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Exploiting the Dual Role of Ethynylbenziodoxolones in Gold-Catalyzed C(sp)-C(sp) Cross-Coupling Reactions

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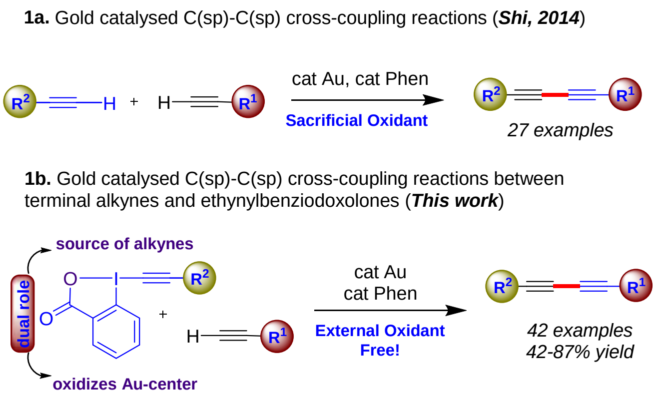
Reported herein is gold-catalyzed alkynylation of terminal alkynes using ethynylbenziodoxolones (EBXs) where EBXs serve dual role as oxidant as well as alkyne transfer agent to access unsymmetrical 1,3-diynes. Hence, the catalytic system requires no external oxidants and is compatible with a broad range of substrates, including those with polar functional groups such as NH, OH and B(OH)$_2$.

Metal-catalyzed C(sp)-C(sp) cross-coupling reactions are an important topic of research because these reactions provide synthetically valuable 1,3-diynes.[1] Conventional methods for synthesis of such heterodiynes include Glaser–Hay coupling[2] and Cadiot–Chodkiewicz coupling.[3] Though over the last four decades, several variants of these reactions have been developed,[4] the suppression of undesired homocoupling product still continues to be challenging besides other drawbacks such as low efficiency and sophisticated reaction conditions.[5]

In recent years, oxidant empowered gold-catalyzed reactions has emerged as a powerful tool for a variety of C-C and C-X bond formation reactions.[6] A landmark contribution in this area was made by Periana[7] as early as 2004 who was able to harness the power of oxidative gold catalysis. After that, it was the research groups of Hashmi,[8a] Zhang,[8b,f] Toste[8c,d] and Nevado[8e,g] who pioneered to discover the vast potential of external oxidant-aided Au(I)/Au(III) catalysis encompassing a diverse spectrum of C–C and C–X bond-forming reactions. Though, Au(I)/Au(III) catalysis chemistry has been exploited for a number of reactions, very little was known on the gold catalyzed C(sp)-C(sp) cross-coupling reactions. The research group of Shi, for the first time, developed gold-catalyzed oxidative cross-coupling of alkynes to unsymmetrical diynes utilizing stoichiometric amounts of PhI(OAc)$_2$ as an oxidant (Scheme 1a).[9] The authors took the advantage of "discrimination effect" provided by Au salt towards electronically biased alkynes for selective formation of specific gold acetylides. We envisioned if we can restrict the gold acetylide formation of one particular alkyne in the reaction mixture by using an alkyne surrogate, chances of the undesired homocoupling can be statistically reduced. It can be even better if the surrogate is able to transfer alkyne through an oxidative insertion fashion eliminating the need for an external oxidant.

