75 °C	AgOTf	K ₃ PO ₄	DCB/MeOH	58%

3	75 °C	AgOTf	NaOAc ^f	DCB/MeOH	10%
4	75 °C	AgSbF ₆	DTBP	DCB/MeOH	72%
5	75 °C	AgBF ₄	DTBP	DCB/MeOH	77%
6	75 °C	AgOTf	DTBP	DCB	86%
7	75 °C	AgOTf	DTBP	DMF/MeOH	92%
8	100 °C	AgOTf	DTBP	DCB/MeOH	80%

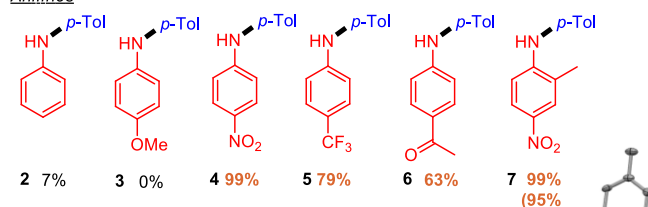
Table 1. Optimization. Yields determined using GC-MS with *n*-dodecane as internal standard, DTBP = 2,6-di-*tert*-butylpyridine. ^aSolvent/MeOH = 50/1.

With optimized conditions in hands, the coupling of 4-iodotoluene with different *N*-nucleophiles was investigated (Figure 2a), starting with anilines. Aniline itself gave a very low yield (7%) and no coupling was observed with *p*-anisidine. Gratifyingly, anilines bearing electron-withdrawing substituents in the *para* position (NO₂, CF₃ or COMe) gave the corresponding C–N coupling products **4–6** in good to excellent yields.¹⁸ The *ortho*-substituted 2-methyl-4-nitroaniline also reacted smoothly and cleanly to afford **7**. Note that the anilines react selectively at the nitrogen atom (no trace of C-arylated products were detected), whereas indole was found to exclusively undergo C3-arylation under similar conditions.⁸

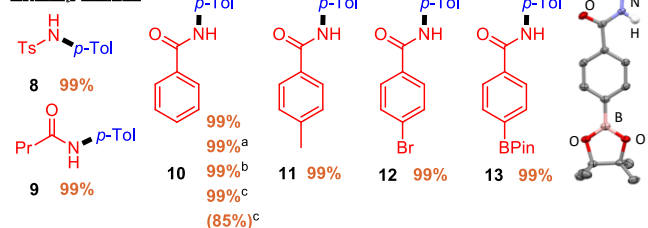


a) Scope of amines

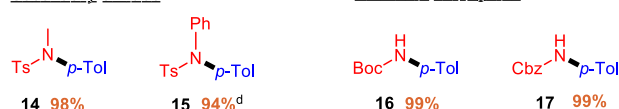
Anilines



Primary Amides



Secondary amides



Ammonia surrogates

b) Scope of aryl iodides

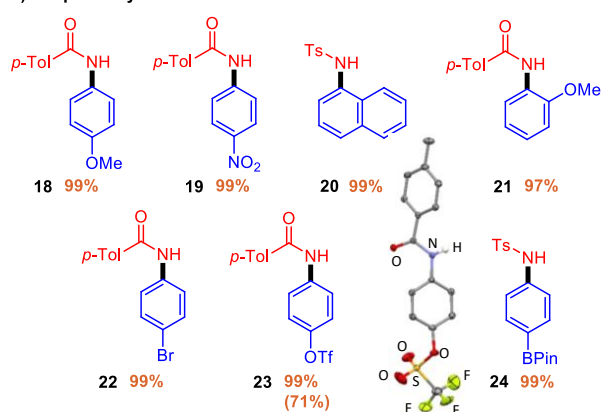


Figure 2. a) Scope of amines. Cross-coupling of *p*-iodotoluene and *N*-nucleophiles catalyzed by (MeDalphos)AuCl at 0.2 M of aryl iodide. ^aBenzamide (1 eq.), 2 mol% (MeDalphos)AuCl, 4 h, 0.6 M. ^bAll reagents weighted in air. ^cBenzamide (2 mmol, 1 eq.), 1 mol% (MeDalphos)AuCl, overnight, 0.6 M. ^d16 h. **b) Scope of aryl**

iodides. Cross-coupling of aryl iodides and *p*-toluenesulfonamide or *p*-toluamide catalyzed by (MeDalphos)AuCl at 0.1 M of aryl iodide. Yields determined using ¹H NMR with *n*-dodecane as internal standard. Isolated yields in parentheses.

