Ligand-Enabled Gold-Catalyzed C(sp²)–O Cross-Coupling Reactions

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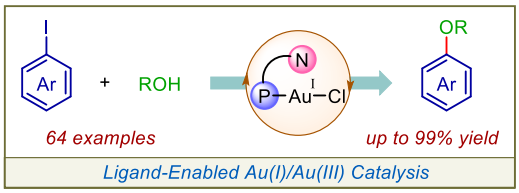


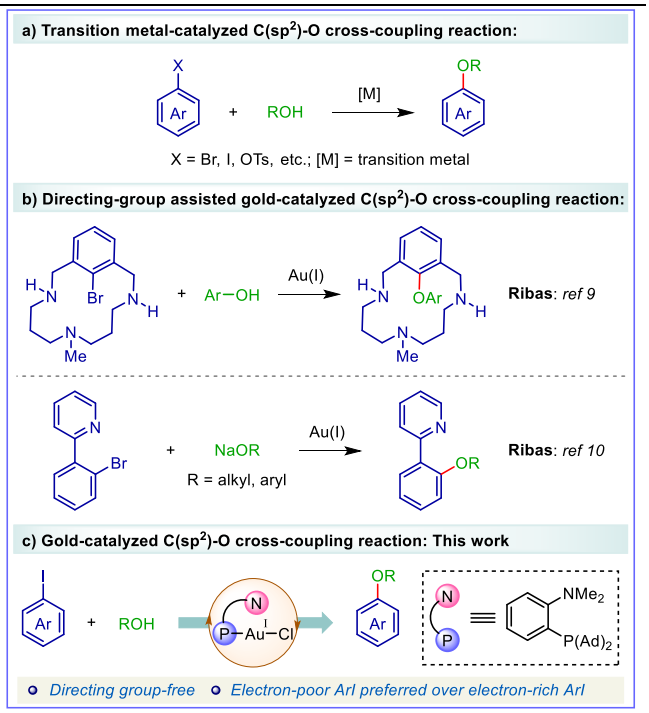
ABSTRACT: Reported herein is a ligand-enabled gold-catalyzed C(sp²)-O cross-coupling reaction of aryl iodides and aliphatic alcohols. The synthesis of a variety of aryl alkyl ethers including complex biomolecules and various medicinally relevant motifs has been achieved to demonstrate the usefulness of the method. The importance of gold catalysis has been highlighted by overcoming the selectivity issues that are in general observed for C-O cross-coupling reactions when other transition metals are used as catalysts.

Aryl alkyl ethers are versatile building blocks present in numerous naturally occurring and medicinally relevant compounds.[1] Transition metal-catalyzed C-O bond forming reactions have emerged as an important technique to access various aryl alkyl ethers (Scheme 1a).[2] In particular, the use of Pd,[3] Cu[4] and Ni[5] catalysts for enabling such C-O cross coupling reactions has witnessed a remarkable surge and a variety of such reactions using various aryl halides and alcohols have been developed.

As far as the realm of gold catalysis is concerned, cross-coupling reactions of aryl halides with various nucleophiles had long been remained under-developed.[6] This could be potentially due to gold's high redox potential[7] and its reluctance to undergo oxidative addition to aryl halides, thereby hampering the development of all such challenging cross-coupling reactions.[8] As far as C-O cross coupling reaction is concerned, Ribas and coworkers demonstrated the gold catalyzed C-O cross-coupling reaction using macrocyclic bromo arenes with phenols (Scheme 1b).[9] Later, the same group successfully developed the C-O cross-coupling reaction of pyridine-tethered bromo arenes with sodium alkoxides (Scheme 1b).[10] Since then the quest for the development of a general and directing group-free gold-catalyzed C(sp2)-O cross-coupling reaction remains open.

