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Gold-Catalyzed Tandem Oxidative Coupling Reaction between β-Ketoallenes and Electron-Rich Arenes to 2-Furylmethylarenes

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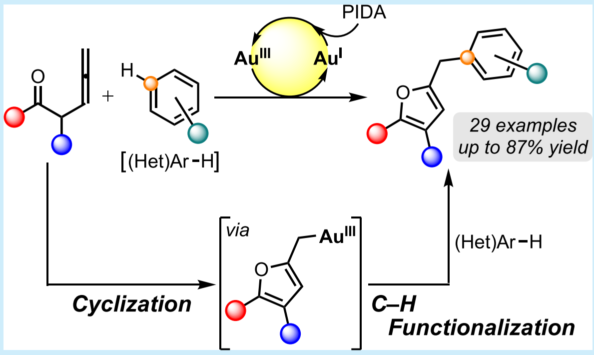
ABSTRACT: A tandem oxidative coupling reaction of β-ketoallenes and arenes was developed, which leads to the formation of 2-furylmethylarenes using $AuCl_3$ and phenyliodine diacetate. The Au^{III} salt catalyzed the cyclization of β-ketoallenes to form a 2-furylmethyl gold intermediate, and the subsequent C−H functionalization of arenes proceeded smoothly. During the oxidative coupling, nucleophilic additions occurred at the center and terminal carbon atoms of the allene moiety to form C−O and C−C bonds.



Biarylmethanes are ubiquitous and important chemical motifs for various functional materials, such as biologically active compounds, pharmaceuticals, and polymers.[1] Among them, 2-furylmethylarenes as furan-based biarylmethane derivatives also exhibit useful bioactivities (Scheme 1A).[2−4] Gold salt catalysts possessing the π-activation ability of C−C multiple bonds have emerged as powerful tools for accessing various heterocyclic skeletons via the intramolecular cyclization of alkynyl or allenyl substrates bearing heteroatoms (hydroxy and carbonyl functionalities) within the same molecule.[5−8] β-Ketoallenes also could undergo the gold-catalyzed intramolecular cyclization to provide multisubstituted furans.[6] These traditional gold-catalyzed reactions have been applied to construct complicated 2-furylmethylarenes by using tandem reactions. Some examples of such reactions are the intramolecular cyclization of 1-oxiranyl-2-alkynyl acetates and the subsequent Friedel−Crafts arylation (Scheme 1B-a),[7] as well as the cyclization of *N*-(2-alkynylphenyl)imines accompanied by the addition of vinyldiazo ketones and the subsequent furan ring construction via 1,3-group migration (Scheme 1B-b).[8] Meanwhile, the Au^I/Au^{III} catalytic system using additional oxidants can achieve a remarkable intermolecular cross-coupling reaction based on the oxidative C−H functionalization of arenes.[9,10] Following the pioneering discovery of the gold-catalyzed oxidative $C(sp^2)−C(sp)$ cross-coupling between arenes and terminal alkynes to ethynylarenes,[10a] the C−H alkynylation of furans[10b] and various C−H arylations of arenes with aryl silanes,[10c,d] aryl boronic acids,[10e,f] aryl halides,[10g] aryl germanes,[10h] and other arenes[10i] to (hetero)-biaryls have been reported. Additionally, the gold-catalyzed oxi/amino-arylation of alkenes via the intramolecular cyclization and subsequent oxidative coupling of aryl boronic acids[11a−c] or aryl silanes[11d] using Selectfluor as an oxidant has been accomplished to afford 2-arylmethyl-substituted heterocyclic compounds (Scheme 1C). Photoredox/gold dual catalysis using aryl diazonium salts[12] and a Au^I/Au^{III} catalytic system with P and N ligands and aryl iodides[13] has also been applied to the oxi/amino-arylation of alkenes. Herein, we demonstrate a novel synthetic method for 2-furylmethylarenes (**2**) via the gold ($AuCl_3$)-catalyzed cycloisomerization of β-ketoallenes (**1**) and subsequent C−H functionalization of arenes (benzene and indole derivatives) in the presence of phenyliodine diacetate (PIDA) as an oxidant (Scheme 1D). During the oxidative coupling presented here, the allenyl moiety acted as a bis-electrophile. The double nucleophilic substitutions at the center and terminal carbon atoms of β-ketoallenes (**1**) occurred in tandem to form C−O and C−C bonds.

