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# Gold-Catalyzed Cadiot–Chodkiewicz-Type Cross-Coupling of Terminal Alkynes with Alkynyl Hypervalent Iodine Reagents: Highly Selective Synthesis of Unsymmetrical 1,3-Diynes

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**Abstract:** A new and efficient method for the synthesis of unsymmetrical 1,3-butadiynes by gold-catalyzed C(sp)-C(sp)cross-coupling of terminal alkynes with alkynyl hypervalent iodine(III) reagents has been developed. The reaction features high selectivity and efficiency, mild reaction conditions, wide substrate scope, and functional-group compatibility, and is a highly attractive complement to existing methods. Mechanistic studies reveal that formation of a phenanthrolinyl-ligated gold(I) complex is crucial for the efficiency and selectivity of the target transformation.

Transition metal catalyzed cross-coupling reactions for access to useful carbon frameworks constitute an important area in organic synthesis. Conjugated 1,3-diynes and polyynes are attractive compounds since they are frequently found in biologically active substances and natural products.<sup>[1]</sup> They have also shown a wide application in advanced organic materials, organic synthesis, and organometallic chemistry.<sup>[2]</sup> Therefore, the development of efficient methods for the construction of conjugated divnes has gained much attention.<sup>[3]</sup> The most challenging aspect in this area is the development of an efficient synthesis of unsymmetrical 1,3diynes with a high level of selectivity control, as the undesired symmetrically substituted products by homocoupling can be competitively formed and are difficult to separate from the cross-coupling products. These compounds are synthesized mainly by Glaser-Hay coupling<sup>[4]</sup> and Cadiot-Chodkiewicz<sup>[5]</sup> coupling. Classical Glaser-Hay coupling is usually used for homocoupling. Recent progress in this chemistry proved that Cu- or Ni/Cu-based catalytic systems are efficient for the oxidative heterocoupling of terminal alkynes.<sup>[6]</sup> However, these reactions usually require a large excess of one of the terminal alkynes.<sup>[6b,c]</sup> Cadiot-Chodkiewicz reactions of haloalkynes with terminal alkynes are often employed in the synthesis of unsymmetrical diynes, however, they usually suffer from complex reaction conditions,<sup>[1,5,7]</sup> undesired halogen-metal exchange reactions,<sup>[7]</sup> poor selectivity,<sup>[3a]</sup> etc. Various modifications, including Pd/Cu catalysis,<sup>[8c]</sup> have been

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developed recently to improve the efficiency of this reaction.  $\ensuremath{^{[8]}}$ 

Recently, gold-catalyzed C–C coupling reactions involving gold redox processes using either Selectfluor<sup>[9]</sup> or hypervalent iodine(III) reagents<sup>[10]</sup> as the oxidants, as well as the use of photoredox<sup>[11]</sup> conditions, have emerged as attractive methodologies for access to various functional groups because no prefunctionalization of the C–H substrates is needed.<sup>[12]</sup> In 2014, Shi et al. reported a gold-catalyzed oxidative cross-coupling of two different terminal alkynes,<sup>[13,14]</sup> and thus provided a new route to unsymmetrical diynes with high heteroselectivity (Scheme 1 a). The reaction





 $\ensuremath{\textit{Scheme 1.}}\xspace$  C(sp)–C(sp) cross-coupling reactions.

can be viewed as a gold-catalyzed modification of the Glaser-Hav reaction. The success of this transformation relies on the effective alkyne discrimination towards gold acetylide formation. However, this method is not applicable for selectively coupling two different alkynes with either similar structure or electronic properties, for example, two aromatic or aliphatic alkynes. We envisioned the desired selective C(sp)-C(sp)cross-coupling might be achieved through in situ oxidation of the gold(I)-acetylide to gold(III) by alkynyl hypervalent iodine reagents,<sup>[10d, 15]</sup> with concomitant transfer of an alkynyl group (Scheme 1b). This strategy might afford unsymmetrical butadiynes with wider scope than those of using two terminal alkynes. Herein we describe a new gold-catalyzed C(sp)-C(sp) cross-coupling based on the above strategy, as it allows the coupling of terminal alkynes and alkynyl hypervalent iodine reagents with a high degree of heteroselectivity while obviating the need for excess of either substrate. It turns out that unsymmetrical butadiynes, even with very similar substituents, could be synthesized selectively. The method also represents the first gold-catalyzed version of the Cadiot-Chodkiewicz-type reaction. To the best of our knowledge, the

