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Gold-Catalyzed Alkynylative Meyer−Schuster Rearrangement

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01596 Read Online

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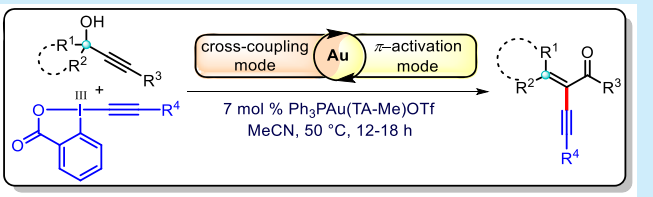
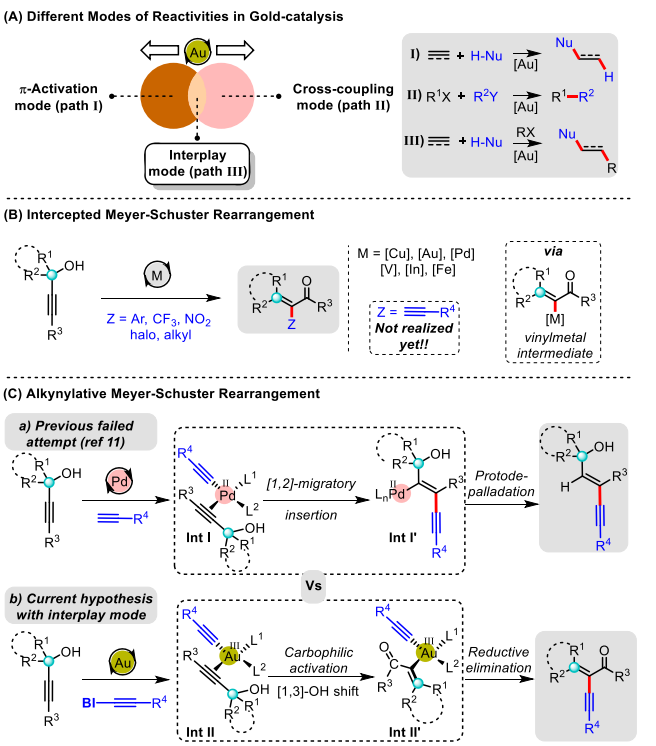
ABSTRACT: By applying the "interplay" mode, which consolidates two key reactivity modes of gold catalysis, namely π-activation mode and cross-coupling mode, the first alkynylative Meyer−Schuster rearrangement is designed and successfully implemented. The current protocol gives straightforward access to enynones, a highly valuable building block, from easily available propargyl alcohol feedstocks. Control experiments suggest an Au(III) catalyst triggers the Meyer−Schuster rearrangement, whereas monitoring the reaction with ESI-HRMS provided strong evidence in favor of a key alkynylgold(III) intermediate which supports the proposed "interplay" scenario.



Over the last two decades, homogeneous gold catalysis has established itself as reliable approach in modern organic synthesis to activate C−C multiple bonds, capitalizing on the tunable soft π-acid nature of gold salts toward intra- or intermolecular attack by nucleophiles ("π-activation mode", Scheme 1A, path I).[1] Under such homogeneous conditions, the cross-coupling reactions were nontrivial for gold catalysts, unlike its other late-transition-metal counterparts, since the comparatively high oxidation potential[2] of Au(I)/Au(III) redox couple restricted gold's redox activities. Later, such gold-catalyzed cross-coupling reactions were realized by employing sacrificial oxidants,[3] visible-light photoredox catalysis,[4] or rational ligand design[5] which enabled access to the Au(I)/Au(III) catalytic cycle ("cross-coupling mode", Scheme 1A, path II). While exploration of both of the activation modes, i.e., paths I and II, is still being actively pursued, concurrent research endeavors have also witnessed considerable attention on merging the two modes of reactivity ("interplay mode", Scheme 1A, path III).[6] In this context, the research teams of Toste, Zhang, Russell, Glorius, and a few others have deployed the "interplay mode" in executing gold-catalyzed 1,2-difunctionalization reactions of C−C multiple bonds.[7] However, all such reactions are either based on the use of sacrificial oxidants or highly reactive aryl diazonium salts. Overcoming these limitations, our group has recently inducted a unique approach to the interplay mode, involving a ligand-enabled cross-coupling mode and the typical π-activation mode of gold complexes, to perform the very first gold-catalyzed 1,2-diarylation of alkenes.[8] Even though the reactivities and selectivities exhibited by this interplay mode of gold catalysis have been unique as compared to other transition metals in almost all of the cases, the application of this mode of gold catalysis has remained confined to 1,2-difunctionalization reactions of C−C multiple bonds.[7,8] We believe that there exists a lot of potential for the "interplay mode" in unlocking

