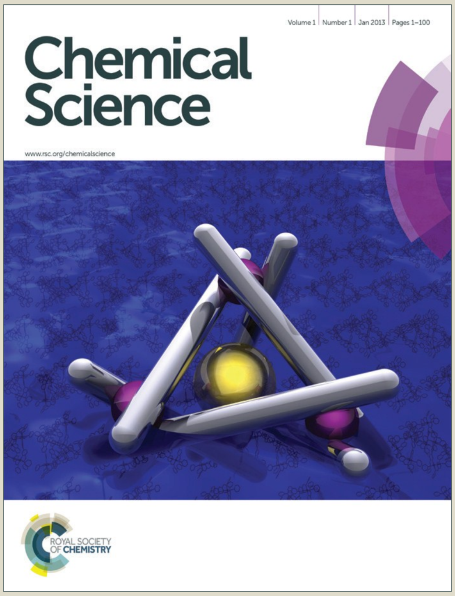

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Nucleophile Promoted Gold Redox Catalysis with diazonium: C-Br, C-S and C-P Bond Formation through Catalytic Sandmeyer Coupling

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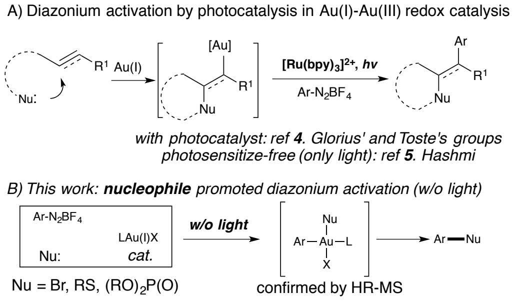
Gold-catalyzed C-heteroatom (C-X) coupling reactions are evaluated without using sacrificial oxidants. Vital to the success of this methodology is the nucleophile-assisted activation of aryldiazonium salts, which could be an effective oxidant to convert Au(I) to Au(III) even without the addition of assisting ligand or photocatalyst. By accelerating reaction kinetics to outcompete C-C homo-coupling or diazonium dediazoniation, gold-catalyzed Sandmeyer reactions were achieved with different nucleophiles, forming C-Br, C-S and C-P bonds in high yields and selectivity.

Homogeneous gold catalysis has been well developed for the activation of C-C multiple bond in the past two decades.[1] However, compared with Pd(0), a d^{10} isoelectronic counterpart, traditional redox chemistry with Au(I) are relatively rare due to the higher oxidation potential between Au(I) and Au(III).[2] To maximize the potential of gold catalysis, extensive effort has been put into the development of this new branch of gold chemistry.[3] Typically, strong external oxidants, such as Selectfluor and hypervalent iodine, are usually required to access catalytically active Au(III) intermediates. The need for strong oxidants made gold redox chemistry less attractive, especially for the synthesis of complex molecules. One of the most significant improvements of gold redox chemistry is the dual photoredox and gold catalysis, first reported by Glorius' and Toste's groups (**Scheme 1**).[4] In their studies, photocatalyst was used to promote the gold redox chemistry under mild conditions. More recently, Hashmi and coworkers further extended the chemistry into photosensitizer-free conditions, achieving alkyne 1,2-difunctionalization with only gold catalyst under visible-light.[5] In this study, a gold(III) intermediate was successfully isolated, which supported a gold redox catalytic mechanism under photo-initiated conditions. Herein, we report the investigations on the nucleophile promoted diazonium activation in promoting gold(I) oxidation. Through the mechanistic investigation using NMR and Electrospray ionization mass spectrometry (ESI-MS) , the nucleophile was identified as a critical factor in promoting this gold redox chemistry. In addition, through suppressing the undesired C-C homocoupling (via trans-metallation and reductive elimination), catalytic Sandmeyer coupling was achieved and C-X bonds (X = Br, S, P) were prepared with good to excellent yields.[6] Under this new condition, no strong oxidants or photocatalysts are required to promote gold oxidation, which will potentially open new avenues for future development of gold redox chemistry.


