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Stable Au(I) catalysts for oxidant-free C-H Functionalization with Iodoarenes

R. Tyler Mertens^a, Charles E. Greif^a, James T. Coogle^a, Gilles Berger^b, Sean Parkin^a, Mark D. Watson^a, Samuel G. Awuah^{a,c,*}

^aDepartment of Chemistry, University of Kentucky, Lexington, KY 40506 USA

^bDepartment of Medicinal Chemistry, Université libre de Bruxelles

^cCenter for Pharmaceutical Research and Innovation, College of Pharmacy and Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536, USA

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ABSTRACT: The development of oxidant-free gold-catalyzed cross coupling reactions involving aryl halides have been hamstrung by the lack of gold catalysts capable of performing oxidative addition at Au(I) centers. Herein, we report the development of novel tricoordinate Au(I) catalysts supported by N,N-bidentate ligands and ligated by phosphine or arsine ligands for C-H functionalization without external oxidants to form biaryls with no homocoupling. The unsymmetrical character of the Au(I) catalyst is critical to facilitating this necessary orthogonal transformation. This study unveils yet another potential of Au(I) catalysis in biaryl synthesis.

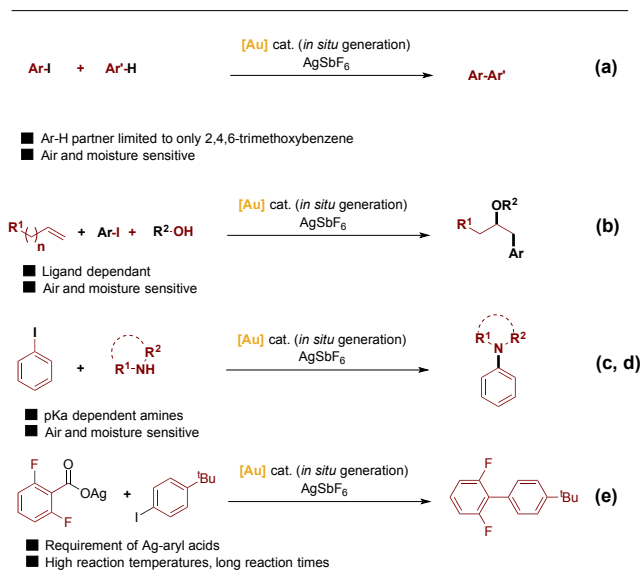
1. Introduction

Biaryl frameworks are common structural motifs found in prescribed pharmaceuticals, agrochemicals, pigments, and organic materials including light emitting diodes (LED), polymer conductors, and liquid crystals.[1, 2] Significant gains have been made in biaryl synthesis primarily using metal-catalyzed strategies that employ aryl halides (Ar¹-X) and aryl organometallic compounds (Ar²-M).[3-12] Direct arylation methods involving cross-coupling of arenes (Ar¹-H) and activated coupling partner (Ar²-M) or the use of two non-functionalized arenes (Ar¹-H) have been engaged in biaryl synthesis.[13-17] Drawbacks to these oxidative direct arylation include the formation of homocoupled side-products, low reactivity, poor selectivity, high catalyst loading, and the synthesis of specialized pre-activated coupling partners for use in the construction of complex biaryl-containing compounds. To circumvent these challenges, for example, selectivity is achieved by using excess of coupling partners and the use of directing groups.

Seminal work by Lloyd-Jones and Russell paved the way for oxidative direct arylation that invoked Au^I/Au^{III} catalysis for biaryl synthesis using simple arenes and electron-deficient arylsilanes as coupling partners.[14, 18-20] The use of gold(I)-catalyzed oxidative arylation of arenes with electron-deficient arylboronic acids further expanded the scope of oxidative direct arylation.[4, 21-23] Other gold(I)-catalyzed cross-coupling methods employing the combined strength of electron-deficient arenes and/or activated arenes with strong bases or silver salts have emerged as important routes to C – C bond formation.[24-26] [27-29] In all these methods, the use of external oxidants stifles catalytic development.[30-37]

Scheme 1. Previous reports on gold-catalyzed cross-coupling reactions and our work.

