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Gold-catalyzed formal $[4\pi + 2\pi]$ -cycloadditions of propiolate derivatives with unactivated nitriles†

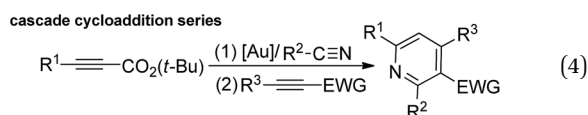
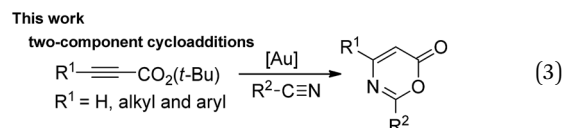
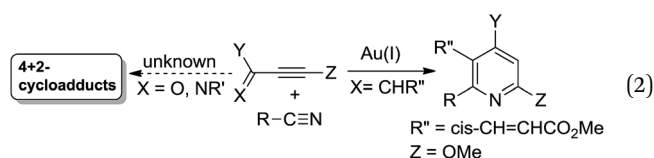
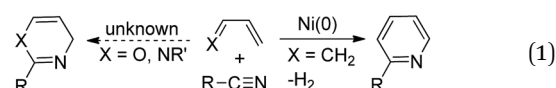
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Gold-catalyzed hetero- $[4\pi + 2\pi]$ -cycloadditions of *tert*-butyl propiolates with unactivated nitriles are described; the resulting 6*H*-1,3-oxazin-6-ones are not easily accessible via conventional methods. This new finding enables a one-pot gold-catalyzed synthesis of highly substituted pyridines through sequential gold-catalyzed reactions of *tert*-butyl propiolates with nitriles, and then with electron-deficient alkynes in the same solvent. The utility of these $[4 + 2]$ -cycloadditions is further expanded with various aldehydes, ketones and 2-phenyloxetane, yielding satisfactory yields of cycloadducts.

Introduction

Metal-catalyzed $[4\pi + 2\pi]$ -cycloadditions are powerful tools for the construction of carbo- or heterocyclic frameworks.^{1,2} Although common nitriles and alkynes represent common triple bond motifs, nitriles are generally less reactive than alkynes in catalytic $[4\pi + 2\pi]$ -cycloadditions; the chemical stability of nitriles is reflected by their bond energy (854 kJ mol⁻¹), being larger than that of alkynes (835 kJ mol⁻¹).³ For instance, thermal $[4\pi + 2\pi]$ -cycloadditions of dienes with unactivated nitriles required 600 °C (2 min) to give pyridine derivatives in 0.1–0.5% yields.^{4a} In the context of catalytic $[4\pi + 2\pi]$ -cycloadditions, not surprisingly, only one literature report documents both nitrile/1,3-diene and nitrile/1,3-enyne systems (eqn (1) and (2)).^{4b,c} Ogoshi reported the first formal $[4 + 2]$ -cycloadditions of common nitriles with dienes using Ni(0) catalysts (eqn (1)).^{4b} Although Barluenga and Aguilar reported formal $[4\pi + 2\pi]$ -cycloadditions of some 3-en-1-yne with unactivated nitriles,^{4c} such highly functionalized 3-en-1-yne (X = *cis*-unsaturated ester, Z = alkoxy) are too specialized to reflect the reaction generality (eqn (2)). The $[4\pi + 2\pi]$ -nitrile cycloadditions still remain an unsolved task for O- and N-substituted analogues of 1,3-dienes and 1,3-enynes (X = O, NR', eqn (1) and (2)).⁵ In a significant advance, we here report the gold-catalyzed formal hetero- $[4\pi + 2\pi]$ -cycloadditions^{6,7} of various propiolates with nitriles to afford 6*H*-1,3-oxazin-6-ones efficiently (eqn (3)).⁸ These findings enable the development of new cascade cycloadditions using three π -motifs including propiolates, nitriles and alkynes, yielding highly substituted pyridine derivatives. Notably, 6*H*-1,3-oxazin-6-ones are useful intermediates in various organic reactions whereas highly substituted pyridines

are important structural cores commonly found in many bioactive molecules (see ESI Fig. S1†);^{9,10} their availability from convenient *t*-butyl propiolates increases the synthetic utility of this gold catalysis.