Besides *p*-toluenesulfonamide, the reaction works very well with aliphatic and aromatic amides as shown by the quantitative formation of products **9-13**. Importantly, the presence of functional groups is compatible with the gold-catalyzed arylation, as shown by the high-yield preparation of Br- and Bpin-substituted *N*-aryl amides **12** and **13**. The structure of **13** was unambiguously confirmed by X-ray diffraction analysis.¹⁹ Selective activation of aryl iodides in the presence of Ar–Br and Ar–BPin bonds is particularly noteworthy as it raises selectivity issues with Pd catalysts.

In all cases, the C–N coupling of the primary aromatic amines and amides is highly selective in monoarylation and diarylation products were not detected. Nevertheless, the gold catalyst also promotes the arylation of secondary amides as exemplified by the formation of **14-15**. The synthesis of **15** is particularly noteworthy. Starting from *p*-toluenesulfonamide, compound **1** can be obtained by C–N coupling with iodobenzene and further arylated with 4-iodotoluene using extended reaction times. Thereby, it is possible to sequentially introduce two different aryl groups at nitrogen.

The preparation of primary anilines in protected forms is also possible and straightforward using *tert*-butyl carbamate (Boc) and benzyl carbamate (Cbz) as ammonia surrogates. The corresponding products **16** and **17** were readily obtained in quantitative yields.

The robustness and scalability of the gold-catalyzed reaction was assessed using 4-iodotoluene and benzamide as substrates. The corresponding product **10** was also obtained in excellent yield in air and with technical grade solvents, showing that no stringent precautions are needed. Very good results were obtained at larger scale. Starting from 2 mmol of substrates with only 1 eq. of benzamide and 1 mol% of (MeDalphos)AuCl, the arylated product **10** was obtained in 99% yield after overnight reaction.

The scope of aryl iodides was then assessed (Figure 2b). The reaction works well with electron-rich, electron-poor and *ortho*-substituted substrates, as shown by the quantitative formation of **18-21**. Complete selectivity for C–I bond activation in the presence of C–Br, C–OTf and C–Bpin functional groups is observed upon synthesis of **22-24** (the structure of **23** was confirmed by X-ray diffraction analysis),¹⁹ highlighting the complementarity and orthogonality of gold and palladium catalysis.

Having established the efficiency and generality of the gold-catalyzed C–N coupling, we sought to gain insight into the reaction mechanism. As schematically depicted in Figure 3a, two main pathways can be envisioned. They differ essentially in the order of the transmetalation/oxidative addition steps.

Toste *et al* have shown that in the gold-promoted C–N coupling of succinimide and aryl diazoniums under photoredox conditions, transmetalation precedes aryl transfer to gold (path I).¹³ To assess the feasibility of this route with our system, the amido Au(I) complex **A** was prepared (Figure 3b). Its structure was analyzed by multi-nuclear NMR. Of note, the ¹H–¹⁵N HSQC NMR spectrum shows ¹⁵N NMR signals at δ 38.1 ppm for the NMe₂ group (close to that of the (MeDalphos)AuCl complex, δ 37.0 ppm) and δ 110.2 ppm for the NHTs group with a J_{NP} coupling constant of 37 Hz. X-ray diffraction data for the 2LiOTf adduct was also obtained.¹⁹ Despite the presence of the (P,N) ligand to favor oxidative addition and stabilize the ensuing Au(III) species,^{7,8,20} complex **A** was found to be completely inert towards iodobenzene (no sign of a reaction after 3 days at room temperature in the presence of 3 eq. of PhI).¹⁹

From this observation, we surmised that oxidative addition precedes transmetalation in our case (Path II). To support this hypothesis, we studied the influence of *N*-nucleophiles as additives on the oxidative addition of iodobenzene to the (MeDalphos)AuCl complex.²¹ No significant impact was noticed with *p*-nitroaniline and *p*-toluenesulfonamide, complex **B** forms very rapidly and quantitatively. Conversely, the presence of either aniline or *p*-anisidine slows down the reaction and the oxidative addition is not complete even after 5 h, in line with the absence or very low catalytic activity observed with those substrates.¹⁹

