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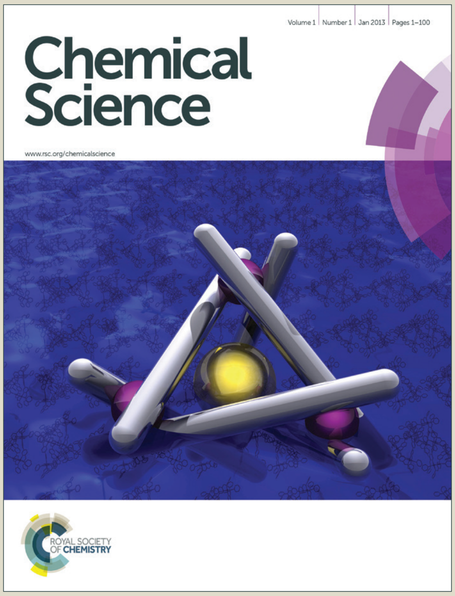

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EDGE ARTICLE

# Gold-catalyzed Formal [4π+2π]-Cycloadditions of Propiolate Derivatives with Unactivated Nitriles

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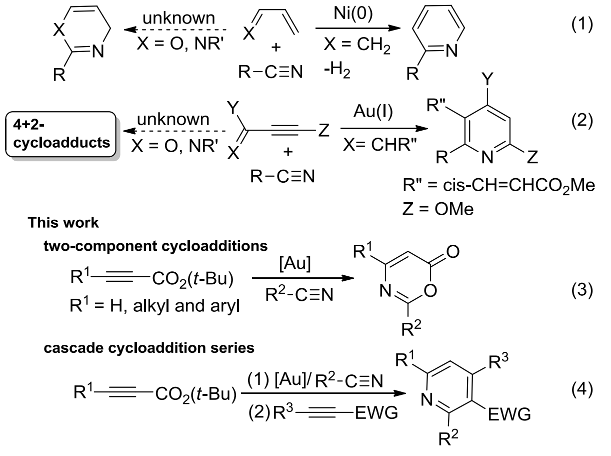
Gold-catalyzed hetero-[4π+2π]-cycloadditions of *tert*-butyl propiolates with unactivated nitriles are described; the resulting 6*H*-1,3-oxazin-6-ones are not easily accessible from conventional methods. This new finding enables a one-pot gold-catalyzed synthesis of highly substituted pyridines through 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, 2-phenyloxetane, yielding satisfactory yields of cycloadducts.

## Introduction

Metal-catalyzed [4π+2π]-cycloadditions are powerful tools to construct 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 [4π+2π]-cycloadditions; the chemical stability of nitriles is reflected by their bond energy (854 kJ/mol), larger than that of alkynes (835 kJ/mol).[3] For instances, thermal [4π+2π]-cycloadditions of dienes with unactivated nitriles required 600 ℃ (2 min) to give pyridine derivatives in 0.1-0.5 % yields.[4a] In the context of catalytic [4π+2π]-cycloadditions, not surprisingly, only one literature report documents both nitrile/1,3-diene and nitrile/1,3-enyne systems (eqs 1-2).[4b-c] Ogoshi reported the first formal [4+2]-cycloadditions of common nitriles with dienes using Ni(0) catalysts (eq 1).[4b] Although Barluenga and Aguilar reported formal [4π+2π]-cycloadditions of some 3-en-1-ynes with unactivated nitriles,[4c] such highly functionalized 3-en-1-ynes (X = *cis*-unsaturated ester, Z = alkoxy) are too specialized to reflect the reaction generality (eq 2). The [4π+2π]-nitrile cycloadditions still remain an unsolved task for O- and N-substituted analogues of 1,3-dienes and 1,3-enynes (X = O, NR', eqs 1-2).[5] In a significant advance, we here report the gold-catalyzed formal hetero-[4π+2π]-cycloadditions[6-7] of various propiolates with nitriles to afford 6*H*-1,3-oxazin-6-ones efficiently (eq 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 Supporting Information Figure 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 [4π+2π]-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-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 $AuCl_3$ (5 mol %) in hot DCE (70 ℃, 16 h), affording desired product **3a** in an only slight yield (5 %) together with initial **1a** in 45% recovery (entry 1). The use of $PPh_3AuCl/AgSbF_6$ significantly increased the yield of desired **3a** to 51% (entry 2). We examined also other cationic gold catalysts (5 mol %)

