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Gold(I)-Catalyzed Reactions between 2-(1-Alkynyl)-2-alken-1-ones and Vinyldiazo Ketones for Divergent Synthesis of Nonsymmetric Heteroaryl-Substituted Triarylmethanes: *N*- versus *C*-Attack Paths

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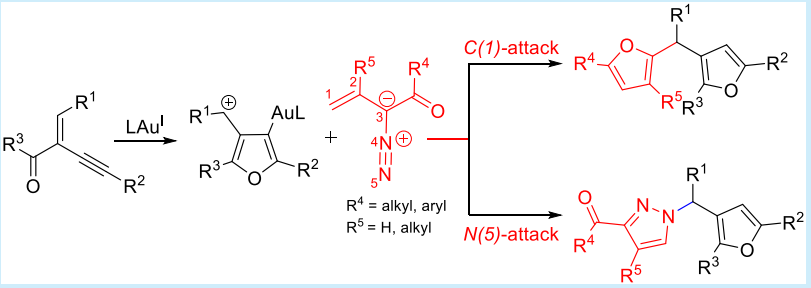

ABSTRACT: Gold-catalyzed synthesis of nonsymmetrical heteroaryl-substituted triarylmethanes using 2-(1-alkynyl)-2-alken-1-ones and vinyldiazo ketones is described. In this catalytic sequence, vinyldiazo ketones attack gold-containing 3-furylbenzyl cations to form the observed C(1)-addition products. We also note that vinyldiazo ketones can be thermally cyclized to yield pyrazole derivatives, which can react with 3-furylbenzyl cations to afford pyrazole-containing triarylmethanes, corresponding to a N(5)-addition path.

Vinyldiazo carbonyl species serve as versatile all-carbon building blocks in numerous cycloaddition reactions, forming valuable carbocyclic and heterocyclic rings of various sizes.[1,2] These diazo carbonyl species are nucleophilic so as to react with electrophilic π-bond motifs to form products of five- or six-membered rings; they serve as 2C- or 3C-building units.[3] These diazo species can alternatively form electrophilic metal carbenes that can be functionalized with nucleophilic π-bond motifs, thus serving as 1C- or 3C-building units (Scheme 1a). This *umpolung* nature is an appealing character for vinyldiazo species as building units.[4] We recently reported bicyclic annulation[5] between benzopyrilium and vinyldiazo ketones wherein vinyldiazo ketones are first utilized as a five-atom (3C + 2N) building unit (eq 1); we postulated initial [5 + 4]-annulations between benzopyrilium and vinyldiazo ketones. Notably, such annulations were previously unattainable with vinyldiazo esters. In diazo chemistry, few efforts have been devoted to the development of vinyldiazo ketones as diazo ketones and esters are believed to have the same reactivity. In this work, we highlight two distinct approaches to employ vinyldiazo ketones as 1-furyl and 1*H*-pyrazolyl units, whereas vinyldiazo esters are inapplicable. We report the gold-catalyzed divergent synthesis of highly nonsymmetric heteroaryl-substtituted triarylmethanes using 2-(1-alkynyl)-2-alken-1-ones and vinyldiazo ketones. In this system, vinyldiazo ketones react with gold-containing 3-furylbenzyl cations (**In-2**) via distinct C(1)-attack and N(5)-attack paths,[6] leading to 2-(furan-3-yl(phenyl)methyl)furan derivatives **3** and 1-(furan-3-yl(phenyl)methyl)-1*H*-pyrazoles **5**, respectively. The current syntheses of triarylmethanes[7,8] are limited mainly to benzene-based triarylmethanes (TRAM) in symmetric patterns, with only one report of their heteroaromatic analogues.[9]

Importantly, nonsymmetric heteroaryl-substituted triarylmethanes that are relevant in material and medicinal chemistry can be accessed using these two reactions.[10] Compounds **I**–**V** are several representatives that exhibit potent biological effects such as antitubercular,[10e] antiviral,[10f] anticancer,[10g] and anti-inflammatory activity[10h] (Figure 1). Furthermore, nonsymmetric triarylmethanes have found widespread applications as leuco dyes[11a] and photochromic agents.[11b,c] They serve also as building blocks to generate dendrimers[11d] and as substrates on which to perform biological studies.[12]

The optimization of reaction of enynone **1a** with vinyldiazo ketone **2a** (1.2 equiv) to form our target **3a** is shown in Table 1. Our initial test was to use electron-deficient 5 mol % of LAuCl/AgOTf (L = PPh_3 and $P(OPh)_3$) in dry dichloro-