Recent discovery of the ligand-enabled Au(I)/Au(III) catalysis has opened up new avenues for the development of various cross-coupling reactions. In this regard,

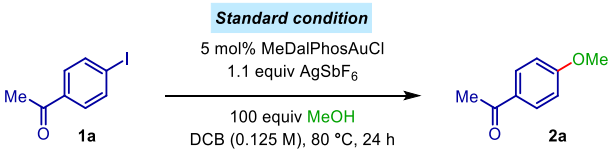
Scheme 1. Gold-Catalyzed C(sp²)-O Cross-Coupling Reactions: Known and Present Work



recently, various C-C,[11] C-N,[12] C-S/Se[13] cross-coupling reactions have been developed. In addition, several reports on the 1,2-difunctionalization of C–C multiple bonds under ligand-enabled Au(I)/Au(III) catalysis have also been reported.[14] Since long, our group has been focused towards the development of various gold-catalyzed cross-coupling reactions.[12,13b,14a,14d,14e,14g,15] Unfortunately, despite persistent attempts, there had not been any success in the development of a C(sp²)-O cross coupling reaction, supposedly due to the facile gold(I)-alkoxide formation[16] rendering it inactive for necessary oxidative addition to aryl halides. Moreover, the reductive elimination from electron rich organogold(III) alkoxide complexes could also pose a

potential challenge.[9,10] During this pursuit of developing a general C-O cross coupling reaction, we screened a wide array of reaction conditions and substrates until we realized that the reaction demanded an electronically poor iodoarene,[17]contrary to the general trend of electron-rich iodoarenes being favoured for cross coupling reactions in ligand-enabled Au(I)/Au(III) catalysis.[11,12] This could perhaps be attributed to the highly electrophilic arene-Au(III) center that is generated in the case of electronically poor iodoarenes, favoring the arduous reductive elimination step. Building onto this crucial observation, we could successfully develop the first C-O cross coupling reaction of aryl iodides and alcohols using ligand-enabled Au(I)/Au(III) catalysis.[18]

Table 1. Optimization of Reaction Conditions[a,b]



Entry	Deviation from *"Standard condition"*	Yield **2a** (%)[b]
1	none	28
2	0.5 equiv K_3PO_4	55
3	1 equiv K_3PO_4	80
4	2 equiv K_3PO_4	75
5	1 equiv DTBP	71
6	1 equiv Cs_2CO_3	70
7	1.1 equiv AgOTf	30
8	1.1 equiv $AgNTf_2$	60
9	DCE	74
10	1,4-Dioxane	56
11[c]	**DCB:MeOH (2:1)**	**85**