A) Diazonium activation by photocatalysis in Au(I)-Au(III) redox catalysis

*with photocatalyst: ref **4**. Glorius' and Toste's groups*
*photosensitize-free (only light): ref **5**. Hashmi*

*B) This work: **nucleophile** promoted diazonium activation (w/o light)*

Scheme 1. Redox gold catalysis

The high-oxidation potential between Au(I) and Au(III) has been a major concern that hindered the development of gold redox catalysis for a long time. Thus, achieving gold oxidation under mild conditions is crucial. Our group recently reported the gold catalyzed C-C coupling between alkyne and aryldiazonium salts.[7] Based on that study, diazonium activation could be achieved with the help of 2,2'-bipyridine (bpy) ligand even without light. Although visible-light condition is extremely mild and readily accessible, understanding the function of bpy ligand will certainly help the elucidation of reaction mechanism, which will beneficially add to further development of gold redox chemistry under mild conditions.

Notably, Shin and coworkers have reported the detection of Au(III) intermediate (using XPS) through mixing PPh_3AuCl and aryl diazonium in $MeOH/CH_3CN$ (20:1) at 60 °C.[8] To explore the role of bpy ligands, we monitored the reaction of diazonium **1a** (*p*-F-$C_6H_4N_2BF_4$) and PPh_3AuCl using ^{31}P NMR. Interestingly, when mixing **1a** and PPh_3AuCl in CH_3CN, no reaction was observed, even under long exposure to light at 50 °C (Figure **1a**). In contrast, with $MeOH/CH_3CN$ (9:1) as the solvent, phosphonium salt **2a** was

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x detected (22.5 ppm, Figure **1b**), though in low yield (23% based on NMR). Interestingly, with the addition of 1.0 equiv bpy, **2a** was formed under a much faster rate and PPh_3AuCl was totally consumed within an hour (Figure **1c**/**d**).[9]

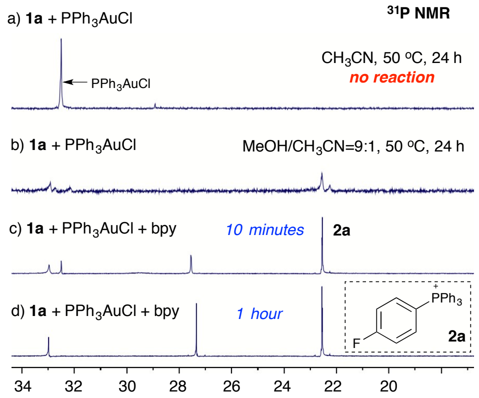
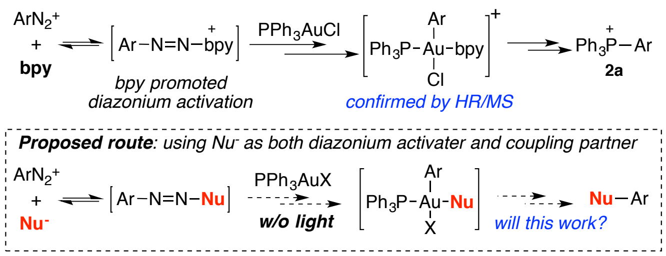