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catalytic alkynylation of terminal alkynes with alkynyl hypervalent iodine(III) reagents has not been reported to date.<sup>[16]</sup>

Initially, the cross-coupling of the aryl alkyne **1a** with phenyl-substituted ethynylbenziodoxole derivatives under gold-catalyzed conditions was chosen to test the possibility of our hypothesis (Table 1). The introduction of

Table 1: Optimization of the reaction conditions.[a]

F-\ 1a	Ph O 5 mol% TA- CF <sub>3</sub> 5 mol% AgC 0.5 equiv P CH <sub>3</sub> CN, F	Au DTs nen RT F—⟨	3a + 	
Entry	Deviation from standard condi-	<i>t</i> [h]	Yield [%] <sup>[b]</sup>	Yield [%] <sup>[b]</sup>
	tions		of <b>3 a</b>	of <b>4a</b>
1	none	0.5	98	1
2	without AgOTs and Phen	12	31	46
3	toluene instead of CH <sub>3</sub> CN, 50°C	12	85	7
4	no AgOTs	24	17	0
5	no Phen	24	13	10
6	no TA-Au	24	0	0
7	NaOTs instead of AgOTs	18	13	0
8	0.1 equiv of Phen was used	12	86	4
9	5 instead of 2a	12	3	0
10	L1 instead of Phen	12	90	8
11	L2 instead of Phen	1.5	87	7
12	bpy instead of Phen	13	72	8
13	AuCl instead of TA-Au	1	78	20
14	AuCl₃ instead of TA-Au	8	18	4
15	PicAuCl <sub>2</sub> instead of TA-Au	4	82	12
16	PPh₃AuCl instead of TA-Au	13	76	23
17	$PPh_3AuNTf_2$ instead of TA-Au	1.5	95	1

[a] **1a** (0.20 mmol), **2a** (0.20 mmol), TA-Au (0.01 mmol), AgOTs (0.01 mmol), Phen (0.10 mmol) in CH<sub>3</sub>CN (0.1 M) at room temperature under argon. [b] Yields determined by <sup>19</sup>F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard. Phen = 1,10-phenanthroline, Tf=trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.



phenylethynyliodine(III) reagents to the gold-catalyzed direct alkynylation reactions is highly desired, but more challenging as only silvl-substituted ethynyliodine(III) reagents, such as 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX), display good performance.<sup>[15b]</sup> A thorough optimization study of the alkynyl source, gold catalysts, and additives led us to discover that the use of 5 mol% of TA-Au,<sup>[17]</sup> 5 mol% AgOTs, and 0.5 equivalents of Phen, with the bis(trifluoromethyl) benziodoxole 2a as the alkynylation reagent enabled the reaction to go to completion at room temperature within 30 minutes.<sup>[18]</sup> The desired unsymmetrical diyne 3a was obtained with a high yield and excellent heteroselectivity (entry 1). However, using TA-Au alone as the catalyst led to a deleterious effect on the selectivity (entry 2). Additionally, the coupling reaction occurs faster in CH<sub>3</sub>CN than in toluene (entry 3). In the absence of AgOTs, significant erosion in the yield was

observed, thus suggesting the vital effect of silver in the transformation (entry 4). As expected, not adding Phen resulted in poor yield and selectivity (entry 5). A control experiment demonstrated the necessity of the gold catalyst for the cross-coupling reaction (entry 6). The amount of Phen also played an important role in this reaction, since decreasing the amount of Phen to 0.1 equivalents afforded 3a in a decreased yield with longer reaction time (entry 8). This result is likely due to the competitive coordination of Phen to silver to form a  $[Ag(Phen)_2]^+$  complex,<sup>[19]</sup> which consumes some of the Phen. Such results suggested that additional free Phen was required, possibly as a ligand to complex with gold. When the alkynylbenziodoxolone 5 was used instead of 2a, only trace amounts of 3a were observed, thus indicating the superior reactivity of 2a (entry 9). Specifically, we found Phen and its derivatives L1 and L2 showed better reactivity than bipyridine, presumably because of their significant backbone rigidity compared to the nonfused analogues (entries 10-12). Various gold(I) and gold(III) complexes were also examined (entries 13-17). Among them, PicAuCl<sub>2</sub> led to formation of 3a in 82% yield, and the commonly used PPh<sub>3</sub>AuNTf<sub>2</sub> showed comparable activity to that of TA-Au.