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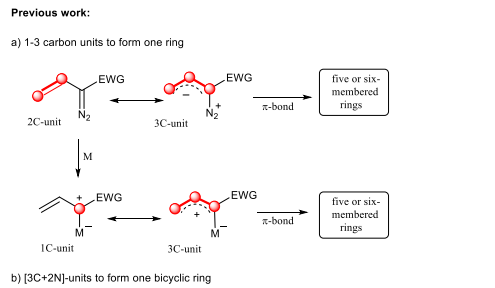
Scheme 1. Chemodivergence of Vinyldiazo Carbonyls and This Work



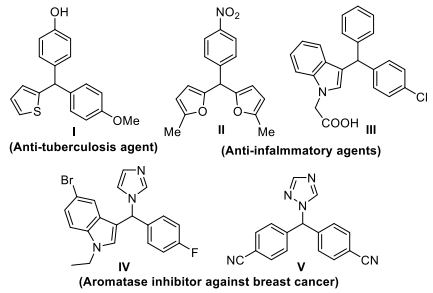
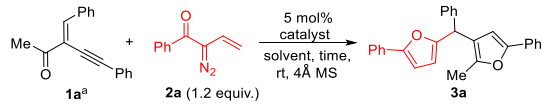


Figure 1. Representatives of bioactive heteroaryl-substituted TRAM.

Table 1. Catalyst Screening with Various Gold Catalysts



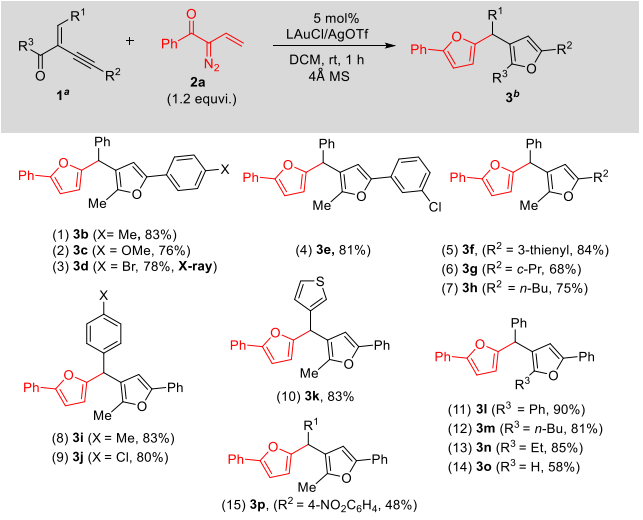
entry	catalyst	solvent	time (h)	yield[b] (%) 3a	1a
1	$(PhO)_3PAuCl/AgOTf$	DCM	2	30	
2	$Ph_3PAuCl/AgOTf$	DCM	4	27	
3	LAuCl/AgOTf	DCM	1	88	
4	IPrAuCl/AgOTf	DCM	3	56	
5	$LAuCl/AgNTf_2$	DCM	1.5	61	
6	$LAuCl/AgSbF_6$	DCM	5	33	
7	LAuCl/AgOTf	DCE	1	74	
8	LAuCl/AgOTf	toluene	12	40	16
9	LAuCl/AgOTf	THF	12	0	30
10	LAuCl/AgOTf	CH_3CN	14	21	27

[a][1a] = 0.05 M. [b]Isolated yields of 3a. L= P(*t*-Bu)$_2$(*o*-biphenyl).

methane near 23 °C; these conditions afforded triarylmethane derivative **3a** in 27−30% yield (entries 1 and 2). To our delight, the use of electron-rich LAuCl/AgOTf (L = P(*t*-Bu)$_2$(*o*-biphenyl) provided **3a** in 88% yield (entry 3). IPrAuCl/AgOTf gave desired compound **3a** in 56% yield (entry 4). For variation of silver sources as in P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgX, (X = NTf_2 and SbF_6) the yields of compound **3a** were 61% and 33%, respectively (entries 5 and 6). For P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgOTf, the yields of compound **3a** in specified solvents follow: DCE 74%, toluene 40%, THF 0%, and MeCN 21%. The X-ray diffraction studies of related compound **3d** confirmed the molecular structure of compound **3a**; the molecule contains one 1-furyl, one 2-furyl, and one phenyl group linked to a methine moiety.