As a part of our ongoing interest in Au(I)/Au(III) catalysis[10] and inspired by the Waser's reports[11] on direct alkynylation of *N*-heteroaromatics with ethynylbenziodoxolones (EBXs),[12] we wondered whether it is possible to exploit the dual role of EBXs as an oxidant as well as an alkyne surrogates. Herein, for the first time, we report the dual role of EBXs to selectively effect the C(sp)-C(sp) cross-coupling[13] with terminal alkynes leading to unsymmetrical 1,3-conjugated diynes under external oxidant free conditions (Scheme 1b).[14]



Scheme 1. Literature report and present work

To test our hypothesis, 4-ethynyl toluene (**1a**) and TIPS-EBX (**2a**) was selected as model coupling partners in the presence of 10 mol% AuCl in CH$_3$CN (Table 1). Pleasingly, the desired cross-coupled product **3a** was obtained; albeit, with poor heteroselectivity (entry 1). The necessity of the gold catalyst was subsequently validated by a control experiment (entry 2). Improved heteroselectivity was observed with Ph$_3$PAuCl as Au(I) precatalyst (entry 3). However, screening other gold catalysts led to poor or no conversions (entries 4, 5 and 6). We then speculated that application of a suitable π-

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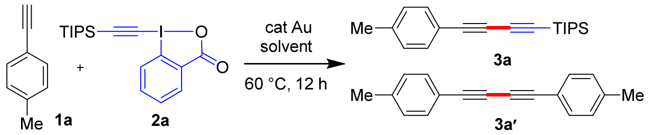
acceptor ligands (e.g, bipy, phen) may further improve the reaction performance since they are reported to assist the reductive elimination of highly oxidative Au(III) complexes.[4b,15] To our delight, that was indeed the case with bidentate ligand bipyridine (bipy) giving the desired cross-coupling product in good yield (60%, entry 7). The homocoupled product was also suppressed substantially in this case. Keeping bipy as ligand, comparable yield was obtained even with 3 mol% of catalyst loading (entry 8). Increasing the reaction temperature, however, had a deleterious effect on the outcome of the reaction (entry 9). Switching to other ancillary ligand such as 1,10-phenanthroline (phen) drastically boosted the yield of the cross-coupled product to 78% with the homodimer reduced to below 10% (entry 10). Finally, the optimum condition for the C(sp)-C(sp) cross-coupling was obtained when 15 mol% of phen was utilized (entry 11). Screening other solvents such as DCE or toluene was deemed unsuccessful (entries 12 and 13).

Table 1. Optimization studies[a]



entry	cat Au (mol%)	ligand (mol%)	solvent	yield (%)[b] **3a**	**3a'**
1	AuCl (10)	---	CH_3CN	38	44
2	---	---	CH_3CN	NR	NR
3	Ph_3PAuCl (10)	---	CH_3CN	64	23
4	IPrAuCl (10)	---	CH_3CN	trace	trace
5	JohnPhosAuCl (10)	---	CH_3CN	trace	trace
6[c]	$Ph_3PAuOTf$ (10)	---	CH_3CN	NR	NR
7	Ph_3PAuCl (10)	bipy (10)	CH_3CN	60	14
8	Ph_3PAuCl (3)	bipy (10)	CH_3CN	58	12
9[d]	Ph_3PAuCl (3)	bipy (10)	CH_3CN	35	27
10	Ph_3PAuCl (3)	phen (10)	CH_3CN	78	08
11[e]	**Ph_3PAuCl (3)**	**phen (15)**	**CH_3CN**	**87**	**≤05**
12	Ph_3PAuCl (3)	phen (15)	DCE	41	30
13	Ph_3PAuCl (3)	Phen (15)	toluene	NR	NR

a] Reaction conditions: 0.20 mmol **1a**, 0.22 mmol **2a**, degassed CH_3CN (0.11 M), 60 °C, 12 h. [b] GC yields were determined by using biphenyl as an internal standard. [c] Generated *in situ* by mixing equimolar amount of Ph_3PAuCl and AgOTf. [d] Reaction was conducted at 80 °C. [e] A mixture of CH_3CN:1,4-dioxane (3:1) was used as solvent. NR = No reaction