Previous work:



This Work:

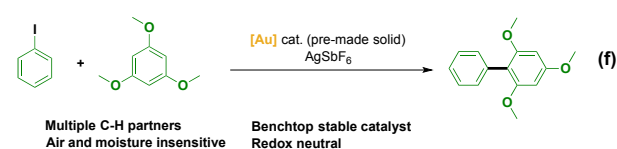


Table 1. Reaction optimization of biaryl cross-coupling

The challenge of oxidant-free gold catalysis is largely because Au(I) is sluggish in undergoing oxidative addition due to the high redox potential.[38-41] Gold-catalyzed cross-

Entry ^[a]	[Au(I)] cat, mol%	Ar-I : Ar'-H	Additive, eq.	Base	% Yield ^[b]
1	1a, 10%	1:1	AgSbF ₆ , 1	K ₃ PO ₄	62%
2	1b, 10%	1:1	AgSbF ₆ , 1	K ₃ PO ₄	trace ^{[c],[e]}
3	1a, 5%	1.5:1	AgSbF ₆ , 1	K ₃ PO ₄	88%
4	1a, 5%	2:1	AgSbF ₆ , 1	K ₃ PO ₄	73%
5	1a, 5%	1.5:2	AgSbF ₆ , 1	K ₃ PO ₄	21%
6	1a, 5%	1.5:1	AgSbF ₆ , 0.5	K ₃ PO ₄	62%
7	1a, 5%	1.5:1	AgSbF ₆ , 0.20	K ₃ PO ₄	31%
8	1a, 5%	1.5:1	no additive	K ₃ PO ₄	n.d. ^{[c],[d]}
9	1a, 5%	1.5:1	4,7-dmp, PPh ₃ (1 eq. each)	K ₃ PO ₄	n.d. ^{[c],[d]}
10	no cat.	1.5:2	AgSbF ₆ , 1	K ₃ PO ₄	n.d. ^{[c],[d]}
11	1a, 5%	1.5:1	AgBF ₄ , 1	K ₃ PO ₄	73%
12	1a, 5%	1.5:1	AgNO ₃ , 1	K ₃ PO ₄	trace ^{[c],[e]}
13	1a, 5%	1.5:1	NaOAc, 1	K ₃ PO ₄	n.d. ^{[c],[d]}
14	1a, 5%	1.5:1	NH ₄ OTf, 1	K ₃ PO ₄	n.d. ^{[c],[d]}
15	1a, 5%	1.5:1	AgSbF ₆ , 1	Cs ₂ CO ₃	73%
16	1a, 5%	1.5:1	AgSbF ₆ , 1	NaO ^t Bu	71%
17	1a, 5%	1.5:1	AgSbF ₆ , 1	Et ₃ N	34%

[a] all reactions were performed at 90 °C for 2 hours in aerobic conditions, [b] unless noted otherwise, all yields were isolated yields after column chromatography, [c] yields based on GC-MS using dodecane (0.022 mmol) as an internal standard, [d] n.d. = not detected upon GC-MS analysis, [e] trace = < 5% detected by GC-MS

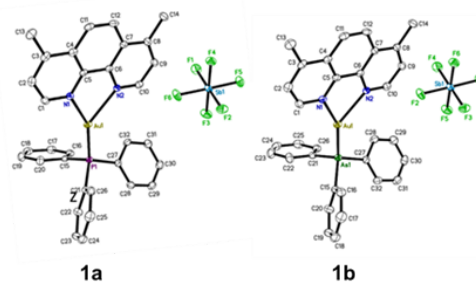
coupling methods that are oxidant-free is an attractive and burgeoning area of research with great promise. Pioneering work by Hashmi and co-workers demonstrated visible light gold(I)-catalyzed C-C cross coupling using aryldiazonium salts without a photosensitizer and the proof of oxidative addition of diazonium salts at gold(I) centers to access organogold(III) complexes.[42-44] Importantly, this photosensitizer-free gold catalysis does not use external oxidants and has been used to synthesize biaryls under mild conditions using substrates with halogen or boronic acid functionality.[45-47] Bourissou and Toste stimulated the pursuit of oxidative addition at gold(I) centers.[15, 48, 49] Gold(I) compounds with tricoordinate configurations were shown to be activated towards oxidative addition by aryl halides and pi systems.[15, 18, 50] The use of hemilabile gold(I) catalysts efficiently promote cross-coupling reactions of electron-rich arenes with aryl iodides (**Scheme 1a**).[15] A remarkable study by Russell et al. led to the establishment of elementary organometallic transformations (oxidative addition, transmetalation, reductive elimination) using bipyridine gold(I) complexed to homoleptic gold ethylene in stoichiometric amounts.[18] Patil et al. demonstrated gold-catalyzed 1,2-heteroarylation of alkenes (**Scheme 1b**) using ligand enabled (MeDalphos)AuCl catalyst, which was further applied to C(sp²)-N cross coupling transformations (**Scheme 1c** and **1d**)[51-54]. Also within the last year, a decarboxylative cross-coupling of iodoarenes was detailed by Topcsewzki and co-workers (**Scheme 1e**).[55] Recently, Shen et al. proposed a diaryl gold-catalyzed reaction to form a C(sp²)-X cross coupled product, where X is a halide.[55] All together, these recent efforts on oxidative