The reaction scope of enynones **1** with vinyldiazo ketone **2a** under the optimized conditions is summarized in Table 2. We

Table 2. Reactions of Various 2-(1-Alkynyl)-2-alken-1-ones



[a][1] = 0.05 M. [b]Isolated yields of **3**. L = P(*t*-Bu)$_2$(*o*-biphenyl).

tested substrates **1b**−**1d** with variable alkynyl substituents 4-XC_6H_4 (X = Me, OMe, and Br); their desired products **3b**−**3d** were isolated in 76−83% yields (entries 1−3). We examined enynone **1e** with a 3-chlorophenyl alkynyl substituent, delivering analogous species **3e** in 81% yield (entry 4). For 3-thienylalkyne moiety **1f**, its resulting product **3f** was isolated in 84% yield (entry 5). We prepared enynones **1g**−**1h** bearing various alkyl-substituted alkynes (R^2 = cyclopropyl and *n*-butyl) that delivered desired compounds **3g**−**3h** in 68−75% yields (entries 6−7). We changed also the alkenyl substituents (R^1) of 2-(1-alkynyl)-2-alken-1-ones **1i**−**1j** with R^1 = 4-XC_6H_4 (X = Me and Cl), delivered corresponding products **3i** and **3j** in 80−83% yields (entries 8 and 9). For 3-thienyl-substituted alkene deivative **1k**, this catalytic reaction furnished all-heteroaryl-substituted compound **3k** in 83% yield (entry 10). Enynones **1l**−**1n** bearing varied ketone substituents (R^3 = Ph, *n*-Bu, and Et) were also well tolerated under optimized conditions, affording expected products **3l**−**3n** in 81−90% yields (entries 11−13). Notably, aldehyde substrate **1o** (R^3 = H) was less efficient for this reaction, rendering product **3o** in 58% yield (entry 14). We performed also a reaction on enynone **1q** with R^1 = 4-$NO_2C_6H_4$, R^2 = Ph ,and R^3 = Me, yielding compound **3p** in 48% yield (entry 15).

The scope of vinyldiazo ketones **2** with (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one **1a** under optimized reaction conditions is summarized in Table 3. We tested vinyldiazo ketones **2b**−**2f** bearing 4-substituted phenylketone (R^4 = 4-XC_6H_4; X = Me, OMe, *tert*-butyl, Cl, and Br); their expected compounds **4a**−**4e** were produced in satisfactorily yields (75−87%, entries 1−5). The vinyldiazo species bearing 3-thienyl moiety **2g** afforded compound **4f** in 84% yield (entry 6). For 2-naphthyl ketone

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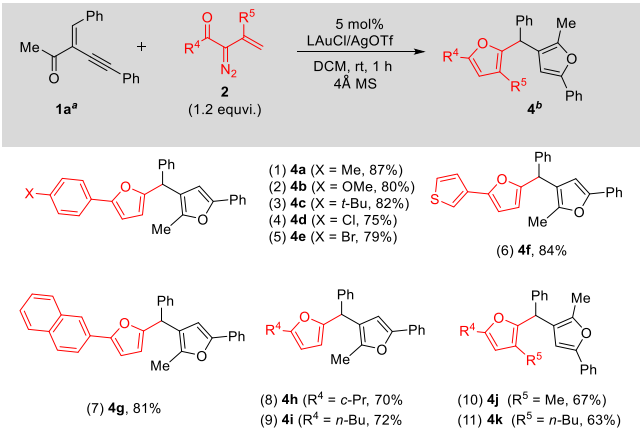
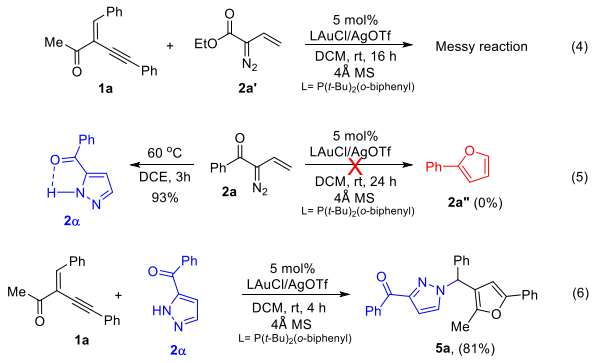
Table 3. Reactions of Various Vinyldiazo Ketones



[a][1a] = 0.05 M. [b]Isolated yields of **4**. L= P(t-Bu)$_2$(*o*-biphenyl).

derivative **2h**, its corresponding product **4g** was isolated in 81% yield (entry 7). The alkylketone derivatives **2i** and **2j** (R^5 = H, R^4 = cyclopropyl and *n*-butyl) were also suitable for this transformation, yielding the desired products **4h** and **4i** in 70% and 72% yield, respectively (entries 8 and 9). We also tested the reaction on 3-alkyl-2-diazo-3-vinyl phenyl ketones **2k** and **2l** (R^5 = Me and *n*-butyl, R^4 = Ph); their resulting compounds **4j and 4k** were isolated in 63−67% yields (entries 10 and 11).