Figure 1. Monitoring the reaction of **1a** and PPh_3AuCl with ^{31}P NMR

The formation of phosphonium **2a** strongly suggested that Au(III) intermediate should be included during the reaction of PPh_3AuCl and diazonium salts with the assistance from bpy. Thus, it is likely that the combination of bpy and diazonium is the actual oxidant for the oxidation of PPh_3AuCl. Notably, it has been reported in the literature that pyridine could promote diazonium activation through nucleophilic addition.[10] Thus, similar function of bpy is expected as nucleophile in assisting diazonium activation, which accounts for the observed gold oxidation even without photo initiation. ESI-MS was used to explore the reaction intermediates. As expected, treating PPh_3AuCl/ArN_2^+/bpy (m/z = 745.12) gave the clear formation of $[PPh_3Au(Ar)bpy]^+$ cation which was also supported by further collision induced dissociation (CID) studies (MS/MS, see details in SI). This result confirmed the gold oxidation by diazonium salts with the assistance of bpy ligand. Encouraged by this discovery of nucleophilic ligand assisted diazonium activation, we wondered whether it is possible to further extend this gold redox chemistry into challenging C-X bond coupling. Our hypothesis was to explore proper anionic nucleophile to achieve both diazonium activation (for gold activation) and coupling (through reductive elimination) under this mild gold redox condition with no need of additional photosensitizers (**Scheme 2**).[11]

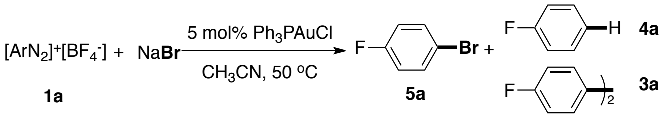


Scheme 2. Proposed Ar-Nu coupling with gold-redox catalysis

It is well known that conversion of ArN_2^+ to ArCl or ArBr can be achieved through standard Sandmeyer conditions using stoichiometric amount of CuX.[12] Successful examples of catalytic Sandmeyer reactions are rare. More importantly, CuX could not promote effective C-S and C-P bond formation through coupling mechanism. Compared with C-C bond coupling, formation of a C-X bond from coupling reaction is thermodynamically less favorable. Thus, there were only few successful examples reported to achieve this important transformation catalytically.[13] Therefore, the proposed gold-catalyzed coupling is attractive not only due to the mechanistic novelty (no need for strong oxidant or photo-activation), but also because of its potential synthetic applications (formation of challenging C-X bonds under catalytic conditions).

In the NMR studies shown in Figure **1**, only a trace amount of aryl chloride was observed, although stoichiometric amount of PPh_3AuCl was used. One possibility is that the reductive elimination of Ar-Cl from Au(III) is unfavorable under gold redox conditions. In fact, Toste group recently confirmed the reductive elimination rate as I > Br > Cl through careful evaluation on different Au(III)-X bond dissociation energies.[14] To explore the proposed catalytic C-X bond formation using gold redox chemistry, we started our investigation from the C-Br bond. To our great satisfaction, excellent yield of aryl bromide **5a** was achieved with the gold catalyst under mild conditions (3% PPh_3AuCl, 81 % in 5 h). Results from some alternative conditions are shown in Table **1**.

Table 1. Exploring reaction conditions [a, b]



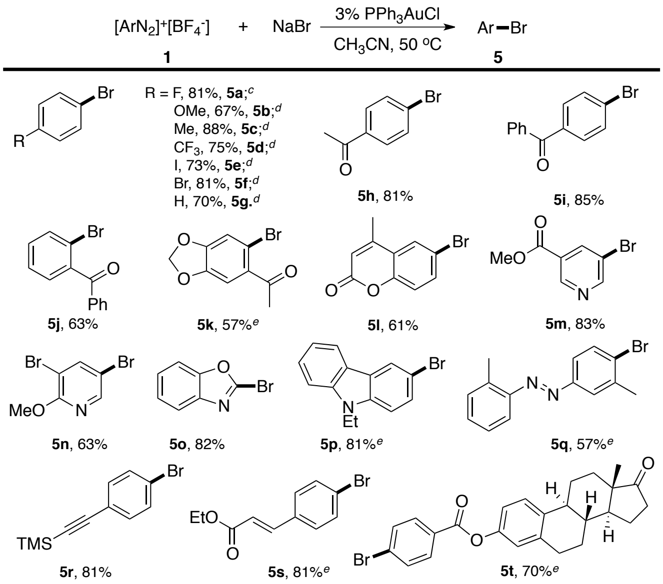
Entry	Variations from above conditions	Time	Conv. (%)	5a (%)	3a (%)	4a (%)
1	none	5 h	100	83	7	<5
2	blue LED, **NO** Ph_3PAuCl	12 h	50	<10	trace	33
3	LiBr instead of NaBr	12 h	100	78	8	<5
4	Acetone instead of ACN	5 h	100	11	37	<5
5	$Ph_3PAuNTf_2$ instead of Ph_3PAuCl	5 h	100	68	10	7
6	$Ph_3PAuNTf_2$ and 20 mol% bpy	12 h	100	63	8	15
7	3 mol% Ph_3PAuCl	5 h	100	81	7	<5
8	1 mol% Ph_3PAuCl	5 h	100	63	13	9
9	**No Light (dark)**	5 h	100	76	8	<5