With a set of optimized reaction conditions in hand, we focused our attention on the preparative scope of this goldcatalyzed C(sp)–C(sp) cross-coupling reaction (Table 2). The scope with respect to alkynes was firstly investigated with 2a as the coupling partner. To our delight, the present method could be applied successfully to a wide variety of aryl-, heteroaryl-, alkenyl-, and alkyl-substituted terminal alkynes. Aryl alkynes, bearing either electron-withdrawing (p-F, p-Cl, p-Br, p-CO<sub>2</sub>Et, p-CF<sub>3</sub>) or electron-donating [p-Me, p-MeO, p-NHCbz and 3,4,5-tri(MeO)] groups coupled readily with 2a to afford aryl, aryl-substituted butadiynes (3a-h and 3k) in high yields (83-96%) within short reaction times. The electronic nature of the aryl substituents had little influence on the product yields. Of note is that halogen groups, which are usually not tolerated in transition metal catalyzed reactions, remained intact under the standard reaction conditions, thus highlighting the orthogonal reactivity of gold over palladium, copper, and nickel catalysis. Sterically demanding o-Me- and o-CF3-, 2,4,6-tri(Me)-, and 1-naphthyl-substituted aryl alkynes reacted smoothly to give 3i-j and 31-m in 80-97% yields, thus indicating that the reaction was not sensitive to steric effects of terminal alkynes. Heteroaryl-substituted alkynes such as 2-thienyl- and 2-pyridyl-substituted ones also turned out to be effective substrates, thus furnishing 3n,o in 73-77% yields. Additionally, 3-en-1-ynes could be satisfactorily coupled in high yield, as exemplified by **3p**. Functional-group tolerance was also observed with aliphatic alkynes. A large variety of alkyl alkynes reacted well with 2a, thus providing the corresponding alkyl,aryl-substituted butadiynes 3q-za in good to excellent yields. Substrates containing nitrile (3v), ether (3w and 3x), and sulfamide (3y) groups were all suitable for this reaction. In particular, propargyl acetate, which is known to easily undergo 1,2-migration reactions in gold catalysis,<sup>[20]</sup> could also be accommodated, thus furnishing 3z in 85% vield. Intriguingly, free aliphatic alcohols (3za) do not interfere, and illustrate the potential of our methodology in

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Table 2: Scope of the gold-catalyzed cross-coupling of terminal alkynes with ethynylbenziodoxole hypervalent iodine reagents.<sup>[a,b]</sup>



[a] 1 (0.30 mmol), 2 (0.30 mmol), TA-Au (0.015 mmol), AgOTs (0.015 mmol), Phen (0.15 mmol) in CH<sub>3</sub>CN (0.1 м) at room temperature under argon.
 [b] Yields of isolated products. [c] 50 °C. [d] 2 equiv 2a was used. [e] 1.2 equiv of 2e was used.

protecting-group-free strategies. Activated alkynes, as a case study of ethyl propiolate, was also suitable for this reaction, thus producing **3zb** in 91% yield. Silyl-substituted terminal alkynes (**3zc**, **3zd**) were also compatible with this reaction, thus providing an additional handle for further functionalization. The tetrayne **3ze**, which has utility in metal-catalyzed hexadehydro-Diels–Alder (HDDA) reactions,<sup>[21]</sup> was easily constructed by this method. The effects of a substituent on the benziodoxole alkyne terminus (R<sup>2</sup>) were also investigated. For aryl-substituted hypervalent iodine reagents, a series of functional groups, such as Me, CN, CO<sub>2</sub>Et, and even the strong-electron withdrawing NO<sub>2</sub>, were tolerated well. To our delight, alkyl (*n*Bu) and silyl (TIPS) ethynylbenziodoxole hypervalent iodine reagents were also successfully employed, and were found to react smoothly with aryl-, alkyl-, and silylsubstituted terminal alkynes, and high product yields were realized for all cases. Especially, the alkyl,alkyl-substituted butadiynes **3zh** and **3zi**, with very similar substituents, could be constructed conveniently by this method. These results further demonstrate the diversity and flexibility of this method. It is worth pointing out that no excess of either substrate is required in most cases in our system, and one purification step by column chromatography is enough to obtain the clean product, thus emphasizing the practicality of the protocol.