We prepared vinyldiazo ester **2a′** to examine its chemical reactivity, but it yielded products in a complicated mixture under standard conditions (eq 4). Treatment of vinyldiazo



ketones **2a** with a gold catalyst in DCM also led to a slow decomposition of this diazo ketone, forming no furan derivative **2a′′** at all. Instead, we found that compound **2a** itself underwent a thermal cyclization to form pyrazole **2*α***; the yield was 93% (eq 5). This pyrazole has a hydrogen bond because the NH proton resonance is down to δ 11.6 ppm, whereas the other tautomer is reported to have N−H at δ 6.45 ppm.[13b] This information indicates that the 1-furyl ring is constructed in the course of this catalytic reaction.

When pyrazole **2*α*** was treated with enynone **1a** under the standard conditions, we obtained compound **5a** in 81% yield; the mechanism will be discussed in Scheme 2 (vide infra). Notably, the availability of pyrazole **2*α*** allows a new synthesis of triarylmethanes bearing an *N*-pyrazole and a 2-furyl ring (eq 6).

We assessed also the reaction generality of these new 1*H*-pyrazole syntheses using 2-(1-alkynyl)-2-alken-1-ones **1** and vinyldiazo ketones **2**; the results appear in Table 4. A general procedure involves an initial heating of vinyldiazo ketones **2** to

Scheme 2. Plausible Mechanism for C(1)- and N(5)-Attack

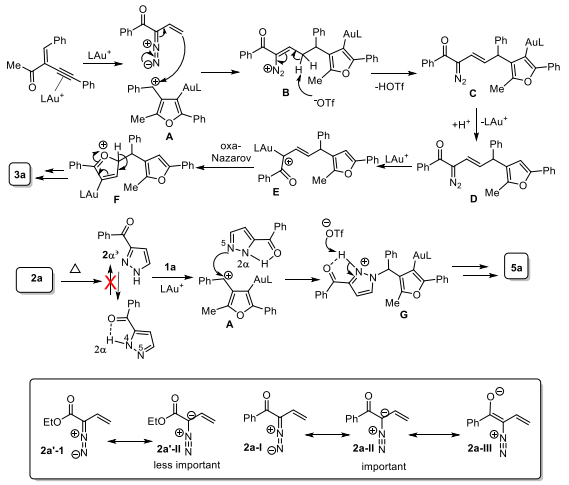
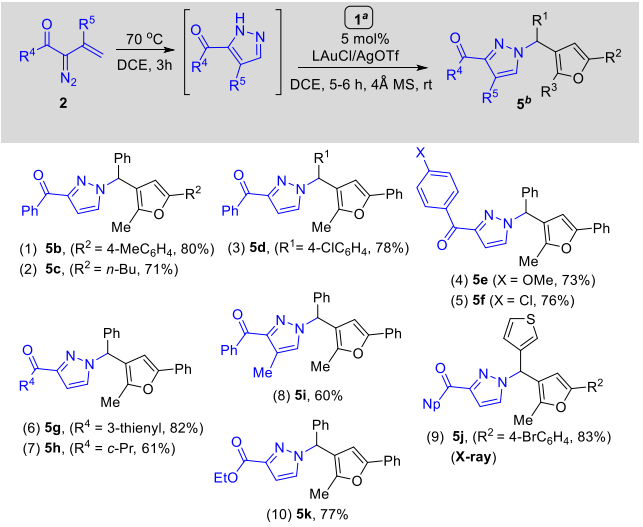


Table 4. Synthesis of *N*-Pyrazole-Based Triarylmethanes



[a][1] = 0.05 M. [b]Isolated yields of **5**. L= P(t-Bu)$_2$(*o*-biphenyl), Np = 2- naphthyl.