[a] Reaction conditions: **1** (0.1 mmol), NaBr (0.4 mmol), *cat.* Au (5 mol%) in acetonitrile (ACN), 50 °C;[b] ^{19}F NMR yield with benzotrifluoride as the internal standard.

First, bpy ligand is not required in this reaction, which suggests that Br^- could act as an activation factor for diazonium. In fact, reacting diazonium with I^- gave the formation of aryl iodide even without any catalyst.[15] Less than 10% Ar-Br was observed without gold catalyst (entry **2**). Switching solvent to acetone caused a significantly increased yield of homo-coupling product **3a**, which suggested either different reductive elimination reaction rate (relative to transmetallation) or alternative radical reaction path. Lowering catalyst loading to 1% led to reduced yield of **5a** (entry **8**, 63%) due to the increased aryl homo-coupling and diazonium decomposition (formation of ArH **4a**). Cationic gold(I) catalyst PPh_3AuNTf_2 also promoted the reaction, though with lower yield (entries **5**, **6**), which is similar to the performance of Ph_3PAuBr catalyst. Importantly, similar reaction rate was observed while conducting the reaction under dark condition (entry **9**), confirming the reaction as nucleophile-promoted activation rather than light-promoted diazonium decomposition. Overall, to the best of our knowledge, this is the first example of catalytic Sandmeyer reaction using only gold catalyst (no photo-activation). With this new optimal condition, various substrates are tested. The reaction substrate scope is shown in Table **2**.

Excellent substrate compatibility was found. Diazonium salts with EWGs and EDGs all furnished the products in good yields (**5a**-**5g**). Notably, aryl iodide is also compatible in this catalytic system (**5e**), highlighting the orthogonal reactivity of Au catalyst over Pd, Cu, and Ni (for which oxidative addition could occur). Carbonyl groups (**5h**, **5i**, **5j**), benzodioxo (**5k**), azobenzene (**5q**) were well tolerated in this reaction. Hetero-aromatic diazonium salts, such as pyridines (**5m**, **5n**) and indole (**5p**) also worked well in this reaction. Moreover, this reaction proceeded with high efficiency and selectivity with α, β-unsaturated ester (**5s**) and *p*-acetylide aryl diazonium (**5r**) to give the corresponding products. To further evaluate the synthetic utility and generality of this reaction, we tested coumarin derivative (**5l**) and estrone derivative (**5t**) to the reaction conditions. The desired products were achieved with good yields, highlighting the good potential of this catalytic system for complex molecular synthesis.

Table 2. Catalytic Ar-Br cross coupling reaction scope [a, b]



[a] Reaction conditions: **1** (0.2 mmol), NaBr (0.8 mmol), PPh$_3$AuCl (3 mol%) in acetonitrile (ACN), 50 °C, 5 h; [b] Isolated yield; [c] determined by ^{19}F NMR with benzotrifluoride as the internal standard; [d] determined by GC-Mass using decane as the internal standard; [e] LiBr (1.0 mmol) instead of NaBr.