In the reported gold-catalyzed oxidative C(sp)-C(sp) cross-coupling<sup>[13]</sup> or homocoupling<sup>[14]</sup> of terminal alkynes to 1,3-diynes, gold(I)-acetylide was suggested as the key inter-

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mediate to start the  $Au^{I}/Au^{III}$  redox cycle. Taking this into consideration, we turned our attention to studying the catalytic activity of the putative gold(I)/acetylide species. The acetylide complex **6**, with a PPh<sub>3</sub> ligand, was first employed for catalyzing the cross-coupling reaction (Scheme 2 a). Unfortunately, only a poor heteroselectivity, as well

a) Investigation on the effect of ligand





**Scheme 2.** a) Control experiments for determining the role of ligands. b) Possible reaction pathways. c) Stoichiometric reactions. The yields of **3a** and **4a** were determined by <sup>19</sup>F NMR analysis of the crude reaction mixture.

as a low reaction rate was observed. However, in the presence of 0.5 equivalents of Phen, comparable yields and heteroselectivity to the catalytic system could be achieved with a ligand-free polymeric gold acetylide,  $[Au-C=C(p-FC_6H_4)]_n$ (7), as the catalyst (Scheme 2a),<sup>[22]</sup> thus confirming that Phen was essential for maintaining a high selectivity and leaving a reasonable speculation about the involvement of the catalytically active species PhenAu(I)X A (Scheme 2b). Starting from A, two different pathways could be conceived for the reaction. A direct oxidation of **A** to **B**, followed by coordination with the terminal alkyne, leads to the dialkynylgold(III) species C, which upon reductive elimination affords the desired cross-coupling product and regenerates A (Path a). Alternatively, the oxidation could occur preferentially on in situ generated gold(I) acetylide **D**, thus forming the common intermediate C (Path b). With TA-Au as the precatalyst, both <sup>31</sup>P NMR spectroscopy and ESI-MS confirmed the formation of [(Phen)AuPPh<sub>3</sub>]<sup>+</sup> upon adding Phen. This species might be further converted into A and initiate the overall transformation, where Phen plays an important role in promoting the oxidation of the gold(I) complex by alkynyl iodine(III) reagents,<sup>[23]</sup> and facilitates a rapid reductive elimination from gold(III).<sup>[24]</sup> The role of the silver additive was not clear, as it may have a positive effect on the formation of either **A** or **D**. A set of stoichiometric experiments were conducted to investigate the two possible pathways (Scheme 2 c). As shown, the stoichiometric reaction of TA-Au with **2a** afforded 1,4-diphenylbuta-1,3-diyne in 24% yield after stirring for 3 hours.<sup>[25]</sup> The results implied that the free gold(I) complex could be oxidized by alkynyliodine-(III) reagents. Albeit with a non-negligible erosion in selectivity (Scheme 2 c versus 2 a), the cross-coupled product **3a** could be observed in 42% yield when reacting **7** with **2a** in a stoichiometric fashion, thus indicating the feasibility of the transformation of **D** to **C**. At this stage, the two reaction pathways could not be distiguished according to the above results. Further investigations will be needed to understand the exact reaction mechanism.

In conclusion, we have developed, for the first time, a new and efficient method for the synthesis of unsymmetrical 1,3butadiynes by gold-catalyzed C(sp)–C(sp) cross-coupling of terminal alkynes with alkynyl hypervalent iodine(III) reagents. This process serves as a highly attractive complement to the existing ones, although it should be mentioned that alkynyl iodine(III) reagents are generally more expensive than the haloalkynes employed in classical Cadiot– Chodkiewicz reactions. We expect that the attributes of this methodology will provide valuable guidelines for designing new cross-coupling reactions involving hypervalent iodine-(III) reagents. Further investigations on the detailed reaction mechanism and application of this chemistry are in progress.

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#### **Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** alkynes · cross-coupling · gold · hypervalent compounds · reaction mechanisms

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Cross-Coupling	
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Gold-Catalyzed Cadiot–Chodkiewicz-Type Cross-Coupling of Terminal Alkynes with Alkynyl Hypervalent Iodine Reagents: Highly Selective Synthesis of Unsymmetrical 1,3-Diynes



**All the hype**: A new method for the title reaction has been developed. The reaction features high selectivity and efficiency, mild reaction conditions, wide substrate scope, and functional-group compatibility. Mechanistic studies reveal that the formation of a phenanthrolinylligated gold(I) complex is crucial for the efficiency and selectivity of the target transformation.

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