Results and discussion

We envisage that direct $[4\pi + 2\pi]$ -cycloadditions of propiolate derivatives with nitriles provide the most convenient synthesis of 6*H*-1,3-oxazin-6-ones such as 3; the current procedures rely mainly on thermal rearrangement of *N*-acyl β -

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lactams.^{8a-d} To test the feasibility, as shown in Table 1, *tert*-butyl hept-2-ynoate (**1a**, 1 equiv.) was treated with benzonitrile **2a** (3 equiv.) and AuCl₃ (5 mol%) in hot DCE (70 °C, 16 h), affording the desired product **3a** in only a small yield (5%) together with the initial **1a** in 45% recovery (entry 1). The use of PPh₃AuCl/AgSbF₆ significantly increased the yield of the desired **3a** to 51% (entry 2). We also examined other cationic gold catalysts (5 mol%) including IPrAuCl/AgSbF₆ and P(*t*-Bu)₂(*o*-biphenyl)AuCl/AgSbF₆, yielding compound **3a** in 64% and 85% yields, respectively (see entries 3 and 4). With the alteration of the silver salts as in P(*t*-Bu)₂(*o*-biphenyl)AuCl/AgX (X = NTf₂ and OTf), the product yields slightly decreased to 77% and 72%, respectively (entries 5 and 6). AgSbF₆ (70 °C, 24 h) and Zn(OTf)₂ (19 h) were found to be inactive in DCE, leading to a recovery of the starting compound **1a** in 72–75% yield (entries 7 and 8). The use of In(OTf)₃, Sc(OTf)₃ and TfOH in DCE gave hept-2-ynoic acid **1a'** in 65–72% yield and amide species **2a-H** (25–35% yield) along with unreacted starting compound **1a** (5–15% yield, entries 9–11). The yields of compound **3a** varied with the solvents (70 °C), with 65% in toluene (22 h), 82% in C₆H₅Cl (18 h) and 56% in 1,4-dioxane (19 h, entries 12–14).

Table 2 assesses the reaction generality using various propiolate derivatives with varied nitriles. We first examined the reactions with unsubstituted propiolate species **1b**; its cycloaddition with benzonitrile **2a** proceeded smoothly to form the formal cycloadduct **3b** in 65% yield (entry 1). The reaction scope is extensible to aliphatically substituted

propiolate species **1c–1e** (R = isopropyl, cyclopropyl and cyclohexyl), yielding the desired products **3c–3e** in satisfactory yields (77–85%, entries 2–4). This formal cycloaddition is also applicable to alkenyl-substituted propiolate **1f** to afford the corresponding product **3f** in 68% yield (entry 5). We tested the reactions on various phenyl-substituted propiolate species **1g–1j** bearing various *para*-substituents (X = H, OMe, F and Cl); their resulting cycloadducts **3g–3j** were obtained in satisfactory yields (65–72%, entries 6–9). We performed an X-ray diffraction study of product **3g** to confirm its molecular structure.¹¹ We also prepared 2- and 3-thienyl-substituted propiolate derivatives **1k** and **1l**; their reactions with benzonitrile afforded cycloadducts **3k** and **3l** in reasonable yields (entries 10 and 11, 55–58%). Entries 12–15 show the tests of *tert*-butyl hept-2-ynoate **1a** with benzonitriles **2b–2e** bearing various *para*-substituents (X = OMe, Me, CO₂Me, Cl) that afforded the desired cycloadducts **3m–3p** in satisfactory yields (62–76%). These catalytic cycloadditions were compatible with disparate nitriles including cyclohexyl nitrile (**2f**), cinnamonnitrile (**2g**) and 3-thienyl nitrile (**2h**), affording the expected products **3q–3s** in satisfactory yields (66–78%, entries 16–18).