The reaction conditions for the synthesis of a 2-furylmethylbenzene derivative (**2a**) using 1-phenylpenta-3,4-dien-1-one (**1a**) as a β-ketoallene substrate and 1,3,5-trimethoxybenzene (5 equiv) as an arene nucleophile were optimized (Table 1). The reaction using $AuCl_3$ (10 mol %) in CH_2Cl_2 (0.4 M) at room temperature for 24 h afforded the desired product (**2a**) in 38% yield, along with the formation of 2-methyl-5-phenylfuran (**3a**) in 41% yield as a protonated

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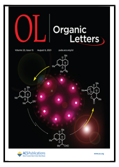

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Scheme 1

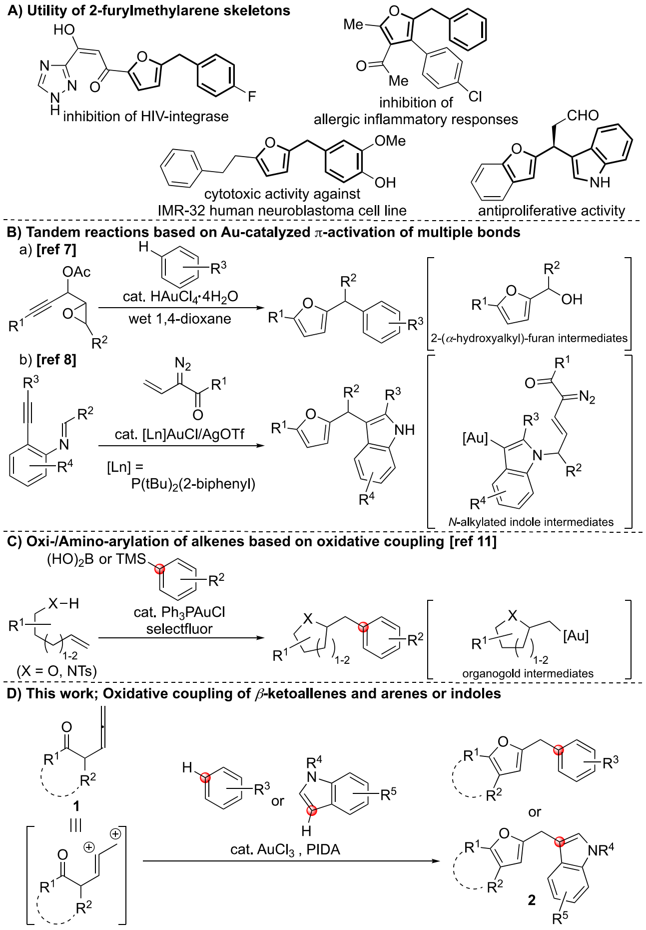
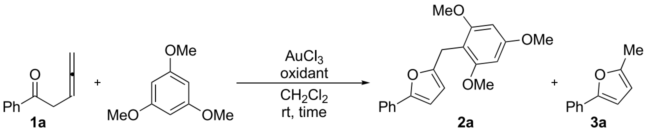


Table 1. Optimization of the Reaction Conditions[a]