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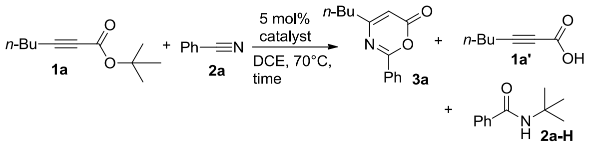
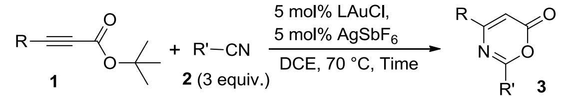
*Table 1.* Tests of propiolate derivatives with gold catalysts.

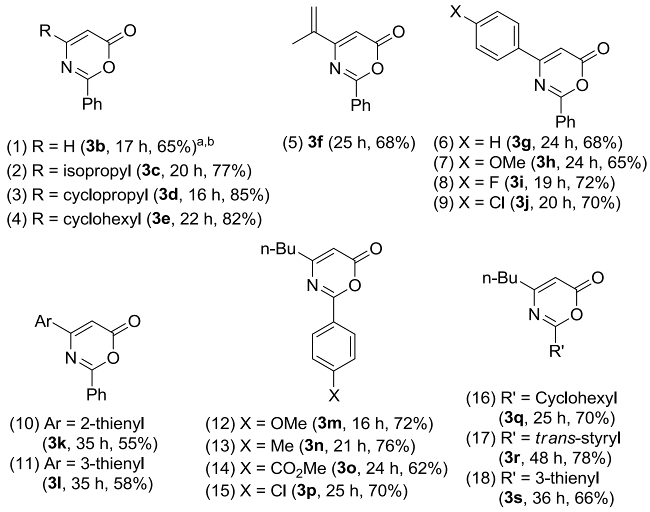


| entries | catalyst | solvent | time (h) | Yields (%)[a,b] 1a | 3a | 1a' | 2a-H |
|---|---|---|---|---|---|---|---|
| 1 | $AuCl_3$ | DCE | 16 | 45 | 5 | - | - |
| 2 | $Ph_3PAuCl$ / $AgSbF_6$ | DCE | 12 | - | 51 | - | - |
| 3 | IPrAuCl / $AgSbF_6$ | DCE | 19 | - | 64 | - | - |
| 4 | LAuCl / $AgSbF_6$ | 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 / $AgSbF_6$ | $C_6H_5Cl$ | 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 = $P(t\text{-}Bu)_2$(*o*-biphenyl), Tf = trifluoromethansesulfonyl. [c] Reactions carried out at room temperature.

*Table 2*. Formal cycloadditions of various propiolates with nitriles





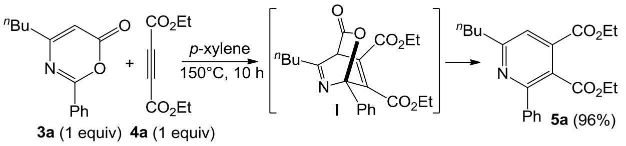
(1) R = H (**3b**, 17 h, 65%)[a,b]
(2) R = isopropyl (**3c**, 20 h, 77%)
(3) R = cyclopropyl (**3d**, 16 h, 85%)
(4) R = cyclohexyl (**3e**, 22 h, 82%)
(5) **3f** (25 h, 68%)
(6) X = H (**3g**, 24 h, 68%)
(7) X = OMe (**3h**, 24 h, 65%)
(8) X = F (**3i**, 19 h, 72%)
(9) X = Cl (**3j**, 20 h, 70%)
(10) Ar = 2-thienyl (**3k**, 35 h, 55%)
(11) Ar = 3-thienyl (**3l**, 35 h, 58%)
(12) X = OMe (**3m**, 16 h, 72%)
(13) X = Me (**3n**, 21 h, 76%)
(14) X = $CO_2Me$ (**3o**, 24 h, 62%)
(15) X = Cl (**3p**, 25 h, 70%)
(16) R' = Cyclohexyl (**3q**, 25 h, 70%)
(17) R' = *trans*-styryl (**3r**, 48 h, 78%)
(18) R' = 3-thienyl (**3s**, 36 h, 66%)

[a] **2** (3 equiv), [**1**] = 0.18 M. [b] Product yields are reported after purification using a silica column. L = $P(t\text{-}Bu)_2$(*o*-biphenyl).