addition to gold(I) have opened new opportunities for gold in cross-coupling reactions. The development of catalysts capable of direct arylation without external oxidants is an unmet need in gold-catalysis toward biaryl synthesis.

We report herein the synthesis of novel three coordinate gold(I) catalysts that are shelf-stable for the direct arylation of simple arenes (Ar'-H) with aryl iodides (Ar-X) to afford biaryls (Ar-Ar') (**Scheme 1f**). The reactions are of good yield and can be carried out in air/moisture. The tolerability of the reaction to other functional groups makes this strategy particularly useful. The catalyst makes use of a 4,7-dimethylphenanthroline (4,7-dmp) ligand coordinated to Au(I) center and ligated to phosphine or arsenic ancillary ligands. Notably, degree of distortion imposed by phosphine or arsenic affects catalyst stability and performance with isolated yields up to >80%.

2. Experimental

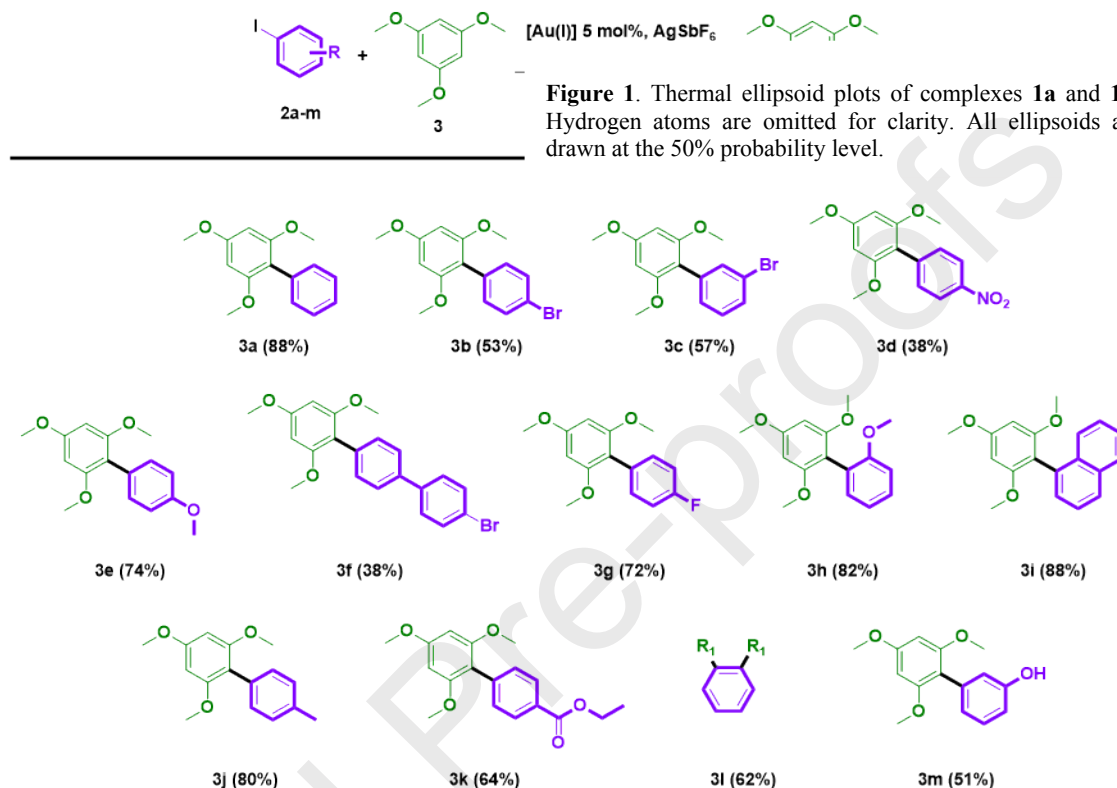
2.1 Catalyst Development



We sought to develop an air-stable three coordinate gold(I) catalyst for direct arylation ($C(sp^2) - C(sp^2)$ cross-coupling) due to their significantly unsymmetrical character that facilitate oxidative addition to arylhalides. Earlier work by Uson et al. and recently by Russell et al. and Hashmi et al. provided impetus to investigate the stability and catalytic performance of

and **1b** reveal a tricoordinate gold complex in trigonal planar orientation with unsymmetrical character. The Au-N bond length in **1a** and **1b** differed from each other, with **1a** displaying a shorter bond length (2.400(2) Å) than that of **1b** (2.511(12) Å). This is indicative of a weaker Au-N bond strength in **1b** which corresponds to overall less stability of the complex.

Scheme 2. Substrate scope of aryl-iodides



bipyridyl gold(I) ligated by Group 15 ligands based on arsenic or phosphorus.[18, 50, 56] We rationalized that these elements vary in σ -donor strength and size, which are capable of distorting the tricoordinate geometry and promote reactivity. The improved stability of the overall complex will subsequently deliver a catalytic outcome without external oxidants or photoredox catalysis as commonly seen with gold(I) arylations. The synthesis of compounds **1a** ($[Au(4,7-dmp)PPh_3][SbF_6]$) and **1b** ($[Au(4,7-dmp)AsPh_3][SbF_6]$) were achieved using ligand substitutions that included chloride abstraction by silver (Fig. 1). Briefly, gold(I) compounds bearing triphenylarsine or triphenylphosphine ligands ($ClAuAsPh_3$ and $ClAuPPh_3$) were reacted with 4,7-dimethylphenanthroline (4,7-dmp) and silver hexafluoroantimonate in dichloromethane at room temperature for 30 minutes. After centrifugation of the silver chloride generated, the target complexes were precipitated by the addition of diethyl ether as off-white solids. The compounds were fully characterized by 1H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy (Figures S4 – S58), and high-resolution mass spectrometry (Figure S59).

2.2 Crystal Growth and Analysis

Single crystals of **1a** and **1b** (Fig. 1) were grown by vapor diffusion of diethyl ether into a solution of concentrated gold complex in acetonitrile for analysis by X-ray diffraction to determine the molecular structure. The crystal structures of **1a**

Additionally, the gold-arsine bond is longer; (Au-As bond length (2.275(6) Å), illustrating further instability of the complex. Overall, complex **1b** is less stable in solution over time, exhibiting rapid deposition to elemental gold on glassware. The observed bond angles and lengths were consistent with other three coordinate complexes prepared by different methods. We hypothesized that the unsymmetrical character due to the weaker Au-N2 bond length relative to Au-N1, coupled with the stronger Au-P bond (2.2179(6) Å) in **1a** will promote oxidative addition and enhance catalytic performance in direct arylation reactions.

2.3 Catalytic Optimization

We explored the feasibility of a direct $C(sp^2) - C(sp^2)$ cross-coupling using simple arenes and aryl iodides by investigating the model reaction between iodobenzene (**2a**) and 2,4,6-trimethoxybenzene (TMB, **3**) under various experimental conditions. Preliminary investigations based on a previous arylation protocol using a catalytic mixture of $[Au(4,7-dmp)PPh_3][SbF_6]$ (**1a**) and additive $AgSbF_6$ in CH_3CN was very exciting and compelled us to consider other conditions. Initially, biaryl **3a** was obtained in moderate yields using 1,2-dichloroethane (DCE) and by adding a base, K_3PO_4 (Table 1, entry 1) with 10 mol% catalyst loading (62%). When **1b** was used as catalyst, the formation of **3a** was possible but in trace yields (Table 1, entry 2). The substantial increase in yields between **1a** and **1b** is as a result of the change in ancillary

ligands from PPh_3 to AsPh_3 , suggesting that the role of the donor ligand in stabilizing the gold center or the degree of distortion of the Au-N bond that led to unsymmetrical gold catalyst may be critical for catalytic performance.