ESI-MS studies were performed to explore the reaction mechanism. As shown in Figure **2**, bisbromide-aryl-gold(III) intermediate was observed in MS under the standard reaction conditions. Through collision induced dissociation (CID) studies (MS/MS), the composition of this intermediate was confirmed (see details in SI). This result provided strong evidence for the formation of Au(III) intermediate as proposed.

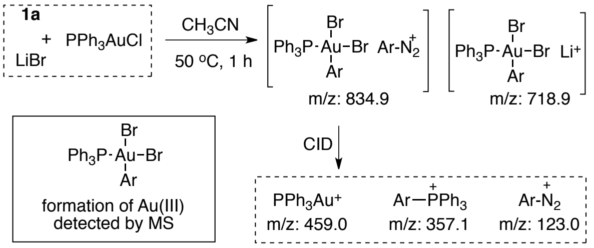
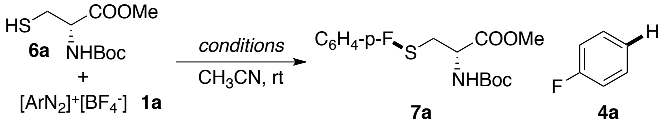


Figure 2. Evidence of Au(III) intermediate from ESI-MS.

Encouraged by the success of gold catalyzed C-Br bond formation, we turned our attention to the synthesis of more challenging C-S and C-P bonds. Unlike C-Br bond, which can be alternatively prepared using stoichiometric amount of CuBr, sulfur and phosphine are not valid nucleophiles under Sandmeyer conditions due to the strong coordination of sulfur or phosphine with Cu cation (completely quenched metal reactivity).

Thiols (RSH) are good nucleophiles in general and can react with arenediazonium through S$_N$Ar mechanism with the assistance of a base, especially for acidic thiophenols.[16] However, as demonstrated above, one major side reaction of diazonium decomposition is the dediazoniation (formation of Ar-H). This side reaction was more prevalent when using proton-containing nucleophiles (NuH). For example, as shown in Table **3**, reaction of cysteine derivative **6a** with diazonium **1a** gave only dediazoniation product **4a** in 23% yield. Addition of base (2 equiv Na$_2$CO$_3$) did help the formation of the desired thioether **7a** (37% yield), however, significant amount of dediazoniation byproduct **4a** was obtained (55%). Application of stoichiometric amount of Cu(OAc)$_2$ did not help the reaction at all.

Table 3. Gold catalyzed C-S bond formation [a, b]

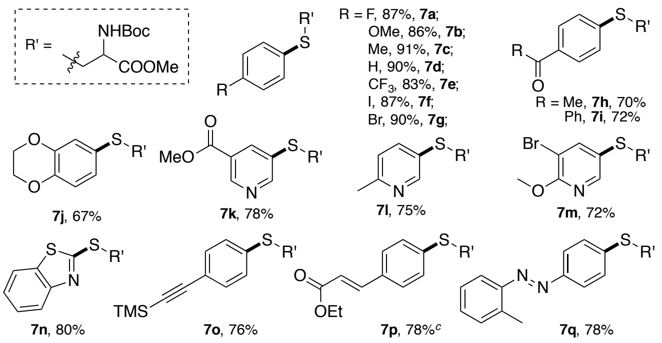


Catalyst (mol%)	Base (equiv)	Time	Conv.(%)	**7a**(%)	**4a**(%)
None	None	24 h	30	0	23
None	Na$_2$CO$_3$ (2)	10 h	100	37	55
Cu(OAc)$_2$ (100)	Na$_2$CO$_3$ (2)	10 h	100	31	65
PPh$_3$AuCl (5)	None	10 h	55	49	38
PPh$_3$AuCl (5)	Na$_2$CO$_3$ (2)	3 h	100	87	8
PPh$_3$AuCl (3)	Na$_2$CO$_3$ (2)	3 h	100	86	7
PPh$_3$AuCl (1)	Na$_2$CO$_3$ (2)	7 h	100	53	30

[a] Reaction conditions: **1a** (0.2 mmol), **6a** (0.1 mmol), *cat.* (5 mol%) and Na$_2$CO$_3$ (0.2 mmol) in acetonitrile (ACN), 50 °C; [b] ^{19}F NMR yield with benzotrifluoride as internal standard.