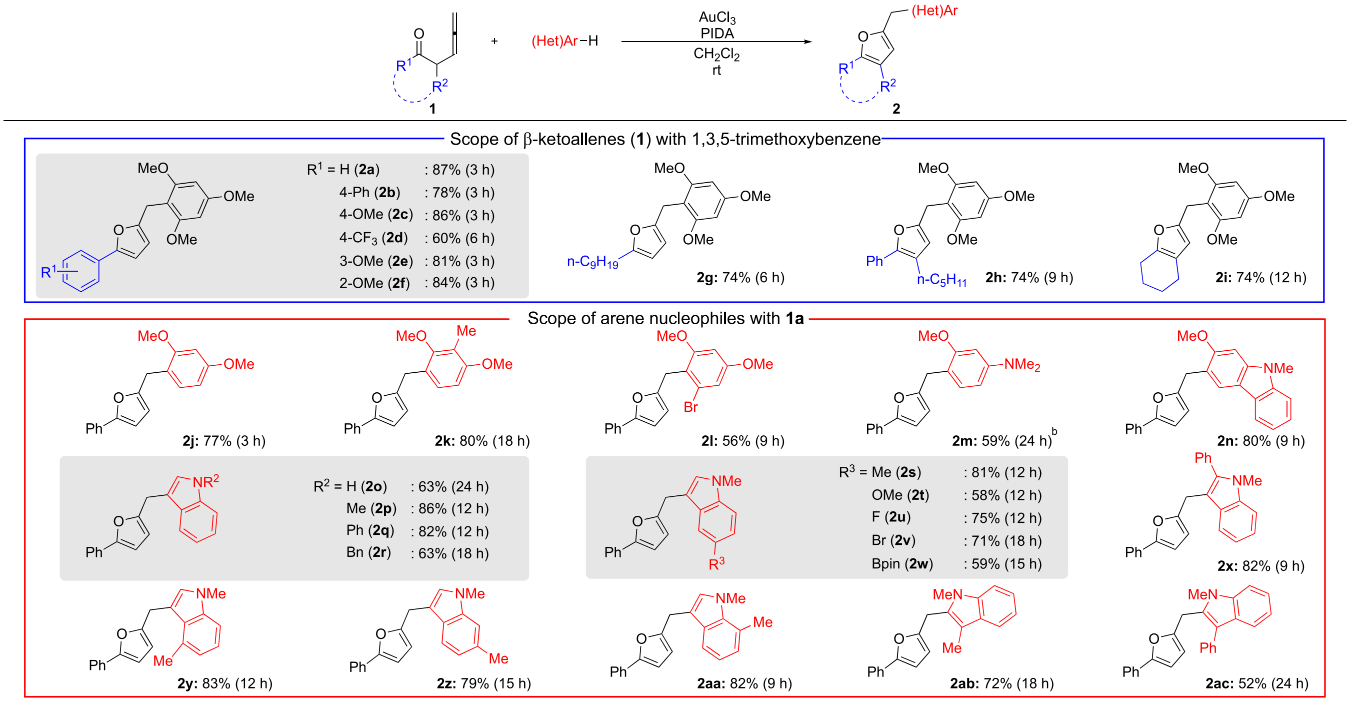
entry	oxidant (equiv)	time (h)	yield (%)[b] 1a	2a	3a
1	–	24	0	38	41
2[c]	–	24	99	0	0
3[c,d]	–	24	0	0	85
4	PIDA (1.2)	1.5	0	75	3
5	PIFA (1.2)	3	3	57	0
6	PhIO (1.2)	12	22	55	0
7	Selectfluor (1.2)	3	0	32	25
8	*t*-BuOOH (1.2)	12	3	39	4
9	PIDA (1.0)	1.5	0	73	5
10	PIDA (0.75)	3	2	62	12
11[e]	PIDA (1.0)	1.5	0	86	4
12[e,f]	PIDA (1.0)	3	0	87	5
13[e−g]	PIDA (1.0)	1.5	0	75	1
14[e,h]	PIDA (1.0)	12	98	0	0
15[e,i]	PIDA (1.0)	3	4	79	5

[a] The reaction was carried out with **1a** (0.1 mmol, 1 equiv), 1,3,5-trimethoxybenzene (5 equiv), and $AuCl_3$ (10 mol %) in CH_2Cl_2 (0.4 M) at room temperature. [b] Isolated yield. [c] Ph_3PAuCl (10 mol %) was used instead of $AuCl_3$. [d] $AgSbF_6$ (10 mol %) was added. [e] In 0.1 M CH_2Cl_2. [f] $AuCl_3$ (5 mol %) was used. [g] 1,3,5-Trimethoxybenzene (2 equiv) was used. [h] Without $AuCl_3$. [i] With 1 mmol of **1a**. See the Supporting Information for a further detailed optimization.