As inferred from the chemistry of 2*H*-pyran-2-ones,^{12,13} one representative compound **3a** (1 equiv.) was treated with diethyl but-2-ynedioate (4 equiv.) in hot *p*-xylene (150 °C, 10 h) to afford tetrasubstituted pyridine **5a** in 96% yield; this reaction sequence presumably proceeds with intermediate **I** that is prone to a loss of CO₂ (eqn (5)). As chlorobenzene is also an effective solvent for such a nitrile/propiolate cycloaddition (Table 1, entry 9), we developed a

Table 1 Tests of propiolate derivatives with gold catalysts

					Yields ^{a,b} (%)			
Entries	Catalyst	Solvent	Time (h)		1a	3a	1a'	2a-H
1	AuCl ₃	DCE	16		45	5	—	—
2	Ph ₃ PAuCl/AgSbF ₆	DCE	12		—	51	—	—
3	IPrAuCl/AgSbF ₆	DCE	19		—	64	—	—
4	LAuCl/AgSbF ₆	DCE	18		—	85	—	—
5	LAuCl/AgNTf ₂	DCE	20		—	77	—	—
6	LAuCl/AgOTf	DCE	22		—	72	—	—
7	AgSbF ₆	DCE	24		75	—	—	—
8	Zn(OTf) ₂ ^c	DCE	19		72	—	—	—
9	In(OTf) ₃ ^c	DCE	18		15	—	72	35
10	Sc(OTf) ₃ ^c	DCE	22		10	—	65	32
11	HOTf ^c	DCE	15		5	—	67	25
12	LAuCl/AgSbF ₆	Toluene	22		—	65	—	—
13	LAuCl/AgSbF ₆	C ₆ H ₅ Cl	18		—	82	—	—
14	LAuCl/AgSbF ₆	1,4-Dioxane	19		—	56	—	—

^a [1a] = 0.18 M. ^b Product yields are reported after purification using a silica column. IPr = 1,3-bis(diisopropyl phenyl)-imidazol-2-ylidene, L = P(*t*-Bu)₂(*o*-biphenyl), Tf = trifluoromethanesulfonyl. ^c Reactions carried out at room temperature.

Table 2 Formal cycloadditions of various propiolates with nitriles

$$\text{R}-\text{C}\equiv\text{C}-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3 + \text{R}'-\text{CN} \xrightarrow[\text{DCE, 70 } ^\circ\text{C, Time}]{5 \text{ mol\% LAuCl}_4, 5 \text{ mol\% AgSbF}_6} \text{R}-\text{C}_5\text{H}_3\text{N}(\text{R}')\text{O}-\text{C}(=\text{O})\text{Ph} \quad \text{3}$$

(1) R = H (**3b**, 17 h, 65%)^{a,b}

(5) **3f** (25 h, 68%)

(6) X = H (**3g**, 24 h, 68%)

(2) R = isopropyl (**3c**, 20 h, 77%)

(7) X = OMe (**3h**, 24 h, 65%)

(3) R = cyclopropyl (**3d**, 16 h, 85%)

(8) X = F (**3i**, 19 h, 72%)

(4) R = cyclohexyl (**3e**, 22 h, 82%)

(9) X = Cl (**3j**, 20 h, 70%)

(10) Ar = 2-thienyl (**3k**, 35 h, 55%)

(12) X = OMe (**3m**, 16 h, 72%)

(16) R' = Cyclohexyl (**3q**, 25 h, 70%)

(11) Ar = 3-thienyl (**3l**, 35 h, 58%)

(13) X = Me (**3n**, 21 h, 76%)