Having established optimized conditions, we explored the generality of the reaction. To start with, the scope of the C(sp)–C(sp) cross-coupling reaction with respect to alkynes was investigated keeping **2a** constant. As can be judged from Scheme 2, substrate scope of the reaction accommodates a diverse range of aryl-, heteroaryl-, alkenyl-, and alkyl-substituted terminal alkynes. For instance, for *p*-substituted aromatic alkynes bearing electron-donating, electron-withdrawing, halo, or alkyl substitutents furnished the conjugated diynes in excellent yields (**3b-h**, 64-85%). Next, when *o*-subtituted aromatic alkynes were used as substates, the reaction delivered **3i-l** in good to excellent yields (60-73%) irrespective of the electronic bias of the corresponding terminal alkynes. Notably, *o*-amino or *o*-hydoxymethyl substituted aromatic alkynes (**1j** and **1l**) does not produce the competing annulation product which is pretty common in case of gold catalysis indicating the mildness of the reaction conditions. Di-substituted, highly electron-rich alkynes, for instance ethynyl-3,5-dimethoxybenene and ethylnyl-1,3-benzodioxole gave the corresponding cross-coupled products in good yields (**3n** and **3o**, 63 and 70%). 3-Chloro, 4-methyl substituted aromatic alkyne was also well tolerated under the reaction condition (**3p**, 76%). Even 1-naphthyl-, 2-naphthyl-, 2-biphenyl-substituted aryl alkynes reacted smoothly to give **3q–s** in 66-86% yields. However, the reaction of alkyne bearing bulkier 1-pyrenyl group probably succumbed to its steric effects giving a rather lower yield of the desired heterocoupled product **3t** (56%). Additionally, (*E*)-1-en-3-ynylbenzene could be suitably coupled with **2a** to produce **3u** in 53% yields. Aliphatic alkynes too demonstrated acceptable tolerability (**3v-w,** 42-46%). Further, substrates such as aminaloalkynes or propargylamines were all suitable for this reaction as exemplified by **3x** (71%) and **3y** (52%). Interestingly, propargyl alcohols, which are well known substrates for Meyer-schuster reactions in gold catalysis,[16] could also be tolerated, furnishing **3z** and **3aa** in 59 and 74% yields, respectively. Sensitive substituents such as *O*-allyl or boronic acid on the aromatic alkynes did not interfere and produced the corresponding diynes **3ab** and **3ac** in 67 and 47% yields, respectively. When ynamides were subjected to optimized reaction conditions, the corresponding conjugated diynes **3ad** and **3ae** were obtained in 81 and 45% yields, respectively. The scope of the reaction was further extended to heteroaryl-substituted alkynes such as 2-thienyl- and 2-pyridyl-substituted ones furnishing **3af** and **3ah** in 66 and 64% yields, respectively. However, 2-ethynyl-1H-indole gave **3ag** exclusively in 56% yields because of the high nucleophilicity of C-3 site of indole.[11d] The practicability of the method was further tested with sugar-derived alkyne moiety. It satisfactorily produced **3ai** in 60% yield. Activated alkynes were equally compatible for the cross-coupling reaction producing **3aj** and **3ak** in 62 and 63% yields, respectively.

Next, we investigated the utility of various EBX analogues for C(sp)-C(sp) cross-coupling. Accordingly, substrate **1a** was treated with TBDMS-EBX (**2b**), TBDPS-EBX (**2c**), Ph-EBX (**2d**), and *n*Pent-EBX (**2e**) under standard reaction conditions. The reaction worked well with **2b** and **2c**, giving rise to the products **3al** and **3am** in 73 and 56% yields, respectively. However, the reaction failed to yield the desired cross-diyne product **3an** when Ph-EBX **(2d)** was employed as alkynylating agent. On the other hand, **3ao** was obtained in moderate yields with *n*Pent-EBX (**2e**). Unfortunately, two different aliphatic alkynes could not be cross-coupled to give **3ap** under this method.