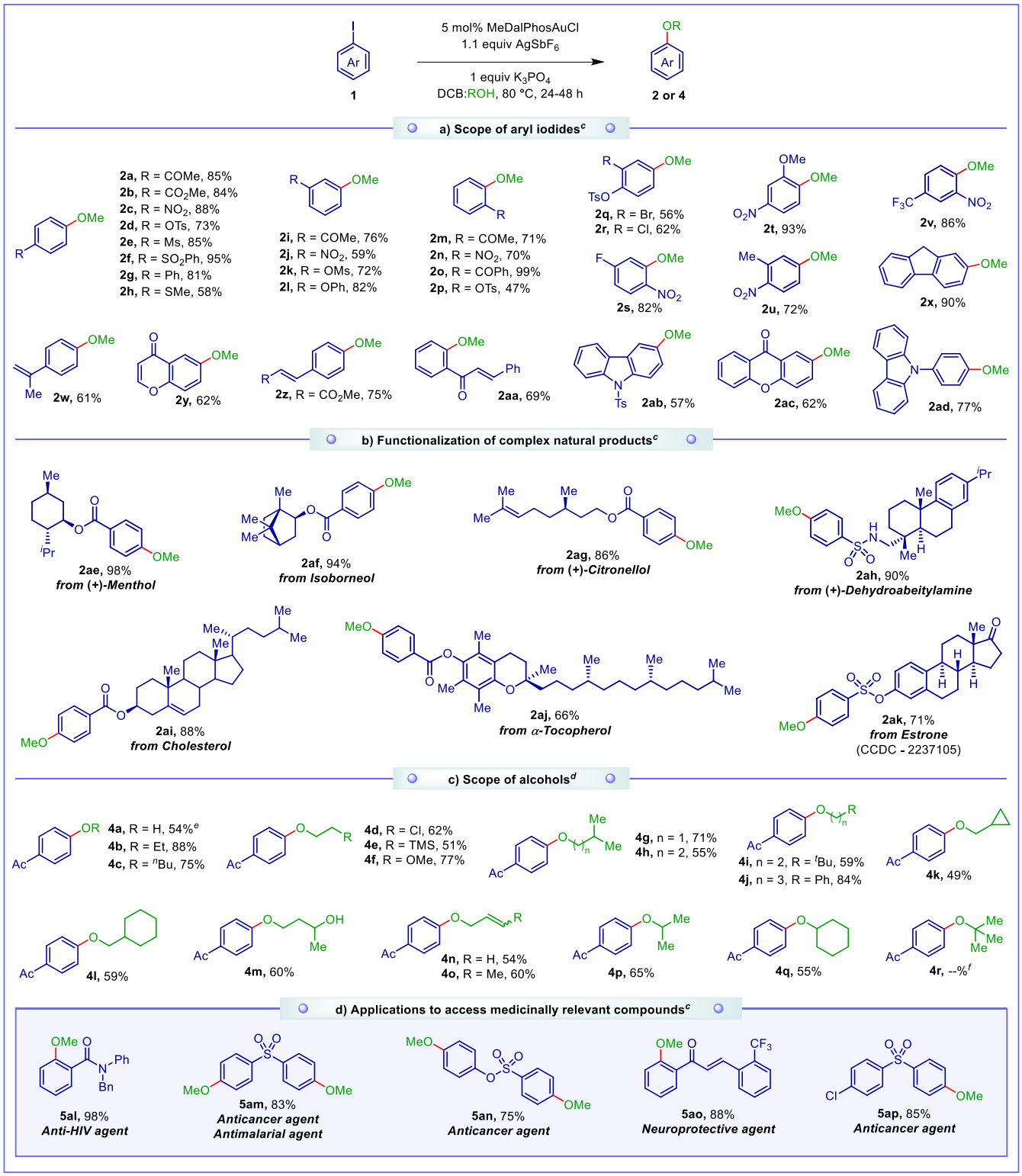
[a]Reaction conditions: 0.10 mmol **1a**, 5 mol% MeDalPhosAuCl, 0.11 mmol $AgSbF_6$, 10 mmol MeOH, DCB (0.125 M), 80 °C, 24 h. [b]Isolated yields. [c]DCB:MeOH (2:1) (0.17 M).

With this initial observation that electron-poor iodoarenes favoured C-O cross coupling reaction, we initiated our reaction development with 4'-iodoacetophenone (**1a**), methanol (100 equiv), MeDalPhosAuCl (5 mol%), and $AgSbF_6$ (1.1 equiv) in 1,2-dichlorobenzene (DCB; 0.125 M), and stirred the reaction mixture at 80 °C for 24 h. To our delight, the desired C-O cross-coupled product **2a** was obtained in 28% yield (Table 1, entry 1). Motivated by this encouraging observation, we turned our attention to improve the efficiency of the reaction. Notably, the addition of 0.5 equiv base (K_3PO_4) afforded 55% of **2a** (entry 2), while use of 1 equiv, afforded **2a** in excellent 80% yields which suggested that role of base is very crucial to achieve the better outcome (entry 3). Further increase in equivalence of K_3PO_4 had a detrimental effect on the yield of the reaction (entry 4). Other than K_3PO_4, 2,6-di-tert-butylpyridine (DTBP) or Cs_2CO_3 as a base resulted lower yields (entry 5-6). Unfortunately, screening of various silver salts and other solvents like DCE and 1,4-dioxane did not afford any better results (entry 7-10). Pleasingly, when 2:1 mixture of DCB and methanol (0.17 M) was used, **2a** was obtained in highest 85% yield (entry 11). Further, a series of sterically and electronically different DalPhos ligands were screened instead of MeDalPhos, but none was found to be fruitful.[17]