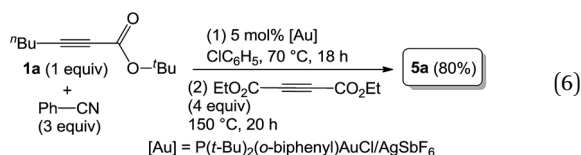
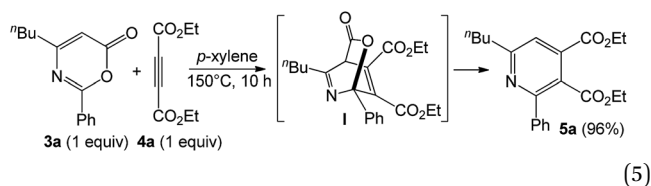
(17) R' = *trans*-styryl (**3r**, 48 h, 78%)

(14) X = CO₂Me (**3o**, 24 h, 62%)

(18) R' = 3-thienyl (**3s**, 36 h, 66%)

(15) X = Cl (**3p**, 25 h, 70%)

one-pot reaction involving the prior heating of a chlorobenzene solution of propiolate derivative **1a**, benzonitrile (3 equiv.) and P(*t*-Bu)₂(*o*-biphenyl) AuCl/AgSbF₆ (5 mol%) at 70 °C (18 h) in a sealed tube to ensure a complete consumption of starting compound **1a**; to this solution was added diethyl but-2-ynedioate (4 equiv.) with further heating at 150 °C for 20 h. This one-pot process delivered the desired pyridine **5a** in 80% yield (eqn (6)). If the three reactants in the same proportions were heated together with a gold catalyst in hot chlorobenzene (150 °C, 20 h), the yield of **5a** was decreased to 38% yield.



The easy operation of this one-pot reaction inspires us to examine the scope of the reaction using various propiolates, nitriles and alkynes; the results are summarized in Table 3. The procedures follow exactly that described in eqn (6). In the second stage of heating, the temperature is 150 °C for entries 1–7 and 180 °C for entries 8–12. Entry 1 shows the compatibility of these cycloadditions with unsubstituted propiolate derivative **1b** (R = H) that reacted sequentially with benzonitrile (**2a**) and diethyl but-2-ynedioate (**4a**) to yield the desired pyridine **5b** in 45% yield. We also tested the reactions on various alkyl-substituted propiolates **1c–1e** (R = isopropyl, cyclopropyl and cyclohexyl) that reacted with the same alkyne and benzonitrile to afford the desired pyridine species **5c–5e** in 73–76% yields (entries 2–4). The reaction is further applicable to aryl-substituted propiolates **1g** and **1l** (R = Ph, 3-thienyl) to deliver the desired pyridines **5f** and **5g** in 61% and 51% yield, respectively (entries 5 and 6). We tested the reactions of model propiolate (**1a**) and diethyl but-2-ynedioate (**4a**) with various nitriles (R¹ = cyclohexyl, 3-thienyl and *trans*-styryl), affording the expected pyridine products **5h–5j** in satisfactory yields (68–75%, entries 7–9). The reactions were extensible to various unsymmetric alkynes **4b–4f** that reacted with propiolate (**1a**) and benzonitrile (**2a**) with excellent or high regioselectivity (entries 11–15). The reactions worked well for terminal alkynes **4b** (EWG = COOMe) and **4c** (EWG = COPh) to afford the desired pyridines **5k** and **5l** as single regioisomers, with respective yields of 83% and 76% (entries 10 and 11). For *n*-butyl propiolate **4d**, this one-pot sequence gave two inseparable isomeric products **5m/5m'** = 4/1, in a combined 82% yield (entry 12). For the other *n*-butyl and phenyl-substituted

ynones **4e** and **4f** (EWG = COPh), their reactions afforded **5n** and **5o** with excellent regioselectivity and satisfactory yields (81–84%) (entries 13–14). The structures of representative compounds **5m** and **5n** were confirmed by proton NOE effects whereas the structure of cycloadduct **5o** was elucidated with an HMBC experiment (see ESI†).