Given the fact that gold(I)-acetylide was reported[9,17] to play the key intermediate in the Au(I)/Au(III) redox cycle for C(sp)-C(sp) couplings, we performed a set of control experiments with Ph_3P-ligated gold(I) acetylide complex **4** (Scheme 2a). But poor heteroselectivity and slower reaction in this case indicated that reaction may not proceed via the intermediacy of **4**. Additionally, no characteristic peak for complex **4** was observed in the ^{31}P NMR monitoring of the cross-coupling reaction between **1a** and **2a** under standard condition. In contrast, yields and heteroselectivity of the

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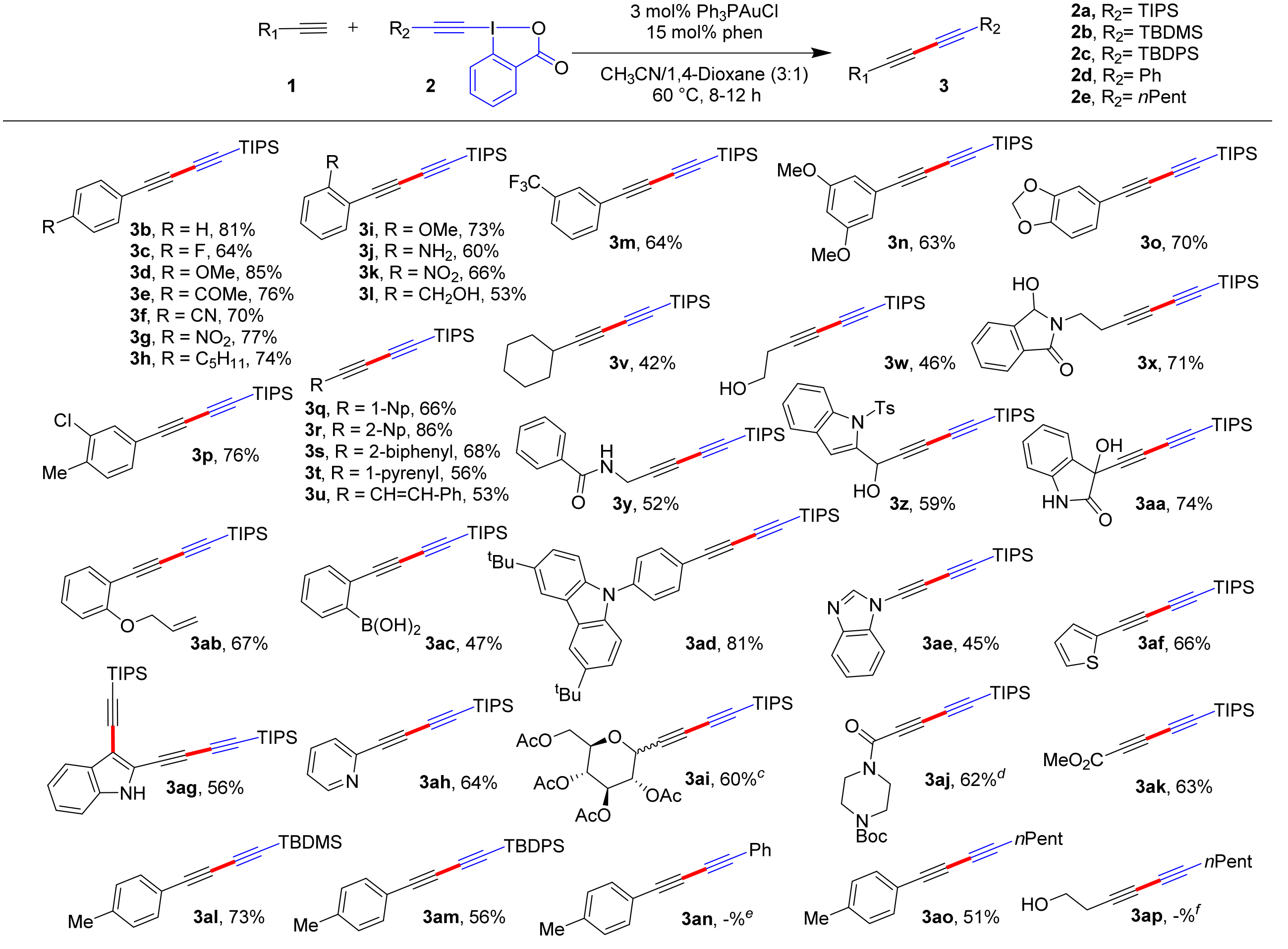
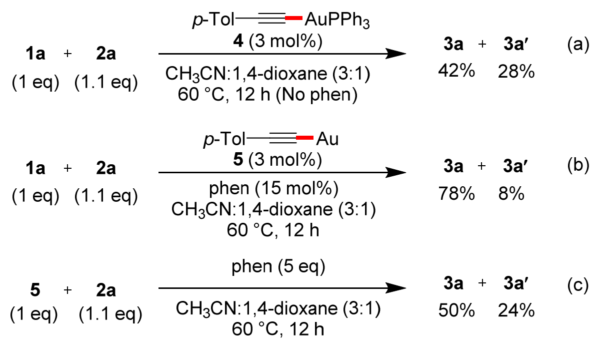
Table 2. Scope of gold catalyzed C(sp)-C(sp) cross-coupling reaction[a,b]



