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Tetrasubstituted 1,3-Enynes by Gold-Catalyzed Direct C(sp^2)−H Alkynylation of Acceptor-Substituted Enamines

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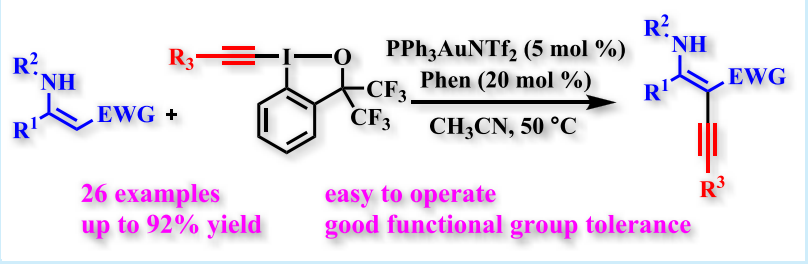
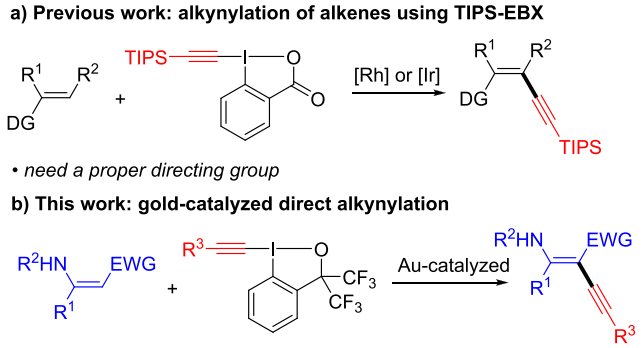


ABSTRACT: A gold-catalyzed synthesis of tetrasubstituted 1,3-enynes from hypervalent iodine(III) reagents and activated alkenes is reported. This reaction involves an in situ formed alkynyl Au(III) species and a subsequent direct C(sp^2)−H functionalization of alkenes, offering 26 enynes in 62−92% yield with excellent functional group tolerance.

1,3-Enynes are important subunits present in natural products, pharmacologically active molecules, and functional materials.[1] They also serve as highly valuable synthetic intermediates participating in diverse organic transformations.[2] Thus, it is not surprising that considerable efforts have been expended in seeking methods for the preparation of conjugated 1,3-enynes. Classical synthetic strategies for the construction of 1,3-enynes include Wittig olefinations of propynals or ynones,[3] dehydrations of propargyl alcohols,[4] cross-dimerizations of alkynes, and Sonogashira as well as Suzuki-Miyaura coupling reactions.[2a,5] Over the past decade, the direct alkynylation of alkenes has gained more attention.[6] Usually, the alkynylation of C(sp^2)−H bonds to give 1,3-enynes is limited to activated olefins or substrates bearing a proper directing group.[7] Consequently, there is still a high demand to develop efficient and simple methods for the direct stereo- and regioselective synthesis of highly substituted enynes.

On the other hand, owing to the nonclassical bond character and the excellent reactivity,[8] alkynyl-substituted hypervalent iodine reagents have attracted increasing attention from many organic chemists.[9] For instance, Waser's group reported several direct alkynylations of heterocycles using alkynyl-substituted hypervalent iodine reagents.[10] Patil's group disclosed a gold-catalyzed aminoalkynylation reaction of alkynes using the TIPS-EBX agent.[11] Liu's group developed a new method for the synthesis of unsymmetrical 1,3-butadiynes by a gold-catalyzed C−H alkynylation reaction of terminal alkynes.[12] To date, alkynylations of alkenes for the synthesis of 1,3-enynes using TIPS-EBX are viable only by employing rhodium or iridium catalysts (Scheme 1a).[7b,13] Our group has been interested in reactions involving Au(I)/Au(III) catalytic

Scheme 1. Metal-Catalyzed Alkynylations of Alkenes



cycles,[14] and we recently reported Au-catalyzed domino cyclization/alkynylation reactions,[15] dual Au/Ag catalyzed direct alkynylations of cyclopropenes,[16] and C−H alkynylations/oxy-alkynylations of phenols.[17] Our previous in-depth mechanistic studies have demonstrated that Au(III) species are key intermediates for the formation of C−C bonds. We herein report the first gold-catalyzed C(sp^2)−H alkynylation of acceptor-substituted enamines with hypervalent iodine re-

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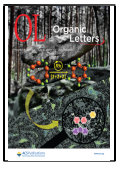

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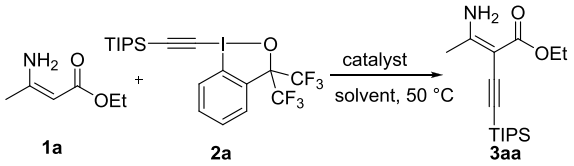
agents for the synthesis of tetrasubstituted 1,3-enynes (Scheme 1b).

