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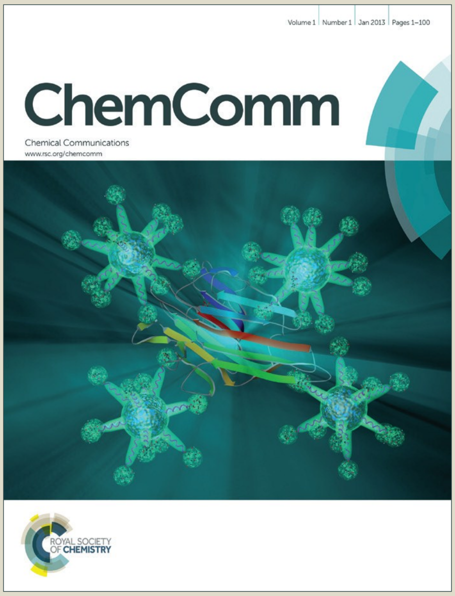

Volume 1 | Number 1 | Jan 2013 | Pages 1–100

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COMMUNICATION

Gold-catalyzed Formal [4π+2π]-Cycloadditions of *tert*-Butyl Propiolates with Aldehydes and Ketones to form 4*H*-1,3-Dioxine Derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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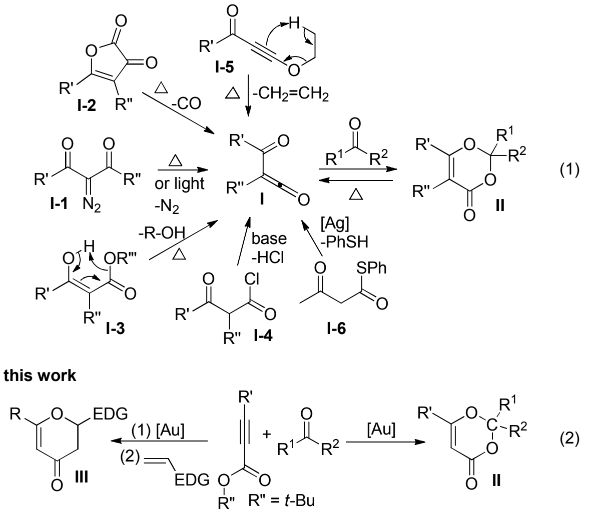
Gold-catalyzed formal hetero-[4π+2π] cycloadditions of *tert*-butyl propiolates with carbonyl compounds proceeded efficiently to yield 4*H*-1,3-dioxine derivatives over a wide scope of substrates. With acetone as a promoter, gold-catalyzed cycloadditions of these propiolate derivatives with enol ethers led to the formation of atypical [4+2]-cycloadducts with skeletal rearrangement.

Metal-catalyzed hetero-[4π+2π] cycloadditions are powerful tools to access six-membered heterocyclic frameworks.[1-2] Prominent examples include the cycloadditions of dienes with carbonyls and 1-oxadienes with alkenes, affording useful 3,6-dihydro-2*H*-pyrans and 3,4-dihydro-2*H*-pyrans respectively.[3-4] Six-membered 4*H*-1,3-dioxines (**II,** eq 1) are important structural cores found in many natural products (see Figure S1).[5] These oxacyclic species serve as versatile species in various organic transformations because their can generate acyl ketenes (**I**) reversibly at elevated temperatures (eq 1).[6] Furthermore, this oxacyclic functionality is comprised in key intermediates toward the synthesis of naturally occurring compounds including spongistatin AB spiroketal,[7a] 2,6-deoxy sugars,[7b] taiwaniaquinol B,[7c] (+)-diplodialide A,[7d] (-)-kromycin,[7d] 16-membered macrolide antibiotic (-)-A26771B,[7e] (+)-ikarugamycin,[7f] cylindramide,[7g] callipeltoside A,[7h] (+)-tetronolide,[7i] kijanolide[7j] and (*S*)-(-)-zearalenone.[7k] The current synthesis of 4*H*-1,3-dioxin-4-ones (**II**) relies exclusively on reactive acyl ketenes,[6,8] commonly generated *in-situ* from the chemical decomposition of precursors, including liberation of N_2 from 2-diazo 1,3-carbonyl species (**I-1**),[8a] liberation of CO from furan-2,3-diones (**I-2**),[8b] thermal dealkoxylation of β-keto esters (**I-3**),[8c] liberation of HCl and ethylene from β-ketoacyl chlorides (**I-4**),[8d] and acylated alkoxyalkynes[8e] (**I-5**) and silver mediated activation of phenyl thioacetoacetate (**I-6**).[8f] The efficiency of this *"acyl ketene*" route is troubled by either inefficient liberation of small molecules or the tedious synthesis of these precursors. A development of a new synthesis of 4*H*-1,3-dioxin-4-ones (**II**) via a "non-acyl ketene" route would be significant and is highly desirable. Here, we report gold-catalyzed cycloadditions of readily available *tert*-butyl propiolates with organic carbonyls, yielding desired 4*H*-1,3-dioxin-4-ones efficiently (eq 2). The success of this cycloadditions is notable because the corresponding reaction between 1-oxadienes and carbonyls was reported in an intramolecular system.[8g] With acetone as a promoter, we also develop new [4π+2π]-cycloadditions of *tert*-butyl propiolates with electron-rich alkenes, yielding skeletally rearranged "atypical cycloadducts" **III** efficiently.