Interestingly, with PPh$_3$AuCl as the catalyst, the desired thioether **7a** was obtained even without base (49% yield). These results suggested that with the help of thiol nucleophile, PPh$_3$AuCl can be an effective catalyst for diazonium decomposition, forming Au(III) even at room temperature. With the aid from base, this challenging C-S coupling was achieved in 86% yield with only 3 mol% gold catalyst loading. Based on the reaction kinetics, the C-S bond formation was dramatically improved with gold catalyst.[17] The reaction scope is shown in Table **4**.

Table 4. C-S cross-coupling reaction scope [a, b]

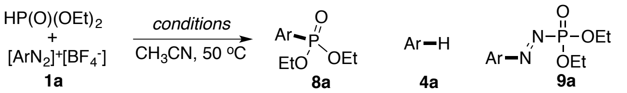


[a] Reaction conditions, C-S formation: **1** (0.4 mmol), **6** (0.2 mmol), PPh$_3$AuCl (3 mol%) and Na$_2$CO$_3$ (0.4 mmol) in acetonitrile (ACN), rt, 3 h; [b] isolated yield; [c] determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard with E/Z selectivity 1:1.

Various cysteine derivatives were successfully prepared in good yields. Both electron-rich (**7b**, **7c**, **7j**) and electron-deficient (**7a**, **7e**-**7i**) diazonium salts were suitable for this transformation with excellent yields. Diazonium with iodide substituent is also tolerated in this reaction (**7f**), which could be a potential synthetic handle for further functionalization. Heterocycles, including various substituted pyridines (**7k**-**7m**) and benzothiazole (**7n**), gave the desired products efficiently with this catalytic system. Acetylide (**7o**) and α, β-unsaturated ester (**7p**) also reacted with good yields. Notably, sulfur containing molecules, as an important class of compounds for both chemical and biological research, are challenging to construct through traditional cross-coupling strategies because of the potential coordination between sulfur and transition metal catalysts.[18] This new catalytic system thus provided an efficient strategy to achieve bioactive amino acids.

Our last attempt is to explore the possibility of C-P bond using this gold redox catalysis. Compared with C-S bond, the C-P bond formation is more challenging as H-phosphonate is much less nucleophilic and it could also be a potential reductant for diazonium.[19] Thus, the C-P bond formation with diazonium cannot be achieved through either S_NAr or Cu-promoted Sandmeyer reactions. Recently, Toste and coworkers reported the application of photocatalyst in gold-catalyzed oxidative coupling to achieve this C-P bond formation.[20] Based on the results discussed above, we were wondering whether this nucleophile-promoted gold redox catalysis can be used to achieve this C-P bond formation.

Table 5. Ligand-assisted gold-catalyzed C-P bond formation [a, b]



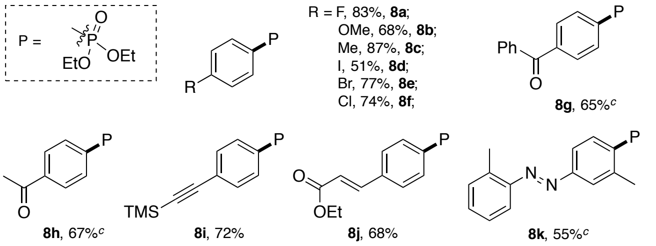
Catalyst (mol%)	Additives (equiv)	Time	conv.(%)	**8a**(%)	**4a**(%)	**9a**(%)
None	None	10 h	50	0	31	0
None	Na_2CO_3 (2)	10 h	100	0	70	0
$Cu(OAc)_2$ (100)	Na_2CO_3 (2)	10 h	100	0	75	0
PPh_3AuCl (5)	None	10 h	50	25	13	0
PPh_3AuCl (5)	Na_2CO_3 (2)	10 h	100	11	38	0
PPh_3AuNTf_2 (5)	bpy (0.2), Na_2CO_3 (2)	10 h	100	<5	53	11
PPh_3AuCl (5) [c]	3-Cl-py (2)	3 h	100	83	7	0
PPh_3AuNTf_2 (5) [c]	3-Cl-py (2)	3 h	100	70	15	0
none[d]	3-Cl-py (2)	10 h	69	0	5	44
none	3-Cl-py (2)	10 h	>90	0	25	4