With the optimized reaction conditions identified, we first decided to explore the scope of aryl iodides (Scheme 2). To our delight, a variety of aryl iodides reacted efficiently under the optimized reaction conditions, leading to the formation of C-O bonds. For instance, aryl iodides bearing electron-withdrawing groups (-COMe, $-CO_2Me$, $-NO_2$, -OTs, -Ms, $-SO_2Ph$, and -Ph) at the *para*-position worked smoothly to provide **2a–2g** in good to excellent yield (73–95%). Next, aryl iodides bearing electron-donating group (-SMe) delivered the cross-coupled product **2h** in 58% yield. Notably, various iodoarenes bearing electron-donating groups did not afford any successful cross-coupling products.[17] Furthermore, aryl iodides bearing electron-withdrawing groups (-COMe, $-NO_2$, -OMs, and -OPh) at the *meta*-position were well tolerated affording corresponding products **2i-2l** in good yields (59-82%). Similarly, iodoarenes (**1m-1p**) having electron-withdrawing groups (-COMe, $-NO_2$, -COPh and -OTs) at the *ortho*-position were also efficiently converted to respective aryl ethers in good to excellent yields (47-99%). Various halo-substituents including -Br, -Cl and -F were well tolerated under the present reaction condition and afforded the corresponding products **2q**-**2s** in 56-82% yield. Next, nitro iodobenzene bearing methoxy, methyl and trifluoromethyl group provided corresponding products **2t-2v** in good to excellent yields (72-93%). Additionally, 9H-Fluorene, styryl and chalcone based iodoarenes (**1x**, **1w**, **1z** and **1aa**) were also well compatible (61-90%) under the optimized reaction conditions. Various heteroaromatic scaffolds such as chromone, xanthone, carbazole-based iodo compounds (**1y, 1ab-1ad**) successfully furnished corresponding products (**2y**, **2ab**-**2ad**) in good yields (57-77%). Delightfully, iodoarenes-containing complex natural products such as menthol (**1ae**), isoborneol (**1af**), citronellol (**1ag**), dehydroabietylamine (**1ah**), cholesterol (**1ai**), tocopherol (**1aj**), estrone (**1ak**) provided corresponding products (**2ae**-**2ak**) in good to excellent yields (66-98%) which demonstrates the generality of the method (Scheme 2b).

The optimal conditions were then implemented to evaluate the scope of aliphatic alcohols using 4'-iodoacetophenone **1a** as a model substrate (Scheme 2c). Interestingly, when water was used as a nucleophile, corresponding C-O cross-coupling product phenol **4a** was obtained in 54% yield. A variety of alcohols such as ethanol, ^{n}butanol, 2-chloroethanol, 2-(trimethylsilyl)ethanol, 2-methoxyethanol were well tolerated to furnish respective products (**4b-4f**) in good to excellent yields (51-88%). When other aliphatic primary alcohols were treated with **1a**, corresponding aryl alkyl ethers (**4g-4l**) are obtained in 49-84% yield. In case of unsymmetrical alcohol, regioselective coupling at the less hindered site was observed (**4m**). Various allylic alcohols and secondary alcohols were also tested and afforded the corresponding aryl alkyl ethers (**4n**-**4q**) in 54-65% yields. However, tertiary alcohol (**3r**) was found to be unreactive, probably because of the high steric encumbrance.