including IPrAuCl/$AgSbF_6$, $P(t\text{-}Bu)_2$(o-biphenyl)AuCl/$AgSbF_6$, yielding compound **3a** in 64% and 85% yields respectively (see entries 3-4). With alteration of silver salts as in $P(t\text{-}Bu)_2$(*o*-biphenyl)AuCl/AgX (X = $NTf_2$ and OTf), the product yields were slightly decreased to 77% and 72% respectively (entries 5-6). $AgSbF_6$ (70 ℃, 24 h) and $Zn(OTf)_2$ (19 h) were found to be inactive in DCE, leading to a recovery of starting **1a** in 72-75% yield (entries 7-8). 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 **1a** (5-15% yield, entries 9-11). The yields of compound **3a** varied with solvents (70 ℃), with 65% in toluene (22 h), 82% in $C_6H_5Cl$ (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 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 desired products **3c**-**3e** in satisfactory yields (77-85%, entries 2-4). This formal cycloaddition is also applicable to alkenyl-substituted propiolate **1f** to render 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 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 10-11, 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, $CO_2Me$, Cl) that afforded desired cycloadducts **3m**-**3p** in satisfactory yields (62-76%). These catalytic cycloadditions were compatible with disparate nitriles including cyclohexyl nitrile (**2f**), cinnamonitrile (**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 ℃, 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 $CO_2$ (eq 5). As chlorobenzene is also



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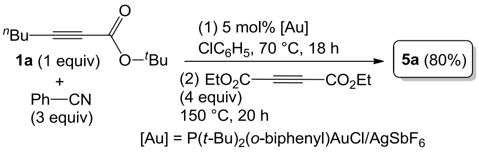

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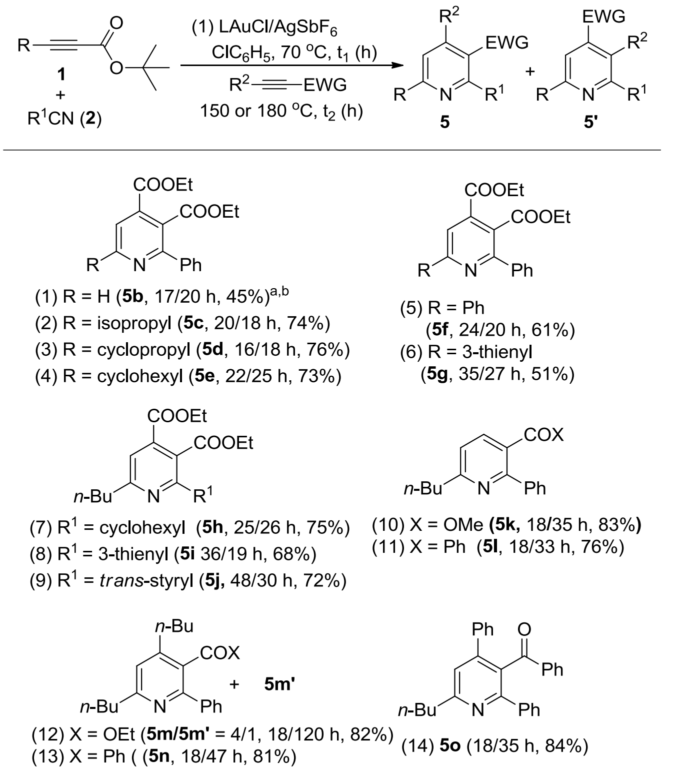
***Table 3.*** One-pot operations with nitriles, propiolates and alkynes.

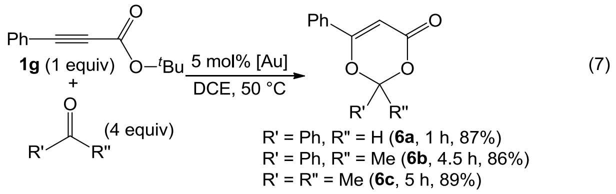


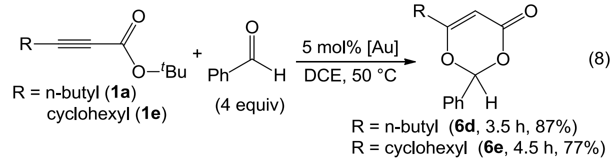
[a] 5 mol% gold catalyst, L= P($t$-Bu)$_2$(o-biphenyl), R$^1$CN (3 equiv), R$^2$CC-EWG (4 equiv), 150 ℃ for entries 1-9 and 180 ℃ for entries 10-14. [b] These data correspond to the reaction time t$_1$/t$_2$