As nitriles are weakly nucleophilic, we envisage that aldehydes and ketones might be applicable substrates. To our pleasure, gold-catalyzed reactions of 3-phenylpropiolate **1g** with benzaldehyde, phenyl methyl ketone and acetone in hot dichloroethane (DCE) proceeded smoothly to afford formal cycloadducts **6a–6c** in high yields (86–89%, eqn (7)). The structure of compound **6a** was determined by X-ray diffraction.¹¹ These carbonyl cycloadditions were also applicable to alkyl-substituted propiolates (**1a**) and (**1e**), yielding the desired compounds **6d** and **6e** in 87% and 77% yield, respectively (eqn (8)). Such a reaction was, notably, accessible to an eight-membered oxacyclic compound **6f** with 2.5 mol% 1,3-bis(diisopropyl phenyl)-imidazol-2-ylidene AuSbF₆; it was isolated as a single regioisomer with 67% yield with 2-phenyloxetane (3 equiv.) and its molecular structure has been confirmed by X-ray diffraction.¹¹ The compatibility of this gold catalysis with aldehydes, ketones and oxetanes truly reflects a broad applicability of these cycloadditions.

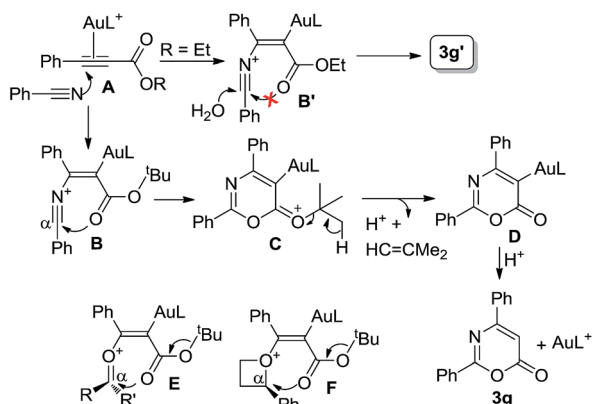
Table 3 One-pot operations with nitriles, propiolates and alkynes

(1) R = H (5b , 17/20 h, 45%) ^{a,b}	(5) R = Ph (5f , 24/20 h, 61%)
(2) R = isopropyl (5c , 20/18 h, 74%)	(6) R = 3-thienyl (5g , 35/27 h, 51%)
(3) R = cyclopropyl (5d , 16/18 h, 76%)	
(4) R = cyclohexyl (5e , 22/25 h, 73%)	
(7) R ¹ = cyclohexyl (5h , 25/26 h, 75%)	(10) X = OMe (5k , 18/35 h, 83%)
(8) R ¹ = 3-thienyl (5i , 36/19 h, 68%)	(11) X = Ph (5l , 18/33 h, 76%)
(9) R ¹ = <i>trans</i> -styryl (5j , 48/30 h, 72%)	
(12) X = OEt (5m/5m' = 4/1, 18/120 h, 82%)	(14) 5o (18/35 h, 84%)
(13) X = Ph (5n , 18/47 h, 81%)	

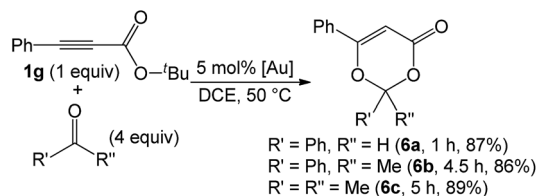
^a 5 mol% gold catalyst, L = P(*t*-Bu)₂(*o*-biphenyl), R¹CN (3 equiv.), R²CC-EWG (4 equiv.), 150 °C for entries 1–9 and 180 °C for entries 10–14.

^b These data correspond to the reaction time *t*₁/*t*₂.