We then sought to lower the catalyst loading and subsequently optimize ratios between coupling partners **2a** and **3**. When 1.5 equivalents of aryl-iodide was used, we were able to improve overall yield of **3a** even at 5 mol% catalyst loading (Table 1, entry 3). The reaction will still proceed even with 1 mol% Au(I) catalyst; however, at reduced yield (41%, Table S3, entry 3). Subsequent optimizations proved that the ratio of aryl-iodide to Ar-H (1.5:1) were crucial, as excess aryl-iodide (Table 1, entry 4) and excess TMB (Table 1, entry 5) resulted in loss of yield of the biaryl product **3a** (see Table S4, entries 1-7 for complete optimization of stoichiometric equivalents of Ar-I and Ar'-H). Next, changing stoichiometric amounts of AgSbF_6 afforded the biaryl product; however, in less yield than when using 1 equivalent (Table 1, entries 6-7).

Control experiments regarding the role of silver, gold catalyst, and ligands were also performed (Table 1, entries 8-10) to ensure the catalytic transformation was not due to trace metal contamination or the organic framework alone. Further studies using different additives and bases were studied (Table entries 11-17 and Figs. S1&S2).

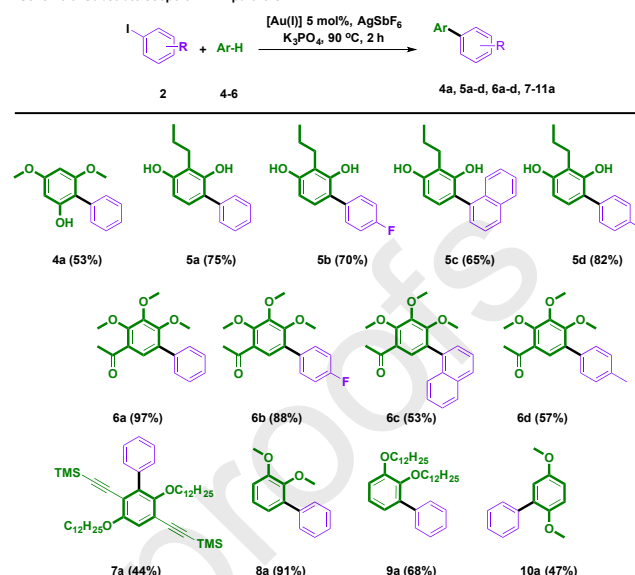
2.4 Expanding Substrate Scope

We first investigated the substrate scope of the aryl iodides as shown in Scheme 2. The use of TMB and iodobenzene gave rise to **3a** in excellent isolatable yield (88%). Similarly, the use of substituted iodoarenes bearing electron donating or electron withdrawing groups gave good to excellent yields. Functional groups such as phenols and ethyl benzoates afforded respectable yields, giving rise to functional group tolerance. The reaction did not discriminate on the position of the iodo-substituents on the benzene ring; *ortho*, *meta*, and *para* substituents all gave acceptable yields. Analysis of the reaction in the presence of bromides and chlorides, suggest that the initial oxidative addition is chemoselective for iodoarenes. Reactions with bulkier groups such as naphthalene and biphenyl also afforded the cross-coupled products in moderate yields. Further exploration resulted in successfully cross coupling two TMB moieties with di-iodobenzene, confirmed by GC-MS (Figure S3) and isolated with column chromatography. Altogether, the reaction presented allows for a diverse use of aryl-iodides to afford unique biaryls (**3a-m**) on moderate to high yields.

Next, we investigated the scope of classes of arenes to undergo an oxidant free, gold-catalyzed C-H activation with iodobenzene (Scheme 3). Given that previous reports of gold catalyzed C-H activation used TMB and other electron rich compounds including indoles as substrates, [15] we sought to expand the arenes with our catalytic system. This will enable a broader library of biaryls to be generated. We screened a variety of electron rich arenes and found the electron donor character of the substituents influenced the rate of reaction. The use of a derivative of TMB, 3,5-dimethoxyphenol underwent C-H functionalization with iodobenzene to afford the target compound (**4a**) in moderate yield. Upon analysis, only the carbon *ortho* to the phenol underwent substitution and was subsequently isolated and well-characterized. The stronger para-directing methoxy substituent may contribute to the observed regioselectivity. Given the success with 3,5-

dimethoxyphenol, we examined the outcome of C-H activation using 2-n-propylresorcinol as a coupling partner. To our delight, this transformation worked across 4 different aryl-iodides tested, illustrating the robust capability of the catalytic reaction (**5a-d**).