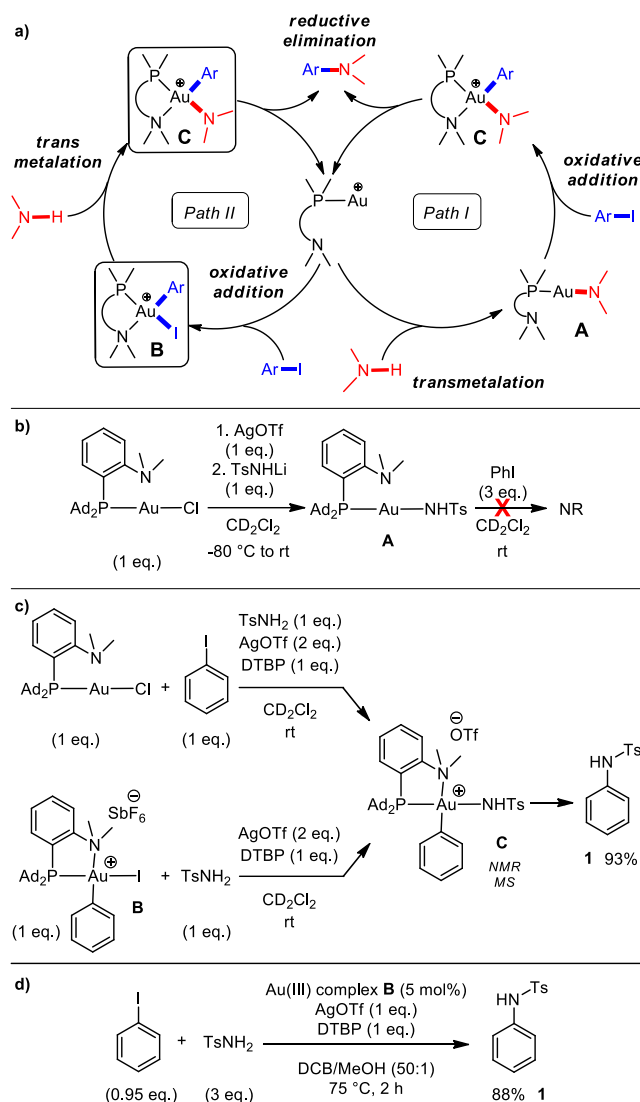


Figure 3. Catalytic cycles envisioned to account for the C–N coupling mediated by bond formation operating via aryl–Au(III) intermediates (a), stoichiometric and catalytic reactions carried out to gain mechanistic insight (b–d). Yields of **1** were determined by ^1H NMR with *n*-dodecane as internal standard.

Next, we sought to characterize reactive intermediates by running a coupling reaction at rt using 1 eq. of (MeDalphos)AuCl (Figure 3c). ^{31}P NMR monitoring showed fast and clean formation of a new product at δ 62 ppm. ^1H – ^{15}N HSQC experiments allowed to identify this species as the aryl amido Au(III) complex **C**. The ^{15}N NMR signal for the NMe₂ now appears at δ 72.8 ppm, in the typical range of (P,N)-chelated Au(III) complexes (δ 71.5 ppm for complex **B**) while the NHTs group resonates at δ 117.8 ppm as a doublet. The value of the J_{NP} coupling constant (36 Hz, very similar to that observed for complex **A**) supports *trans* arrangement of the amido group and phosphorus atom at gold. The structure of **C** was further confirmed by high resolution electrospray ionization mass spectrometry ($m/z = 865.3232$).¹⁹ Complex **C** slowly evolves at rt to regenerate the (MeDalphos)Au(I)⁺ complex and release the cross-coupling product **1** (93% yield after 36 h).²² The aryl Au(III) complex **B** is not observed during the course of the reaction, but its involvement is supported by the following reactions performed starting from isolated samples of **B**: (i) under stoichiometric conditions at rt, it also gives complex **C** that slowly undergoes reductive elimination and releases the C–N coupling product (Figure 3c), (ii) under the optimized catalytic reactions, its activity is very similar to that of the (MeDalphos)Au(I)⁺ complex (Figure 3d).

Thus, all observations are consistent and support the 2e redox cycle II for this gold-catalyzed C–N coupling. Oxidative addition of the aryl iodide precedes transmetalation and reductive elimination is the rate-determining step.

In summary, we have developed a new C–N coupling methodology that proceeds *via* a Au(I)/Au(III) catalytic cycle and draws on the faculty of the (P,N) ligand MeDalphos to promote oxidative addition. The reaction does not require the presence of an external oxidant or a directing group. It is robust, operates under mild conditions and works well with a variety of aryl iodides and amines. Most noticeable is the tolerance of functional groups that tend to raise selectivity issues with the other transition metals. Mechanistic studies, including the characterization of a key Au(III) intermediate, strongly support a catalytic sequence made of oxidative addition, transmetalation and rate-determining reductive elimination.

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