Direct [4π+2π]-cycloadditions of propiolate derivatives with carbonyl compounds is envisaged to be the most convenient synthesis of 4*H*-1,3-dioxines.[8a-f] As shown in Table 1, *tert*-butyl 3-phenylpropiolate (**1a**, 1 equiv) was treated with benzaldehyde **2a** (4 equiv) and $PPh_3AuCl/AgSbF_6$ (5 mol %) in hot DCE (50 ℃, 1 h), yielding the desired 4*H*-1,3-dioxine **3a** in satisfactory yield (83 %) (entry 1). We tested other cationic gold catalysts (5 mol %) including $IPrAuCl/AgSbF_6$ and $P(t\text{-Bu})_2$

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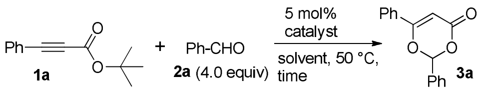
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

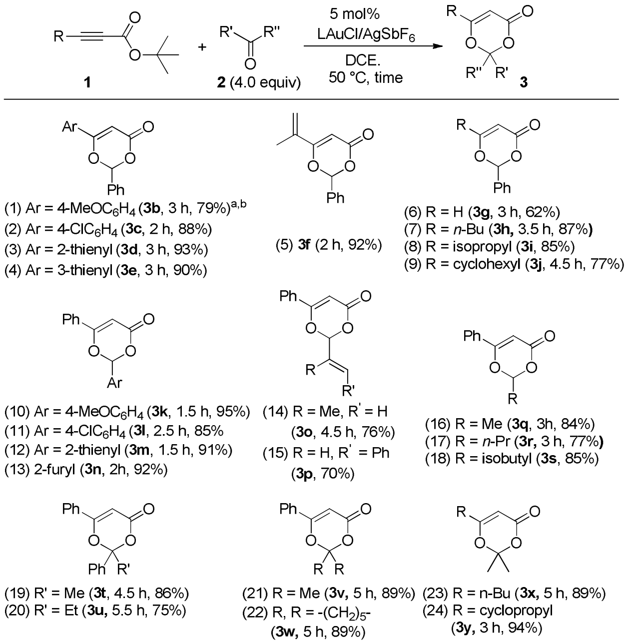
Table 1. Tests of gold catalysts.



entries	catalyst	solvent	time (h)	yield (%)[a,b]	
				1	3a
1	Ph$_3$PAuCl/AgSbF$_6$	DCE	1.0	-	83
2	IPrAuCl/AgSbF$_6$	DCE	1.0	-	84
3	LAuCl/AgSbF$_6$	DCE	1.0	-	87
4	LAuCl/AgNTf$_2$	DCE	1.0	-	85
5	LAuCl /AgOTf	DCE	1.0	-	86
6	AgSbF$_6$	DCE	10	80%	5
7	LAuCl/AgSbF$_6$	toluene	1.5	-	82
8	LAuCl /AgSbF$_6$	CH$_3$NO$_2$	1.0	-	75
9	LAuCl/AgSbF$_6$	1,4-dioxane	1.5	-	84
10	LAuCl/AgSbF$_6$	THF	1.5	-	79

[a] [**1a**] = 0.165 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 = trifluoromethansesulfonyl.