Scheme 1. Conceptual Roadmap toward Alkynylative Interception of Meyer-Schuster Rearrangement[a]



[a]BI = benziodoxolone.

Received: May 10, 2020

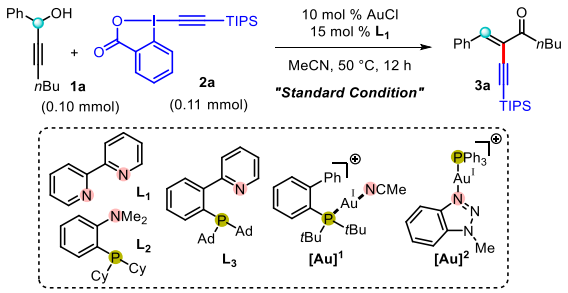
novel reactivities beyond 1,2-difunctionalization, which are challenging and yet unachieved.

One such reactivity which poses a significant challenge is the alkynylative Meyer−Schuster rearrangement. It is to be noted that the Meyer−Schuster rearrangement, although a century old transformation, is very crucial for organic synthesis because it converts readily available propargyl alcohols into α,β-enones in an atom-economical fashion.[9] To broaden the utility of this classical process in synthetic organic chemistry, the "intercepted" Meyer−Schuster rearrangement, in which the vinylmetal intermediate in the rearrangement is intercepted with various coupling partners to obtain highly useful and versatile α-functionalized enones, holds significant merit and has emerged as a highly important protocol (Scheme 1B).[10] However, the corresponding alkynylative interception, termed as the "alkynylative" Meyer−Schuster rearrangement (Z = alkynyl), has remained elusive so far. Although the term "alkynylative Meyer−Schuster rearrangement" was originally coined by Reddy and co-workers, their efforts to develop the same was unsuccessful.[11] In their case, instead of a Meyer−Schuster rearrangement, the reaction between alkynols and terminal alkynes under Pd catalysis resulted in *syn*-alkynopalladation[12] (**Int I′**) via [1,2]-migratory insertion from **Int I** (Scheme 1C, eq a). Such migratory insertions are dominant in regular organotransition-metal complexes and clearly illustrate the difficulties of achieving an alkynylative Meyer−Schuster rearrangement using conventional transition-metal catalysis.

On the contrary, an alkynylgold(III) complex such as **Int II** is supposed to be reluctant to undergo migratory insertion, considering the reactivity of organogold species being frequently complementary to that of analogous organo-transition-metal complexes (Scheme 1C, eq b).[13] We therefore hypothesized that the inherent π-activation capability of Au-complexes would trigger a [1,3]-OH shift in **Int II** required for Meyer−Schuster rearrangement[14] furnishing **Int II′**, which would further undergo reductive elimination to lead to the desired α-alkynylated enones. Because of our continuous involvement in gold-catalyzed alkynylations with ethynylbenziodoxolones (EBXs),[6,15] we believed such alkynylgold(III) complex (**Int II**) can be obtained in situ utilizing EBXs, which, by design, can function as an oxidant as well as an alkyne surrogate. Thus, the idea of applying the interplay mode of gold catalysis, consisting of an EBX-enabled cross-coupling mode and the π-activation mode, in achieving the challenging task of alkynylative Meyer−Schuster rearrangement is conceived and herein, we report the successful implementation of the same. The reaction gives selective straightforward access to (*E*)-enynones, provides moderate to excellent yields and is highly general with respect to both alkynols and EBXs. It is necessary to reiterate the fact that such enynones or 1,3-enyne systems are well-recognized to be highly valuable synthetic building blocks.[16,17]