[a] Reaction conditions: **1a** (0.2 mmol), $HP(O)(OEt)_2$ (0.1 mmol), *cat.* (5 mol%) and base (0.2 mmol) in acetonirile (ACN), 50 °C; [b] ^{19}F NMR yield with benzotrifluoride as internal standard; [c] ACN : EtOH = 6:1; [d] room temperature..[21]

As shown in Table **5**, no desired arylphosphonate (**8a**) was obtained using base and/or copper acetate. Impressively, **8a** was formed even with solely PPh_3AuCl, though in low yield (25%). Addition of Na_2CO_3 did not improve the cross-coupling but promoted the Ar-H formation. Combination of PPh_3AuNTf_2 and bpy in the presence of Na_2CO_3 (previously reported C-C bond coupling conditions) also failed to increase the yield of the desired C-P coupling product. Considering that nucleophilic ligand is crucial in this gold redox catalysis, we put our attention on other pyridine derivatives. Through a comprehensive screening, 3-Cl-pyridine was identified as the optimal nucleophile (see detailed screenings in SI), giving the desired C-P bond coupling product **8a** in 83% isolated yield. Using PPh_3AuNTf_2 as catalyst led to a lower yield of **8a** due to the increasing rate of side reactions. Notably, without gold catalyst, diaza compound **9a** was formed as the major product at room temperature whereas no desired coupling product **8a** was detected.[22] At 50°C, the reaction was very messy and **8a** was not detected at all, which suggested that **8a** was not formed from decomposition of diaza compound **9a**. The reaction substrate scope is shown in Table **6**.

Similar to the C-Br and C-S coupling, broad substrate scope is received in the C-P bond formation reactions. Aryl phosphonates with electron rich (**8b**, **8c**) and electron deficient (**8a**, **8d**-**8h**) substituents could all be generated with good yields. Halogen substitute groups (**8a**, **8e**, **8f**) were all tolerated. Alkyne (**8i**), α, β-unsaturated ester (**8j**) and azobenzene (**8k**) also gave good results, suggesting great synthetic potential of this methodology.

Table 6. Catalytic C-P cross-coupling reaction scope [a, b]



[a] Reaction conditions, **1** (0.4 mmol), $HP(O)(OEt)_2$ (0.2 mmol), PPh_3AuCl (5 mol%) and 3-Cl-Py (0.4 mmol) in acetonitrile (ACN), 50 °C, 5 h; [b] isolated yield; [c] determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Conclusions

In summary, herein we reported the C-Br, C-S, and C-P bond formation through gold redox catalysis. We demonstrated that nucleophiles played a crucial role in the Au(I) promoted diazonium decomposition. With this strategy, various C-X coupling could be achieved with excellent yields and broad substrate scope simply using LAuCl (no need for external oxidant). These results not only provide a new practical strategy to achieve challenging C-X bond coupling, but also, more importantly, revealed some new mechanistic insight regarding gold redox catalysis, which will likely further enrich the pedigree of gold catalysis.

Acknowledgement

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Notes and references

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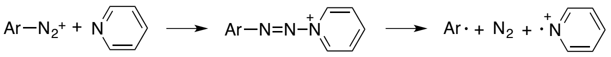

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