byproduct (entry 1). In contrast, Ph_3PAuCl and $Ph_3PAuCl/AgSbF_6$ as catalysts were ineffective for producing **2a** (entries 2 and 3, respectively). The C−H functionalization of arene was reported to be performed by the interaction with the Au^{III} species. The generated Au^{I} needed to be oxidized to Au^{III} to promote the catalytic cycle (Scheme 3).[9−11,14] The addition of PIDA, phenyliodine bistrifluoroacetate (PIFA), or iodosobenzene as a hypervalent iodine oxidant (1.2 equiv) improved the yields of **2a** (entry 1 vs entries 4−6), while Selectfluor and *tert*-butyl hydroperoxide were ineffective as additives (entries 7 and 8, respectively). Decreasing the PIDA load to 1.0 equiv was also found to be effective (entry 9), and a further decrease in the amount of PIDA to 0.75 equiv caused the slight increase in the amount of **3a** as a byproduct (entry 10). A lower concentration of **1a** (0.1 M in CH_2Cl_2) improved the reaction efficiency to afford **2a** in 86% yield (entry 9 vs entry 11), and decreasing the amount of $AuCl_3$ added to 5 mol % maintained the catalytic efficiency and afforded 87% **2a** (entry 12). The use of 2 equiv of 1,3,5-trimethoxybenzene also provided **2a** in 75% yield (entry 13). The reaction without $AuCl_3$ in the presence of PIDA did not afford **2a**, and **1a** was quantitatively recovered (entry 14). The scale-up reaction of **1a** (1 mmol) with **2a** could be successfully performed to afford **2a** in 79% yield (entry 15).