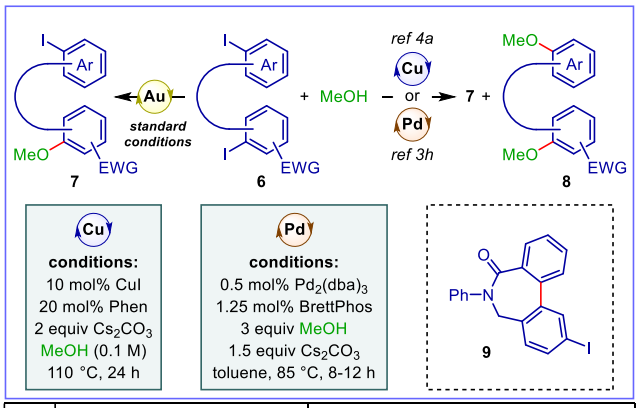
Scheme 2. Scope of reaction[a,b]

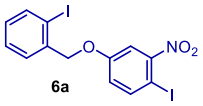
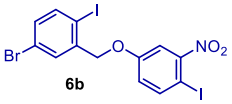
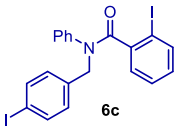
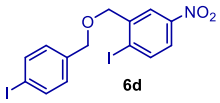


[a]Reaction conditions: 0.20 mmol **1**, 5 mol % MeDalPhosAuCl, 0.22 mmol $AgSbF_6$, 0.20 mmol K_3PO_4, 80 °C, 24-48 h. [b]Isolated yields. [c]DCB:MeOH (2:1) (0.17 M). [d]DCB:ROH (0.75:1) (0.28 M). [e]Moist DCE was used. [f]No Reaction.

Next, we focused our attention towards the synthesis of medicinally relevant aryl alkyl ethers (Scheme 2d). For instance, 2-methoxybenzamide derivative **5al**, an anti-HIV agent[19] was obtained in excellent yield, whereas **5am** which acts as anticancer as well as antimalarial agent,[20] was formed in 83% yield. Moreover, the synthesis of anticancer agents[13,21] **5an**, **5ap** and neuroprotective agent[22] **5ao** in good to excellent yields (75-88%) demonstrates the usefulness of the methodology.

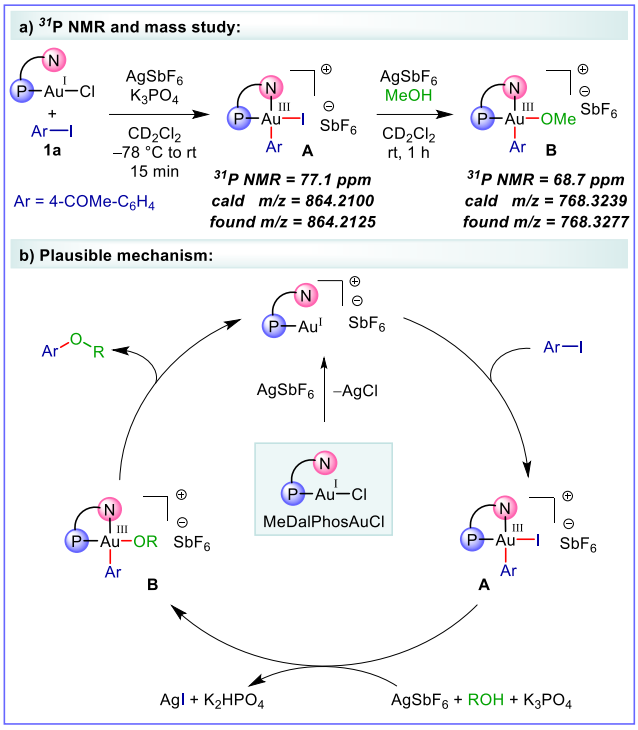
Scheme 3. Site-selective methoxylation in di-iodoarenes[a,b]



Sr. No.	6	Conditions		
		Au	Cu	Pd
1	 6a	**7a**, 86% (CCDC - 2237104)	**7a**, 36% + **8a**, 55%	**7a**, 31% + **8a**, 38%
2	 6b	**7b**, 60%	**7b**, 5% + **8b**, 71%	**7b**, 21% + **8b**, 32%
3	 6c	**7c**, 81%	**7c**, 27% + **8c**, 72%	**9**, 37%
4	 6d	**7d**, 67%	**8d**, 83%	**7d**, 15% + **8d**, 30%