form 1*H*-pyrazoles, which are subsequently treated with enynones **1**. We examined reaction of substrate **1b** with a tolylethynyl moiety (R^2 = 4-MeC$_6$H$_4$); product **5b** was obtained in 80% yield (entry 1). For *n*-butyl substrate **1h** (R^2 = *n*-butyl), its resulting product **5c** was rendered with 71% yield (entry 2). For species **1j** bearing alkenyl substituent R^1 = 4-ClC$_6$H$_4$, resulting product **5d** was formed in 78% yield (entry 3). For vinyldiazo ketones **2c** and **2e** with R^4 = 4-XC$_6$H$_4$; X = OMe and Cl, their reactions with **1a** delivered compounds **5e** and **5f** in 73% and 76% yields, respectively (entries 4 and 5). The reaction maintained a high efficiency for 3-thienyl ketone derivative **2g** (R^4 = 3-thienyl), generating compound **5g** with 82% yield (entry 6). In the case of cyclopropylketone derivatives **2i** (R^4 = cyclopropyl), its corresponding product **5h** was obtained in moderate yield (61%, entry 7). We performed this catalytic reaction also on 3-methyl-2-diazo-3-vinyl phenyl ketone **2k** (R^5 = Me); its desired product **5i** was obtained in 60% yield (entry 8). We prepared also enynones **1p** with R^1 = 3-thienyl and R^2 = 4-BrC$_6$H$_4$; its reaction with 2-naphthylvinyldiazo ketone **2h** delivered all heteroaryl-substituted triarylmethane **5j** in 83% yield (entry 9).

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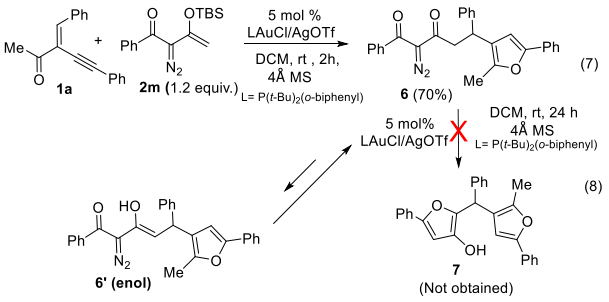
The X-ray diffraction studies confirmed the molecular structure of compound **5j**. Vinyldiazo ester **2a'** was also an applicable substrate that reacted with enynone **1a** to deliver its corresponding product **5k** in 77% yield (entry 10).

Among our triaryl products, the mechanism of the formation of 1-furyl-containing compounds **3** and **4** is unclear; we thus conducted an additional experiment. We prepared 2-siloxyvinyldiazo ketone **2m** that reacted with enynone **1a** to yield α-oxodiazo ketone **6** that was not convertible to our target **7**. A main reason for this unsuccessful reaction is that its keto−enol tautomerization is unfavorable for enol form **6'**, rendering formation of its gold carbene difficult Herein, the cationic gold catalyst coordinates with the 1,3-dicarbonyl oxygens to form a stable chelation species.

We postulate a plausible mechanism in Scheme 2 involving key intermediate **C** that is inferred from isolation of α-oxo diazo species **6** (eq 7). In the presence of a gold catalyst, gold



π-alkyne species forms gold-containing 3-furylbenzyl cation[6] **A**. An initial C(1)-attack of vinyldiazo species **2a** on this cation **A** generates C(1)-addition intermediate **B** that is deprotonated with OTf^- to generate 3-furylgold diazo species **C** and species **D** sequentially. In the presence of the gold catalyst, diazo species **D** forms gold vinylcarbenes that subsequently undergo a known oxa-Nazarov cyclization to give furylinum species **F**, ultimately yielding the observed product **3a**.

To rationalize the *N*-attack of pyrazole intermediates, we postulate two tautomers **2*α*** and **2*α*'** as initial nucleophiles, as depicted in Scheme 2. Tautomer **2*α*** is the isolated form; its reaction with 3-furylbenzyl cation **A** is expected to occur at the N(5)-regioselectivity, so to retain a N−H---O═C hydrogen bond. In this path, resulting iminium intermediate **G** is highly acidic and becomes readily deprotonated with TfO^- to yield observed product **5a** through a N(5)-addition route.

Equation 4 shows the inapplicability of vinyldiazo ester **2a'** to this triarylmethane synthesis because the ester functionality has less electron-withdrawing power. For ester **2a'**, its ester form is best described with resonance structure **2a'-I**, whereas vinyldiazo ketone **2a** has important contributions from two other forms **2a-II** and **2a-III**. Accordingly, vinyldiazo ketone **2a** is better than vinyldiazo ester as a nucleophile.

In summary, we report gold-catalyzed divergent syntheses of nonsymmetric heteroaryl-substituted triarylmethanes using 2-(1-alkynyl)-2-alken-1-ones and vinyldiazo ketones. Our mechanistic analysis indicates that vinyldiazo ketones attack gold-containing 3-furylbenzyl cations[6] to form the observed C(1)-addition products. We found also that vinyldiazo ketones can be thermally activated to yield pyrazoles; this process is also elaborated into pyrazole-containing products using the same reactants and gold catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02765.

Experimental procedures, characterization data, crystallography data, and ^{1}H NMR and ^{13}C NMR for representative compounds (PDF)

Accession Codes

CCDC 2022577−2022578 contain 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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