We initially optimized the reaction conditions by employing 3-aminoacrylate **1a** and TIPS-EBX **2a** as model substrates (Table 1). As expected, the desired product **3aa** was isolated in

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



1a **2a** **3aa**

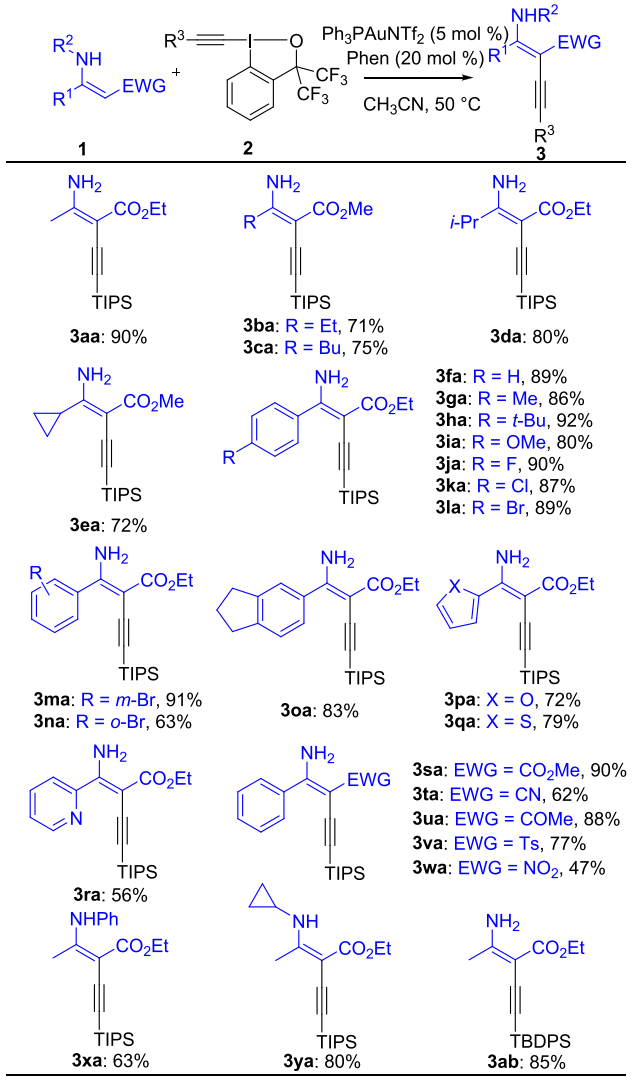
Entry	Catalyst	Ligand	Solvent	Yield (%)[c]
1	$Ph_3PAuNTf_2/AgNTf_2$	Phen[d]	CH_3CN	87 (88)[e]
2	$Ph_3PAuNTf_2$	Phen	CH_3CN	90
3	–	Phen	CH_3CN	n.d.[f]
4	$Ph_3PAuNTf_2$	–	CH_3CN	31
5	Ph_3PAuCl	Phen	CH_3CN	84
6	$(C_6F_5)_3PAuNTf_2$	Phen	CH_3CN	81
7	IPrAuCl	Phen	CH_3CN	12
8	JohnPhosAuCl	Phen	CH_3CN	n.d.[f]
9	$Ph_3PAuNTf_2$	Phen	DCE[g]	76
10	$Ph_3PAuNTf_2$	Phen	CH_3Cl	56
11	$Ph_3PAuNTf_2$	Phen	THF[h]	83
12	$Ph_3PAuNTf_2$	Phen	Toluene	42
13	$Ph_3PAuNTf_2$	Phen	CH_2Cl_2	85

[a]**1a** (0.10 mmol), **2a** (0.12 mmol), catalyst (5 mol %), Phen (20 mol %) in solvent (1 mL) at 50 °C. [b]Replacing **1a** by the corresponding silylenol ether of ethyl acetylacetate did not show conversion under these conditions. [c]NMR yield with CH_2Br_2 as an internal standard. [d]Phen: 1,10-phenanthroline. [e]Isolated yield. [f]n.d.: not detected. [g]DCE: 1,2-dichloroethane. [h]THF: tetrahydrofuran.

88% yield when the reaction was performed at 50 °C in the presence of 5 mol % $Ph_3PAuNTf_2$, 5 mol % $AgNTf_2$, and 20 mol % 1,10-phenanthroline in CH_3CN (entry 1). Different from our previous work,[16a,17] silver is not essential (entry 2). Control experiments showed that gold is key to the formation of product **3aa** (entries 3 and 4). The product yield decreased dramatically in the absence of Phen ligand (entry 4). Other gold catalysts did not improve the reaction (entries 5–8); no product was detected when JohnPhosAuCl was used as catalyst (entry 8). Other solvents were found to be less efficient than CH_3CN (entries 9–13). Other transition metal catalysts proved ineffective (see Table S1 in the Supporting Information), as well as aryl- and alkyl-substituted alkynes.