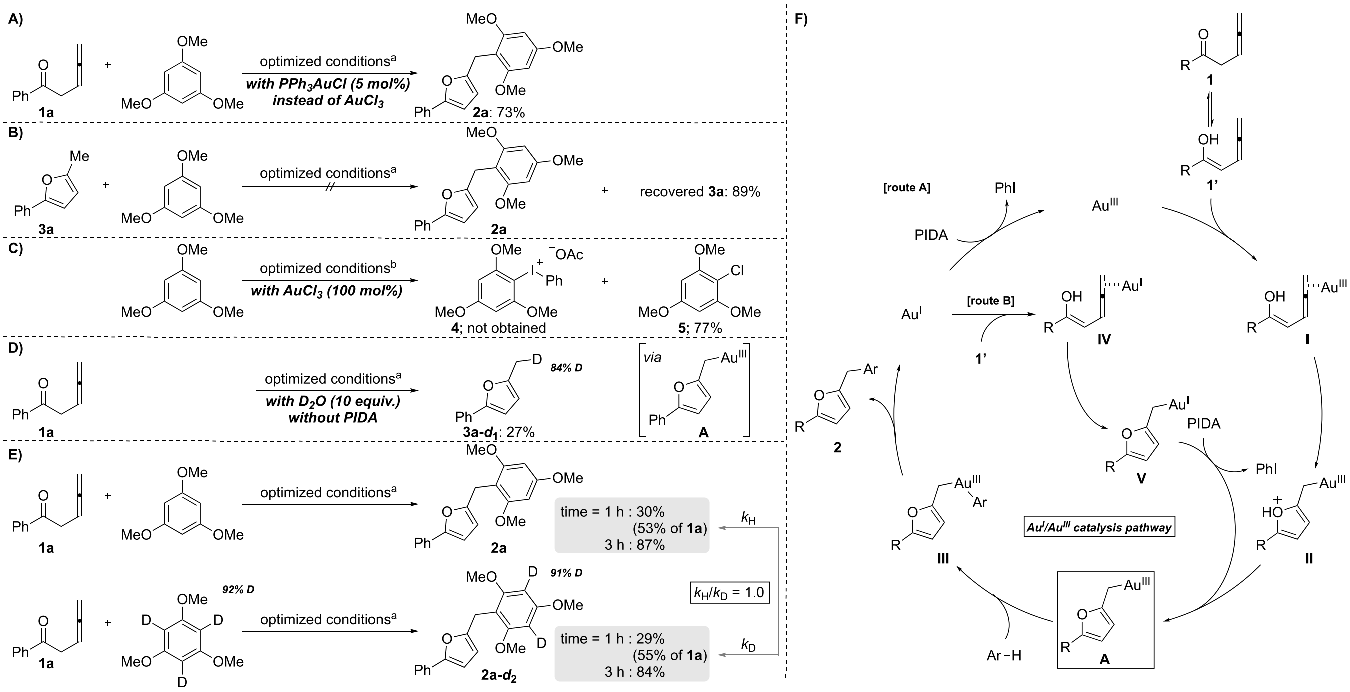
The scope of β-ketoallenes [penta-3,4-dien-1-one (**1**)] with 1,3,5-trimethoxybenzene was investigated next (Scheme 2, top). Various 1-arylpenta-3,4-dien-1-one derivatives (**1b**−**1f**) bearing electron-donating and electron-withdrawing groups at the *para*, *meta*, or *ortho* position of each aromatic nucleus efficiently underwent oxidative coupling to afford the corresponding 2-(5-arylfuryl)methylbenzene derivatives (**2b**−**2f**) in good yields. 1-Nonylpenta-3,4-dien-1-one (**1g**) also reacted with 1,3,5-trimethoxybenzene to form the desired product (**2g**). Furthermore, the reaction allowed the construction of 2-furylmethylbenzenes (**2h** and **2i**) containing a trisubstituted furan ring. The oxidative C−H functionalization of various (hetero)arene nucleophiles with β-ketoallene (**1a**) proceeded to form the corresponding 2-furylmethylarenes [benzylfurans and indolylmethylfurans (Scheme 2, bottom)]. 1,3-Dimethoxybenzene, 2,6-dimethoxytoluene, 1-bromo-3,5-dimethoxybenzene, and 3-methoxy-*N*,*N*-dimethylaniline combined with **1a** to form the corresponding products (**2j**−**2m**) in moderate to high yields and with good regioselectivities. 5-Methoxycarbazole was also applicable to the present reaction as an arene nucleophile to afford the desired bisheteroarylmethane (**2n**). Simple indole and *N*-Me-, *N*-Ph-, or *N*-Bn-indole derivatives smoothly coupled with **1a** at position 3 of the indole nucleus (**2o**−**2r**), and the yield of the reaction using *N*-Me indole was higher. Therefore, the scope of the *N*-Me indole derivative bearing the various substituents was investigated to give the desired product (**2s**−**2aa**) without the effect of electronic or steric influences based on various substitutions. Notably, the aromatic halides (**2u** and **2v**) and boryl groups (**2w**), which can be transformed into various functional groups, were tolerant under the reaction conditions presented here. Meanwhile, reactions using 3-substituted indoles provided 2-adducts (**2ab** and **2ac**). These regioselectivities are consistent with the properties of electrophilic aromatic substitution.[15]

Scheme 2. Scope of Substrates[a]



[a]The reaction was carried out with **1a** (0.1 mmol, 1 equiv), an arene nucleophile (5 equiv), PIDA (1 equiv), and AuCl$_3$ (5 mol %) in CH$_2$Cl$_2$ (0.1 M) at room temperature. [b]AuCl$_3$ (10 mol %) was used.

Scheme 3. Mechanistic Studies and Proposed Reaction Mechanism



[a]The reaction was carried out with **1a** (0.1 mmol, 1 equiv), 1,3,5-trimethoxybenzene (5 equiv), PIDA (1 equiv), and AuCl$_3$ (5 mol %) in CH$_2$Cl$_2$ (0.1 M) at room temperature. [b]The reaction was carried out with 1,3,5-trimethoxybenzene (0.2 mmol), PIDA (0.1 mmol), and AuCl$_3$ (0.1 mmol) in CH$_2$Cl$_2$ (0.1 M) at room temperature to give **5** (0.077 mmol).