On the basis of our prior experience[15a] with alkynylation reactions involving Au(I)/Au(III) catalysis, initial studies into the new alkynylative Meyer−Schuster rearrangement were performed with alkynol **1a** and TIPS-EBX **2a** in MeCN at 50 °C, employing AuCl (10 mol %)/$\mathbf{L_1}$ (15 mol %) as the catalyst system (Table 1, entry 1). However, the reaction conditions did not give us any leads, with **1a** remaining unreacted. A significant improvement of the outcome up to 44% yields is seen when we switched from bidentate (N,N) ligand system ($\mathbf{L_1}$) to hemilabile (P,N) ligand systems ($\mathbf{L_2}$−$\mathbf{L_3}$) (entries 2 and 3). Even with $Ph_3PAuNTf_2$, where "NTf_2" is weakly coordinating, the yield was 36% (entry 4). We therefore surmised that (P,N) ligand systems with stronger "*N*"-coordination might be the key in achieving desired outcomes.[5,8] Gold catalysts were screened accordingly (entries 5 and 6), wherein [**Au**]^{2}OTf, to our delight, stood out with 69% yield (entry 6) and even with decreased catalyst loading the yield could be maintained at 68% (entry 9). Finally, utilizing 1.3 equiv of **2a** delivered us the desired product in 73% yields (entry 10). Notably, variation of Au catalysts, temperature, and solvents did not give us any improvements (entries 7−8, 12, 13) while the omission of [Au] completely halts the reaction (entry 11).

Table 1. Reaction Development



entry	variation of the "standard condition"	yield of **3a**[a] (%)
1	none	<5
2[b]	$\mathbf{L_2}$AuCl/$AgSbF_6$	39
3[b]	$\mathbf{L_3}$AuCl/$AgSbF_6$	44
4[b]	$Ph_3PAuNTf_2$	36
5[b]	[**Au**]$^1SbF_6$	31
6[b]	[**Au**]^{2}OTf	69
7[b]	$AuCl_3$	14
8[b]	$PicAuCl_2$	17
9[b]	7 mol % of [**Au**]^{2}OTf	68
10[c]	1.3 equiv of **2a** was used	73
11[d]	without [Au] cat.	NR
12[c,d]	temp raised to 60 °C	69
13[c,d]	DCE used as a solvent	25

[a]Isolated yields. [b]Instead of AuCl/$\mathbf{L_1}$ as catalyst system. [c][**Au**]^{2}OTf was used as catalyst in place of AuCl/L_1. [d]1.3 equiv of **2a**. NR = no reaction.

Having optimized the reaction conditions (Table 1, entry 10), we began to evaluate the scope of various alkynols **1** in the alkynylative Meyer−Schuster rearrangement keeping the EBX (**2a**) constant (Scheme 2). First, several aryl alkynols (R^1 = Ar; R^2 = H) were tested against **2a**, and it was observed that all such alkynols were well-tolerated to afford products **3b**, **3d**−**n** in up to 83% yields irrespective of their steric or electronic nature. However, a stronger electron-donating $-NMe_2$ group was found to be incompatible, giving a complex reaction mixture (**3c**). Substrates appended with sterically encumbered 1-naphthyl (**1o**) and 9-anthracenyl (**1p**) moieties efficiently underwent alkynylative Meyer−Schuster reaction to provide the corresponding enynones in 65 and 77% yields, respectively. Intriguingly, the alkynylated product **3q** could be exclusively produced from alkynol **1q** over a potentially competing Rautenstrauch rearrangement.[18] Aryl alkynols with varied R^3 groups (**1r**−**v**) could be successfully engaged in the reaction to form enynones **3r**−**u** in good yields (58−73%), whereas with **1v** the yield suffered a little (45%). Acyclic and cyclic tertiary substituted alkynols also performed well under the reaction