Table 2. Cycloadditions of various propiolates with carbonyls



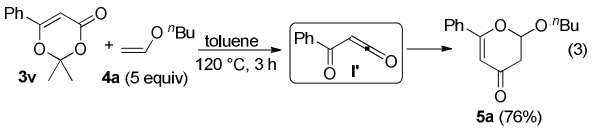
(1) Ar = 4-MeOC$_6$H$_4$ (**3b**, 3 h, 79%)[a,b]
(2) Ar = 4-ClC$_6$H$_4$ (**3c**, 2 h, 88%)
(3) Ar = 2-thienyl (**3d**, 3 h, 93%)
(4) Ar = 3-thienyl (**3e**, 3 h, 90%)
(5) **3f** (2 h, 92%)
(6) R = H (**3g**, 3 h, 62%)
(7) R = *n*-Bu (**3h**, 3.5 h, 87%)
(8) R = isopropyl (**3i**, 85%)
(9) R = cyclohexyl (**3j**, 4.5 h, 77%)
(10) Ar = 4-MeOC$_6$H$_4$ (**3k**, 1.5 h, 95%)
(11) Ar = 4-ClC$_6$H$_4$ (**3l**, 2.5 h, 85%
(12) Ar = 2-thienyl (**3m**, 1.5 h, 91%)
(13) 2-furyl (**3n**, 2h, 92%)
(14) R = Me, R' = H (**3o**, 4.5 h, 76%)
(15) R = H, R' = Ph (**3p**, 70%)
(16) R = Me (**3q**, 3h, 84%)
(17) R = *n*-Pr (**3r**, 3 h, 77%)
(18) R = isobutyl (**3s**, 85%)
(19) R' = Me (**3t**, 4.5 h, 86%)
(20) R' = Et (**3u**, 5.5 h, 75%)
(21) R = Me (**3v**, 5 h, 89%)
(22) R, R = -(CH$_2$)$_5$- (**3w,** 5 h, 89%)
(23) R = n-Bu (**3x,** 5 h, 89%)
(24) R = cyclopropyl (**3y,** 3 h, 94%)

[a] **2** (4 equiv), [**1**] = 0.165 M. [b] Product yields are reported after purification using a silica column. L = P(t-Bu)$_2$(*o*-biphenyl).

(*o*-biphenyl)AuCl/AgSbF$_6$, affording desired **3a** in 84% and 87% yields respectively (entries 2-3). With other silver salts as in P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgX (X = NTf$_2$ and OTf), the product yields of **3a** were 85% and 86% respectively (entries 4-5). AgSbF$_6$ alone was inactive in hot DCE (50 ℃, 10 h), leading to unreacted **1a** in 80% recovery. Solvents affected the yields of compound **3a** with 82% in toluene (1.5 h), 75% in nitromethane (1 h), 84% in 1,4-dioxane (1.5 h) and 79% in THF (1.5 h, entries 7-10). We performed X-ray diffraction study of compound **3a** to confirm its 4*H*-1,3-dioxine structure.[11]