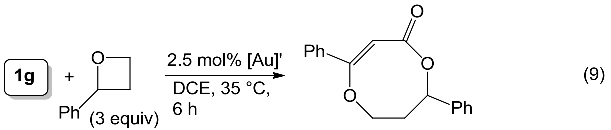
an effective solvent for such a nitrile/propiolate cycloaddition (Table 1, entry 9), we develop a one-pot reaction involving a prior heating a chlorobenzene solution of propiolate derivative **1a**, benzonitrile (3 equiv) and P($t$-Bu)$_2$($o$-biphenyl) AuCl/AgSbF$_6$ (5 mol %) at 70 ℃ (18 h) in a sealed tube to ensure a complete consumption of starting **1a;** to this solution was added diethyl but-2-ynedioate (4 equiv) with further heating at 150 ℃ for 20 h. This one-pot process delivered desired pyridine **5a** in 80% yield (eq 6). If the three reactants of the same proportions were heated together with gold catalyst in hot chlorobenzene (150 ℃, 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 eq 6. In the second stage of heating, the temperature is 150 ℃ for entries 1-7 and 180 ℃ for entries 8-12. Entry 1 show 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 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 same alkyne and benzonitrile to afford 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% yields respectively (entries 5-6). We tested the reactions of model propiolate (**1a)** and diethyl but-2-ynedioate (**4a**) with various nitriles (R$^1$ = 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 10-11). 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 Supporting Information).

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%, eq 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 desired compounds **6d** and **6e** in 87% and 77% yields respectively (eq 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 AuSbF$_6$; that was isolated as a single regioisomer with 67% yield with 2-phenyloxetane (3 equiv); its molecular structure has been confirmed by X-ray diffraction study.[11] The compatibility of this gold catalysis with aldehydes, ketones and oxetanes truly reflects a broad applicability of these cycloadditions.

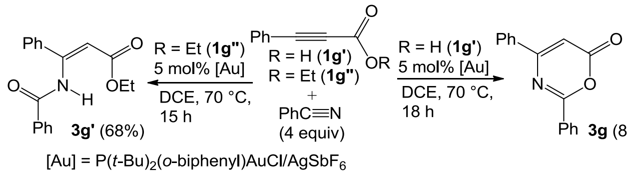






[Au] = P($t$-Bu)$_2$($o$-biphenyl)AuCl/AgSbF$_6$
[Au]' = 1,3-bis(diisopropyl phenyl)-imidazol-2-ylidene AuCl/AgSbF$_6$

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 desired **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 reactions. For ethyl propiolate **1g''**, its corresponding reaction with benonitrile gave amide-addition product **3g'** in 68% yield (eq 10); under this condition, benzonitrile was not effectively transformed into benzamide with this gold catalyst.[14]



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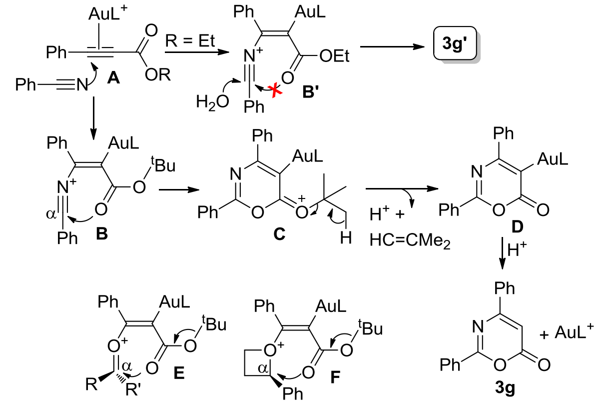

Scheme 1. A postulated reaction mechanism.

The control experiments in eq 10 indicate a mechanism involving a prior formation of nitrilium species **B** via a π-alkyne activation, proceeding with an attack of nitrile at gold-π-alkyne species **A**. As shown in Scheme 1, we postulate that the *tert*-butyoxy 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 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 4π-bond motifs and other small molecules have few successful examples.[15] This work reports the hetero-[4π+2π]-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, 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

We thank National Science Council, Taiwan, for financial support of this work.

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