[a]Reaction conditions: 0.20 mmol **1**, 0.22 mmol **2**, Ph_3PAuCl (3 mol%), phen (15 mol%), degassed CH_3CN:1,4-dioxane (1.8 ml:0.6 ml), 60 °C, 8-12 h. [b]Isolated yields. [c]1:1 mixture of C-1 anomers was used as starting material. [d]Stirred for 36 h. [e]Only homocoupling product of terminal alkyne was obtained. [f]Complex mixture was obtained.



Scheme 2. Mechanistic investigation

reaction was improved with a ligand-free polymeric gold acetylide **5** (Scheme 2b)[18] in the presence of 15 mol% of phen. This probably suggests the involvement of a phen-ligated gold complex; for instance, [phen]Au(I)X **(A)** as catalytically active species (Scheme 3). Further, from Ph_3PAuCl, MALDI-TOF analysis suggests the formation of $[(phen)AuPPh_3]^+$ which could be a possible precursor for **A.**[19] Initiating from **A**, the reaction may follow two different pathways based on the order of events leading to **D** from **A** (Scheme 3). Oxidation might occur either at the stage of Au(I) salt (cycle a) or at the stage of gold(I) acetylide (cycle b). Once formed, the Au(III) species **D** then reductively eliminates to give the desired heterocoupled product **3** with regeneration of the active catalyst. At this stage, the two reaction pathways could not

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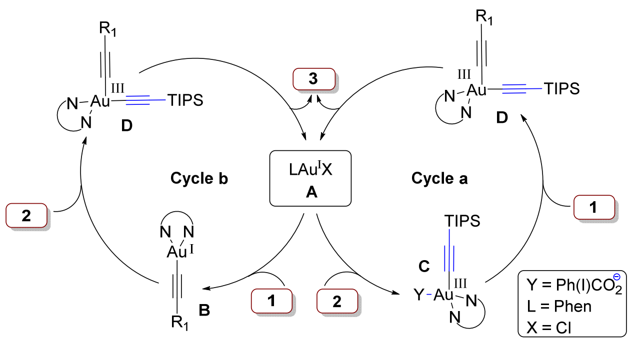
be distinguished. Nevertheless, the cross-coupled product **3a** was observed in 50% yield when reacting **5** with **2a** in a stoichiometric fashion (Scheme 2c) indicating the feasibility of gold(I) acetylide **B** formation (cycle b) prior to catalyst oxidation (cycle a). Further investigations are required to understand the precise reaction mechanism.



Scheme 3. A plausible mechanism

In conclusion, we report gold-catalyzed alkynylation of terminal alkynes with EBXs to access unsymmetrical diynes. The key feature of the work is the dual role of EBXs which serve as oxidants as well as alkyne transfer agents.

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