Table 2 shows the generality of the reaction using various propiolate derivatives with varied aldehydes and ketones. We first examined the reactions on phenyl-substituted propiolates **1b**-**1c** bearing para-substituents (X = OMe, Cl), which reacted with benzaldehyde **2a** to deliver desired cycloadducts **3b**-**3c** in satisfactory yields (79-88%, entries 1-2). We prepared also 2- and 3-thienyl-substituted propiolates **1d** and **1e**; their gold-catalyzed reactions with benzaldehyde **2a** afforded cycloadducts **3d** and **3e** in excellent yields (90-93%, entries 3-4). This formal cycloaddition is applicable also to alkenyl-substituted propiolate species **1f** to render desired product **3f** in 92% yield (entry 5). We tested the reactions with unsubstituted propiolate species **1g** that provided a formal cycloadduct **3g** in 62% yield (entry 6). The scope of the reaction is extensible to aliphatically substituted propiolates **1h**-**1j** (R = *n*-Bu, isopropyl and cyclohexyl), providing expected products **3h**-**3j** in 77-87% yields (entries 7-9). Entries 10-18 show successful examples with various aldehyde substrates **2b**-**2i.** Benzaldehyde derivatives bearing various *para*-substituents (X = OMe **2b**, Cl **2c**) afforded cycloadducts **3k**-**3l** in high yields (85-95%, entries 10-11). This cycloaddition was compatible with thiophene-2-carbaldehyde **2d** and furan-2-carbaldehyde **2e**, giving desired compounds **3m** and **3n** in 91–92% yields (entries 12-13**)**. These gold-catalyzed cycloadditions worked well with methacrylaldehyde **2f**, cinnamaldehyde **2g**, acetaldehyde **2h**, butyraldehyde **2i** and 3-methylbutanal **2j**, delivering expected products **3o**-**3s** in satisfactory yields (70-85%, entries 14-18). To our pleasures, the gold-catalyzed cycloadditions are operable with various ketones including acetophenone **2k**, propiophenone **2l**, acetone **2m**, cyclohexanone **2n**, yielding the desired 4*H*-1,3-dioxin-4-ones **3t**-**3w** in 75-89% yield (entries 19-22). We examined the cycloaddition of *tert*-butyl hept-2-ynoate **1h** and *tert*-butyl 3-cyclopropylpropiolate **1k** with acetone **2m**, which proceeded well to form expected products **3x** and **3y** with yields exceeding 89% (entries 23–24).

The preceding 4*H*-1,3-dioxine derivatives can generate reactive acyl ketene species **I'** reversibly at high temperature (eqs 1 and 3);[6,9] one representative compound **3v** (1 equiv) was treated with 1-(vinyloxy)butane (**4a**, 6 equiv) (120 ℃, 3 h) to afford 2-butoxy-6-phenyl-2*H*-pyran-4(3*H*)-one **5a** in 76% yield. A separate treatment of compound **3v** with (*E*)-*N*-benzylideneaniline in hot toluene (120 ℃, 25 min), smoothly



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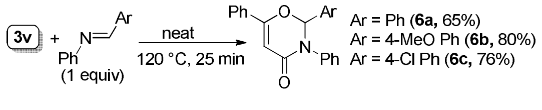
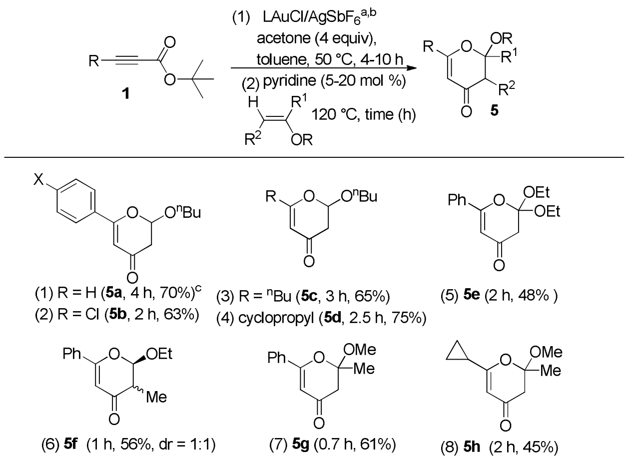


Ar = Ph (**6a,** 65%)
Ar = 4-MeO Ph (**6b,** 80%)
Ar = 4-Cl Ph (**6c,** 76%)

(4)