Under the optimized reaction conditions (Table 1, entry 2), we investigated the reaction scope. We first tested different enamines. As shown in Scheme 2, a series of alkyl (R^1 = Me, Et, Bu, *i*-Pr, cyclopropyl) substituents were tolerated (**3aa**–**ea**). The structure of **3aa** was confirmed by single-crystal X-ray structure analysis (Figure 1). Phenyl-substituted alkyl 3-aminoacrylates **1f** delivered product **3fa** in 89% yield. Substrates containing electron-donating groups such as Me–, *t*-Bu–, MeO–, and cyclopentane– on the arene rings were smoothly converted to the corresponding products (**3ga**–**ia**, **3oa**) in 80–92% yield. 3-Aminoacrylates bearing aryl halides at the 3-position afforded the target products (**3ja**–**na**) in 63–92% yield. Furthermore, heteroaryl-derived products (**3pa**–**ra**) were readily prepared in moderate to good yield under the standard conditions. Notably, replacements of the ethoxycarbonyl group in substrate **1f** with other electron-withdrawing

Scheme 2. Reaction Scope[a,b]



[a]Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), $Ph_3PAuNTf_2$ (5 mol %), Phen (20 mol %) in CH_3CN (1.0 mL) at 50 °C. [b]Isolated yield.

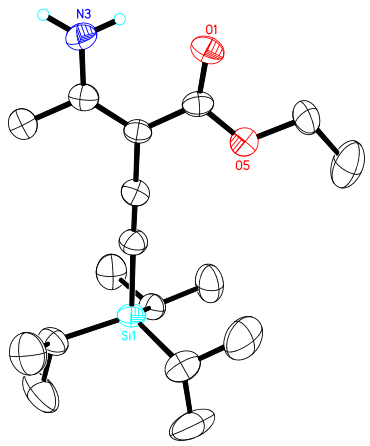


Figure 1. Solid state molecular structure of **3aa**.

groups, including COOMe, CN, Ac, Ts, and NO_2 groups, gave the corresponding functionalized products (**3sa**–**wa**) in good 47–90% yield. *N*-Phenyl and -cyclopropyl substituted

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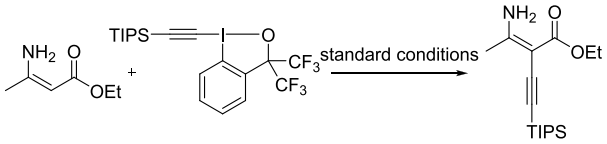
enamines **1x** and **1y** were well-tolerated, affording the desired products **3xa** and **3ya** in good yield. Replacement of the TIPS group of **2a** by TBDPS gave product **3ab** in 85% yield. Furthermore, the gram-scale synthesis of **3aa** was efficiently executed (Scheme 3); other alkenes than the ones shown in Scheme 2 could not be used (e.g., ethyl acrylate or styrene).

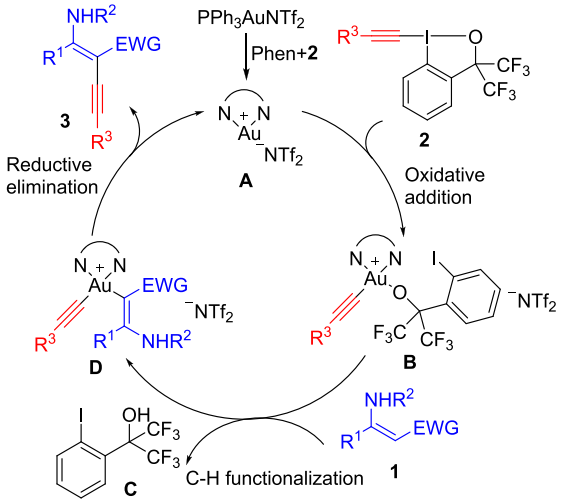
Scheme 3. Gram-Scale Synthesis



1a (4.0 mmol) **2a** (4.8 mmol) **3aa** (1.03 g, 83% yield)

A plausible mechanism is described in Scheme 4 on the basis of previous reports.[16a,17] First, Au(I) species **A** is formed under

Scheme 4. Proposed Reaction Mechanism



the optimized reaction conditions. Subsequently, species **A** undergoes an oxidative addition with hypervalent iodine reagent **2** to produce alkynyl Au(III) complex **B**. In comparison with simple olefins, the carbon−carbon double bond of enamine **1** is more electron-rich because of the electron-donating ability of the nitrogen atom.[18] Au(III) complex **D** is then formed via a direct C−H functionalization of **1** with Au(III) complex **B**. Finally, the reductive elimination of Au(III) complex **D** releases the desired product **3**, meanwhile Au(I) species **A** is regenerated to complete the catalytic cycle.

In summary, we revealed the applicability of Au(I)/Au(III) catalytic cycles by employing gold-catalyzed direct C(sp^2)−H alkynylation of acceptor-substituted enamines with hypervalent iodine reagents for the synthesis of 1,3-enynes. The broad substrate scope, good functional group tolerance, and good efficiency render this method useful for organic synthesis, especially for the synthesis of nitrogen-containing compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01486.

Experimental procedures and compound characterization (PDF)

Accession Codes

CCDC 2080692 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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