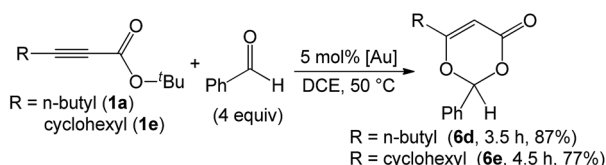




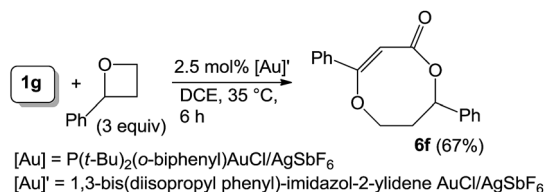
Scheme 1 A postulated reaction mechanism.



(7)

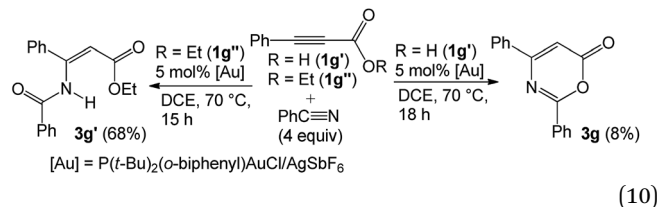


(8)



(9)

Prior to this work, Shin reported gold-catalyzed [4 + 2]-cycloadditions of alkenes with propiolic acid, which was, however, the only applicable substrate.^{6a} Here, we employ diverse propiolate substrates to comply with not only nitriles but also aldehydes, ketones and oxetanes. To understand this discrepancy, we performed the reaction of 3-phenylpropiolic acid (**1g'**) with benzonitrile with the same gold catalyst in DCE, but the yield of the desired compound **1g** was only 8%, much smaller than that (68%) of its *tert*-butoxy derivative **1g** (Table 2, entry 5). Clearly, prior transformations of *t*-butoxy propiolates to the propiolate acids do not occur in the course of the reactions. For ethyl propiolate **1g''**, its corresponding reaction with benzonitrile gave the amide-addition product **3g'** in 68% yield (eqn (10)); under this condition, benzonitrile was not effectively transformed into benzamide with this gold catalyst.¹⁴



(10)

The control experiments in eqn (10) indicate a mechanism involving a prior formation of nitrilium species **B** via a π -alkyne activation, proceeding with an attack of nitrile at the gold- π -alkyne species **A**. As shown in Scheme 1, we postulate that the *tert*-butoxy group of species **B** increases the nucleophilicity of a carbonyl group to attack this nitrilium moiety efficiently. This process releases a *tert*-butyl cation to induce a demetalation to form the observed cycloadduct **3g**. Beside nitriles, various aldehydes, ketones and oxetanes are more reactive than alkenes upon comparison of their applicable propiolates. We postulate that these nucleophiles generate intermediates **B**, **E** and **F** bearing a large positive charge on the reacting C $_{\alpha}$ -carbons because of their adjacent oxonium and ammonium centers. We envisage that the propiolate cycloadditions match well with those nucleophiles that can develop highly polarized carbocations through π -alkyne activations.

Conclusions

Unactivated nitriles are known to be stable triple-bond species, and their [4 + 2]-cycloadditions with 4 π -bond motifs and other small molecules have few successful examples.¹⁵ This work reports the hetero-[4 π + 2 π]-cycloadditions of *tert*-butyl propiolates and nitriles catalyzed by gold catalysts. Such formal cycloadditions are applicable to diverse *tert*-butyl propiolates and nitriles, yielding useful 6*H*-1,3-oxazin-6-ones, which are not readily prepared with current methods.⁸ This new finding enables a one-pot gold-catalyzed synthesis of highly substituted pyridines through sequential reactions of *tert*-butyl propiolates with nitriles, and then with electron-deficient alkynes in the same solvent. The utility of these [4 + 2]-cycloadditions is further expanded with various aldehydes, ketones and 2-phenyloxetane, yielding satisfactory yields of cycloadducts. This work provides a new version of *tert*-butyl propiolates that feature useful four-atom building blocks with polar π -bond motifs such as nitriles, aldehydes and ketones, although their reactions with alkenes were reported to be restrictive.⁸

Acknowledgements

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