The reaction of **1a** with a combination of Ph$_3$PAuCl as a one-valent gold catalyst and PIDA afforded **2a** in 73% yield (Scheme 3A), while **1a** was not converted to **2a** without the addition of PIDA (Table 1, entry 2). Moreover, 2-methyl-5-phenylfuran (**3a**) was not transformed to **2a** under the optimized AuCl$_3$-catalyzed reaction conditions, and 89% of **3a** was recovered (Scheme 3B). Although electron-rich arenes have been reported to react with PIDA to form a diaryliodonium salt,[16] the diaryliodonium salts (**4**) derived from 1,3,5-trimethoxybenzene and PIDA in the presence of AuCl$_3$

(100 mol %) could not be detected during this reaction in the absence of **1a** and 2,4,6-trimethoxychlorobenzene (**5**) was obtained in 77% yield (Scheme 3C) However, during the key reaction of β-ketoallene (**1**) and 1,3,5-trimethoxybenzene presented here, **5** or 2-furylmethylarene derived from **5** could not be detected, which indicates that gold species preferentially activated β-ketoallenes rather than arene nucleophiles under the optimized reaction conditions. These results also confirm that PIDA acts as an oxidant to convert the Au^{I} species to a Au^{III} species, thereby promoting the oxidative coupling of β-ketoallenes and arenes. The addition of deuterium oxide (D_2O) under the optimized conditions without arene and PIDA provided a deuterium-incorporated product (**3a**-d_1) generated after deuterodeauration of the 2-furylmethyl gold intermediate (**A**), which was formed by the gold-catalyzed intramolecular 5-exocyclization of **1a** (Scheme 3D). Because the reaction rates using nonlabeled and deuterium-labeled[17] 1,3,5-trimethoxybenzene were quite similar [H/D kinetic isotope effect (KIE, k_H/k_D) of 1.0] (Scheme 3E), C−H functionalization of arene would not be the rate-determining step.

The possible catalytic cycles based on these experiments are shown in Scheme 3F.[18] The β-ketoallene (**1**) is converted into the enol intermediate (**1′**).[6] Then, coordination of $AuCl_3$ with **1′** forms a gold−allene complex (**I**), which undergoes intramolecular 5-exocyclization to form **II**, and the subsequent olefin isomerization to afford a 2-furylmethyl Au^{III} intermediate (**A**). C(sp^2)−H auration of arene proceeds via electrophilic aromatic substitution (S_EAr) on the gold species to afford complex **III**,[10] and subsequent reductive elimination produces **2** together with the Au^{I} species. PIDA oxidizes the Au^{I} species to regenerate the Au^{III} species (route A). Alternatively, in situ-generated Au^{I} species can also coordinate with **1′** to form gold−allene complex **IV**, and subsequent intramolecular 5-exocycloisomerization produces Au^{I} intermediate **V**. Subsequent oxidation of Au^{I} intermediate **V** by PIDA affords Au^{III} intermediate **A** in a manner similar to that shown in ref 18 (route B). As the result of PIDA-mediated oxidation of Ph_3PAuCl as a Au^{I} species, iodobenzene as a reduced form of PIDA was obtained in <10% yield (see the Supporting Information). Therefore, route B might be the major route; however, route A cannot be completely ruled out. In contrast, the $AuCl_3$ (10 mol %)-catalyzed reaction of **1** with 1,3,5-trimethoxybenzene in the absence of PIDA afforded **2** in 38% yield (Table 1, entry 1). The reason is unclear (the proposed reaction mechanism is described in the Supporting Information).

In conclusion, we have developed an efficient synthesis of 2-furylmethylarene derivatives via the gold-catalyzed oxidative coupling of β-ketoallenes and arenes (benzene and indole derivatives). Highly functionalized furan derivatives were efficiently constructed in good to excellent yields in the presence of catalytic $AuCl_3$ and PIDA at room temperature. This novel synthetic method can be efficiently applied to synthesize various furan-based biarylmethanes by choosing the appropriate arene nucleophiles, such as electron-rich benzene, indole, or carbazole nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02007.

General information, preparation of substrates, typical procedures in gold-catalyzed 2-furylmethylarene synthesis, optimization of gold-catalyzed 2-furylmethylarene synthesis, spectroscopic data of the synthesized products, mechanistic studies and the proposed reaction mechanism, kinetic isotope effect (KIE) experiments, limitation of substrates, scale-up reaction, references, and ^1H and ^{13}C NMR spectra of the newly synthesized substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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