https://dx.doi.org/10.1021/acs.orglett.0c01596
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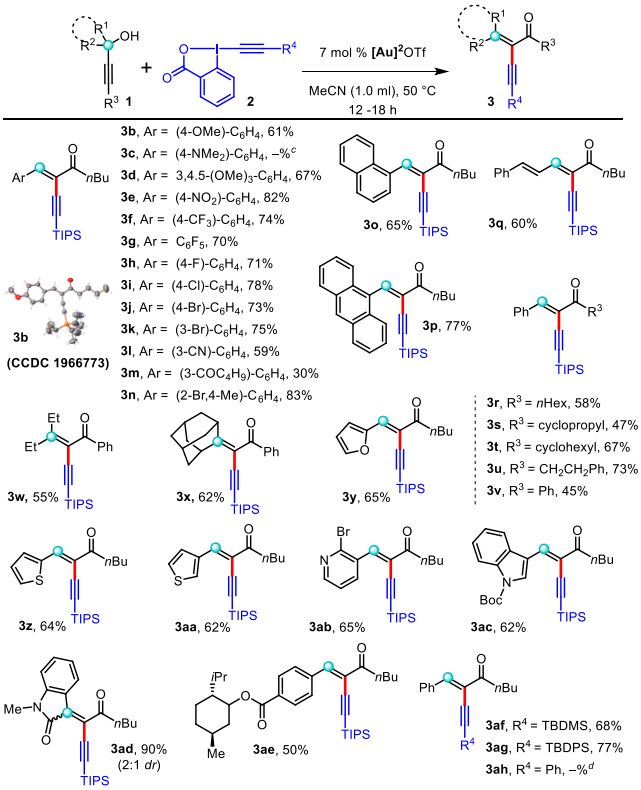
Scheme 2. Scope of Alkynylative Meyer–Schuster Reaction[a,b]

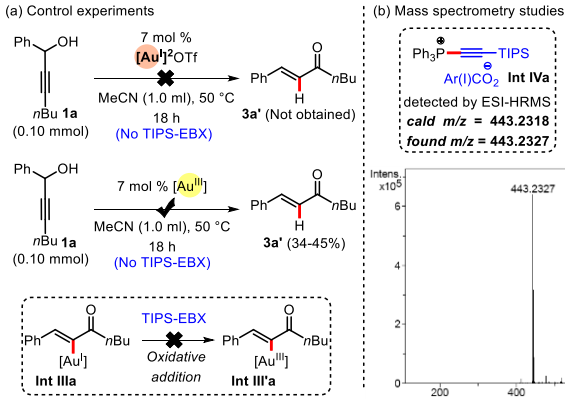


[a]Reactions performed with 0.10 mmol **1** and 0.13 mmol **2**. [b]Isolated yields. [c]Complex mixture obtained. [d]The alkynol **1a** remained unreacted.

conditions and led to tetrasubstituted enone products (**3w–x**, 55–62%), outcompeting any Rupe rearrangement products.[9c,19] Further, heteroarenes were also remarkably tolerated, as demonstrated by the synthesis of furan, thiophene, pyridine, indole, and isatin derivatives of enynones (**3y–ad**) in good to excellent yields (62–90%). The chemoselectivity of the reaction is clearly marked when the thiophene and indole-tethered alkynols **1aa** and **1ac** furnished exclusively the desired enynones **3aa** and **3ac**, respectively, instead of their regular C-2 alkynylated products.[20] In order to apply this protocol for the late-stage alkynylation of biologically important molecules, we performed the title reaction on menthol-based alkynol **1ae** which was indeed functionalized with moderate efficiency under the standard reaction conditions (**3ae**, 50%). We next set out to explore the scope with respect to various EBXs using the aryl alkynol **1a** as partner. Accordingly, alkynol **1a** were treated with TBDMS-EBX (**2b**), TBDPS-EBX (**2c**), and Ph-EBX (**2d**), respectively, under the standard reaction conditions. While the reaction worked well with **2b** and **2c**, giving rise to products **3af** and **3ag** in 68 and 77% yields, respectively, it failed to deliver the desired enynone **3ah** upon using Ph-EBX (**2d**). Of note, the X-ray crystallographic analysis for **3b** unequivocally confirmed the (*E*)-selectivity of the reaction.