Table 3. Acetone-promoted propiolates/alkene cycloadditions

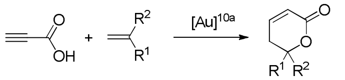


[a] L= P(t-Bu)$_2$(*o*-biphenyl), [**1**] = 0.099 M, enol ethers (5 equiv). [b] 1 mol % Au catalyst and 5 mol % pyridine for entries 5-8; 5 mol % Au and 20 mol % pyridine for entries 1-4 [c] Product yields are reported after separation from a silica column.

delivered 2,3,6-triphenyl- 2*H*-1,3-oxazin-4(3*H*)-one **6a** in 65% yield (eq 4). The same reactions worked well with (*E*)-*N*-(4-methoxybenzylidene)aniline and (*E*)-*N*-(4-chlorobenzylidene) aniline giving the expected products **6b-6c** in 76-80% yields, respectively.

As toluene is also an effective solvent for such a carbonyl/propiolate cycloaddition (see Table 1, entry 7); we developed new gold-catalyzed three-component cycloadditions involving prior heating a toluene solution of a propiolate derivative **1a** with acetone (4 equiv) and P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgSbF$_6$ (5 mol %) at 50 ℃ (5 h) to consume starting **1a** completely**;** to this solution was added 1-(vinyloxy)butane **4a** (5 equiv) and pyridine (20 mol %) with further heating at 120 ℃ for 4 h. This reaction sequence delivered desired product **5a** in 70 % yield (Table 3, entry 1). Herein, acetone functions as a promoter to direct the formation of an atypical [4+2]-cycloadduct **5a** with structural reorganization. This cascade reaction sequence failed to proceed in acetone because acy ketene intermediate can not be produced in this solvent. The occurrence of such atypical cycloadditions inspired us to examine their reaction scope using various propiolates and enol ethers **4**; the results are summarized in Table 3. For various propiolate derivatives (R = 4-ClC$_6$H$_4$ **1c**, *n*-Bu **1h** and cyclopropyl **1k**), their sequential reactions with acetone **2m** and then with diethyl 1-(vinyloxy)butane **4a**, afforded desired cycloadducts **5b-5d** in 63-75% yields (entry 2-4). With acetone as a promoter, the reactions of model *tert*-butyl propiolate **1a** with 1,1-diethoxyethene **1b**, 1-ethoxyprop-1-ene (1:1 *E*/*Z* mixture) **4c** afforded the corresponding cycloadducts **5e** and **5f** in 48% and 56% yields (entries 5-6). For 1-methyl-1-methoxyethene **4d,** its reaction sequence with *tert*-butyl propiolates **1a** (R = phenyl) and **1k** (R = cyclopropyl) delivered the products **5g** and **5h** in 61% and 45% yields respectively. The structures of the two diastereomers of cycloadducts **5f** were confirmed by proton NOE effects (see Supporting Information).

Before this work, Shin reported gold-catalyzed [4+2]-cycloadditions of alkenes with propiolic acid, which was, however, the only applicable substrate (eq 5).[10a] Here, we employ diverse *tert*-butyl propiolates to comply with a broad scope of aldehydes and ketones. Accordingly, we performed the reaction of 3-phenylpropiolic acid **1a’** with acetone with the same gold catalyst in DCE, giving desired product **3v** in 72% yield (eq 6), slightly smaller than that (87%) of its *tert*-butyl derivative **1a** (Table 1, entry 3). Accordingly, propiolic acids proves to be active substrates, but less efficient than their *tert*-butyl derivatives.



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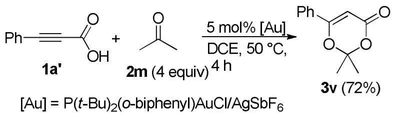

(6)

In summary, new and efficient synthesis of 4*H*-1,3-dioxine derivatives via gold-catalyzed [4+2]-cycloadditions of *tert*-butyl propiolates with carbonyl compounds is described;[12] this synthetic method eludes an ‘acyl ketene’ route currently used in literature procedures. The synthetic utility of such cycloadditions is manifested by a wide scope of *tert*-butyl propiolate, aldehydes and ketones. With acetone as a promoter, we developed new cascade cycloadditions of *tert*-butyl propiolates with carbonyl compounds to give atypical cycloadducts with skeletal rearrangement.

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