We wondered if this biased cross-coupling reactivity towards electronically different iodoarenes could potentially be utilized to achieve site-selective C-O cross-coupling in substrates bearing multiple iodoarenes. To test this, we designed a series of substrates **6** bearing an electronically neutral iodoarene and an electronically deficient iodoarene, and subjected these substrates to C-O cross-coupling reactions using Au, Cu[4a] and Pd[3h] catalysis. When **6a** was subjected under Au catalysis, C-O cross coupling product **7a** was observed exclusively with electronically deficient iodoarene keeping electronically neutral iodoarene intact. However, under Pd or Cu catalysis, di-iodoarene **6a** results in the formation of mixture of mono- and di-methoxylated products (**7a** and **8a**). Similar observation was found in case of di-iodoarene **6b**. Additionally, gold catalyzed C-O cross coupling of **6c** only forms **7c** in 81% yield, and Cu-catalysis provides the mixture of products (**7c** and **8c**) while a new seven-membered cyclic product **9** was formed under palladium catalysis. Furthermore, di-iodoarene **6d** undergoes mono-methoxylation (**7d**) under Au-catalysis and upon treatment of Cu catalysis, it exclusively forms di-methoxylated product **8d**. However, a mixture of **7d** (15%) and **8d** (30%) was formed under Pd catalysis. The success of these site-selective methoxylation reactions suggests that gold-catalyzed C-O cross coupling offers complementary site-selectivity in comparison to those in Cu or Pd catalysis.

Scheme 4. Control experiments and plausible mechanism



A series of control experiments were performed to gain insights about the mechanistic premise of the reaction (Scheme 4). A stoichiometric reaction was studied using NMR spectroscopy, wherein, when **1a** was treated with MeDalPhosAuCl in presence of $AgSbF_6$, a prominent peak in ^{31}P NMR was observed at 77.1 ppm after 15 min which supposedly belong to the Au(III) complex **A** (Scheme 4a). To this reaction mixture, $AgSbF_6$ and methanol were added which resulted in the appearance of a new peak in ^{31}P NMR at 68.7 ppm suggesting the formation of Au(III) complex **B**.[17] Further, these putative Au(III) intermediates **A** (m/z = 864.2125) and **B** (m/z = 768.3277) were also confirmed by mass spectrometric studies. Based on the mechanistic investigations and literature precedence, a plausible mechanism has been proposed in Scheme 4b. First, the cationic Au(I) complex, generated after the halide abstraction by $AgSbF_6$ would undergo oxidative addition with iodoarene **1a** to form aryl-Au(III) complex **A**. The subsequent iodide abstraction by silver salt from Au(III) complex **A** would trigger nucleophilic attack of alcohol to furnish Au(III) complex **B** (detected in ESI-HRMS), which upon reductive elimination leads to the formation of C(sp^2)-O cross-coupling product.

In conclusion, we have developed the ancillary ligand-enabled gold-catalyzed C(sp^2)-O cross-coupling reactions of aryl iodides with aliphatic alcohols. The reaction displays wide functional group tolerance and has been extended for

the methoxylation of various complex as well as medicinally relevant molecules. Furthermore, by comparing the reactivities of Pd and Cu with Au, we demonstrate the complementary reactivity of the present approach in enabling site-selective C-O cross-coupling reactions. Moreover, mechanistic investigations including NMR and mass spectrometric studies strongly support the proposed mechanism of the reaction. The realization of the C-O cross coupling reaction is expected to lay a foundation for the development of various other challenging cross coupling reactions that remain unachieved in gold catalysis.

ACKNOWLEDGMENT

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(18) During the final stage of preparation of this manuscript, Xu and co-workers reported gold-catalyed C-O cross coupling reaction: Chen, G.; Xu, B. Hydrogen Bond Donor and Unbalanced Ion Pair Promoter-Assisted Gold-Catalyzed Carbon−Oxygen Cross-Coupling of (Hetero)aryl Iodides with Alcohols. *ACS Catal*. **2023**, *13*, 1823-1829. There are some notable differences between our work and Xu's work. Hence the work presented herein is complementary to that reported by Xu and coworkers.

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