Next, a series of control experiments were designed to gain deeper mechanistic insights (Scheme 3). First, we wanted to ascertain whether the oxidative addition concerned takes place at the stage of [**Au**]^{2}OTf or at the stage of vinylgold(I) species **Int IIIa** (Scheme 3a). Interestingly, we observed that [**Au**]^{2}OTf fails to catalyze the blank Meyer–Schuster reaction

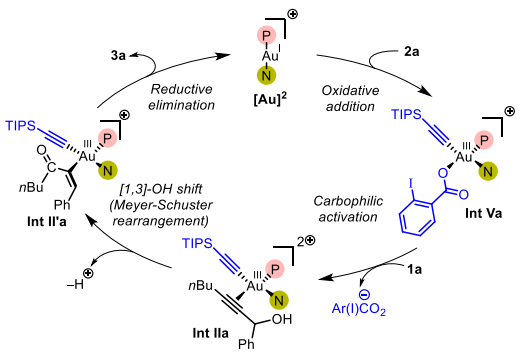
Scheme 3. Mechanistic Studies



(**1a** to **3a′**), indicating the fact that formation of **Int IIIa** (and consequently **Int IIIa′**) is improbable under the reaction conditions. On the contrary, since with Au(III) catalysts[21] the reaction concerned can obtain moderate yields of the blank Meyer–Schuster product (**3a′**), it is likely that first the EBX must undergo oxidative addition to [**Au**]^{2}OTf to generate an intermediate alkynylgold(III) complex which is capable of performing [1,3]-OH shift (Meyer–Schuster rearrangement) on **1a**. Further probing the reaction with mass spectrometry (Scheme 3b) revealed the formation of alkynyl(Ph$_3$P)$^+$ (**Int IVa**, *m*/*z* = 443.2327) which may have resulted out of a reductive elimination from a phosphine-ligated alkynylgold-(III) intermediate.[22]

The mechanistic studies mentioned above are in agreement with our mechanistic hypothesis described in Scheme 1. First, the oxidative addition to the linear two-coordinate Au(I) complex, [**Au**]^{2}OTf, proceeds with **2a** to afford the putative **Int Va** (Scheme 4).[22] Thereafter, it proceeds to coordinate

Scheme 4. Proposed Mechanistic Rationale



with the alkynol **1a** to generate the key intermediate (**Int IIa**) which is now able to activate the alkyne toward Meyer–Schuster rearrangement leading to **Int II′a**. Finally, a reductive elimination from **Int II′a** delivers the desired enynone **3a** and regenerates the active catalyst [**Au**]^{2}OTf.

In summary, we have accomplished the first alkynylative Meyer–Schuster rearrangement, which was not successful previously under Pd catalysis. The current reactivity has been achieved by harnessing the potential of the "interplay mode" of gold catalysis, which integrates the π-activation mode and an EBX-enabled cross-coupling mode. This mechanistic paradigm is further corroborated with our mechanistic investigation involving typical control experiments and mass-spectrometry

https://dx.doi.org/10.1021/acs.orglett.0c01596
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studies that indicate the formation of a key alkynylgold(III) intermediate. The reaction offers a straightforward and exclusive access to a wide range of highly valuable(*E*)-enynones, barring the formation of any undesired enone side product. The reaction reported herein again proved that the "interplay mode" of gold catalysis should find important implications in discovering new reactivities which are not possible by other transition metals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01596.

All experimental procedures, mechanistic studies, detailed optimization studies, analytical data, and copies of ^{1}H and ^{13}C NMR spectra of all newly synthesized products and X-ray data of **3b** (PDF)

Accession Codes

CCDC 1966773 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.

■ ACKNOWLEDGMENTS

Generous financial assistance by the Science and Engineering Research Board (SERB), New Delhi (File Nos. EMR/2016/007177 and DIA/2018/000016) is gratefully acknowledged. S.B., S.B.A., and R.D.M. thank UGC and CSIR for the award of Research Fellowships. We heartily acknowledge all the necessary laboratory support provided by Dr. Senthilkumar in CSIR-NCL to conduct the research work when Dr. Patil moved to IISER Bhopal.

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https://dx.doi.org/10.1021/acs.orglett.0c01596
Org. Lett. XXXX, XXX, XXX−XXX