Scheme 3. Substrate scope of Ar'-H partners



We used 2,3,4-trimethoxyacetophenone, as another C-H partner. We found that this framework undergoes C-H activation with multiple aryl-iodides bearing different substituents ranging from electron donating to electron withdrawing ones (**6a-d**). We further confirmed selective arylation to the carbon which is meta to the acetyl group with the use of HMBC (Figures S52, S55, and S58). Interestingly, fluoro-substituted arenes can undergo C-H functionalization under these conditions. Additionally, we expanded the substrate scope to include dialkoxy benzenes with implications for polymer materials as shown in **7a** bearing the trimethylsilylacetylene and dodecyloxy functionality and **8a**, **9a** and **10a**. We observed that para-substituted alkoxy arenes afford lower yields compared to 1,2-alkoxy arenes. This could be attributed to electronic factors that contribute to electron-rich carbon sites for C-H activation in 1,2-alkoxy arenes compared to their 1,4-alkoxy arene counterparts.

3.0 Conclusions

In conclusion, we report the use of pre-formed tricoordinate Au(I) complexes to catalyze the formation of biaryls through C(sp²)-C(sp²) coupling under aerobic conditions. This work expands upon previous reports of gold-catalyzed C(sp²)-C(sp²) cross-coupling. We are able to demonstrate functional group tolerance, a broad scope of acceptable iodoarenes which vary in donor properties and are able to expand the scope of C-H activation partners. Plausible mechanisms associated with the described hydroarylation put forth in this work may be mediated by i) aryl-halide oxidative addition to Au(I) center or ii) dual Au-Ag catalysis as described by Hashmi and Zhu.[57-60]. Considerable research effort is ongoing to elucidate the mechanism of the C-H functionalization by reaction kinetics and labeling experiments to be reported appropriately. Taken together, this work provides fundamental experimentation that can be further developed and applied to different catalytic cycles and applications.

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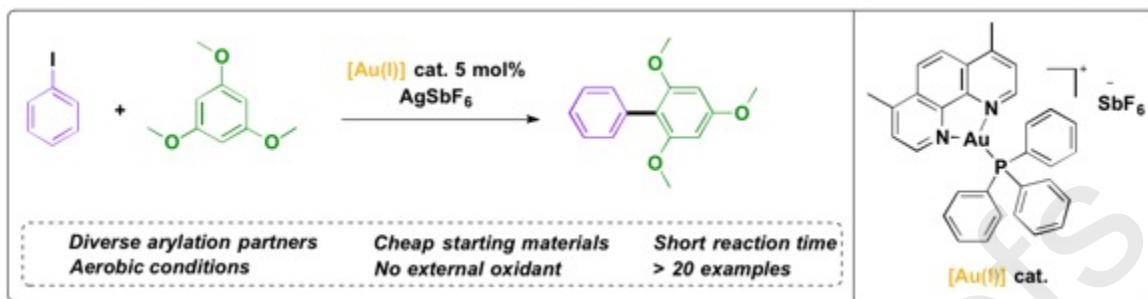
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Graphical abstract



Highlights

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- Redox neutral, oxidant-free gold catalysis
 - Homogenous catalysis under aerobic conditions by distorted tri-coordinate Au(I) catalyst
 - Air-, bench-stable gold catalysts
 - Biaryl synthesis of aryl-iodide and C-H arene coupling partners providing moderate to high yields

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Samuel G. Awuah reports financial support was provided by University of Kentucky. Samuel G. Awuah reports a relationship with University of Kentucky that includes: funding grants. Samuel G. Awuah has patent THREE-COORDINATE AU(I) PROBES AND USE IN SELECTIVELY DISRUPTING MITOCHONDRIA IN CANCER CELLS pending to University of Kentucky Research Foundatio.

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