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Synthetic Methods

Zn^{II}- and Au^{I}-Catalyzed Regioselective Hydrative Oxidations of 3-En-1-ynes with Selectfluor: Realization of 1,4-Dioxo and 1,4-Oxohydroxy Functionalizations

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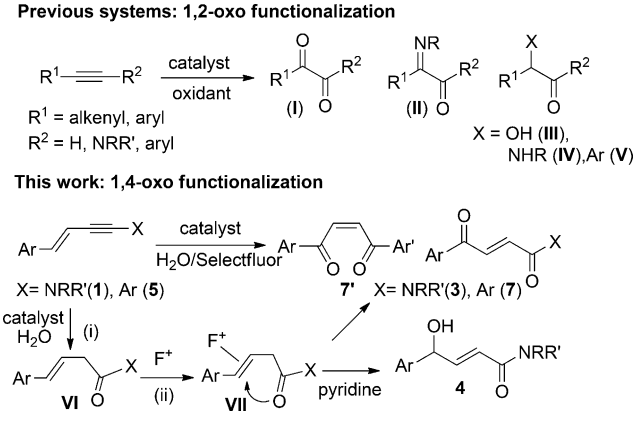
Abstract: Catalytic 1,4-dioxo functionalizations of 3-en-1-ynes to (*Z*)- and (*E*)-2-en-1,4-dicarbonyl compounds are described. This regioselective difunctionalization was achieved in one-pot operation through initial alkyne hydration followed by in situ Selectfluor oxidation. The presence of pyridine alters the reaction chemoselectivity to give 4-hydroxy-2-en-1-carbonyl products instead. A cooperative action of pyridine and Zn^{II} assists the hydrolysis of key oxonium intermediate.

Considerable interest has focused on the regioselective 1,2-oxo functionalizations of alkynes to generate a new carbonyl group. Numerous reactions have been developed for the syntheses of 1,2-dicarbonyl products (**I**),[1–3] with scattered reports on α-hydroxylcarbonyl,[4] α-aminocarbonyl,[5] α-iminocarbonyl[5a] or α-arylcarbonyl[6] derivatives (**II**–**V**), (Scheme 1). 1,2-Dicarbonyl species **I** are readily available from catalytic oxidations of alkynes with O_2,[1]organic[2] or inorganic oxidants.[3] 1,3-Enynes are readily available from unsaturated four-carbon motifs; conceivably, their oxo functionalizations pose an eminent challenge because of two regioselective routes, that is, 1,2- versus 1,4-additions. The preceding oxidations on 3-en-1-ynes were accessible only to 1,2-addition products,[7,8] as exemplified by Scheme 1. Regioselective control of 1,4-difunctionalizations on 3-en-1-ynes remains a formidable task with no literature precedent.

We report the first 1,4-dioxo and 1,4-oxohydroxy reactions of readily available 3-en-1-ynes **1** and **5** to furnish *Z*- and *E*-2-en-1,4-dicarbonyl compounds **3** and **7**/**7′** and *E*-4-hydroxy-2-en-1-amides **4**. Our synthetic advance adopts a prior hydration strategy,[9] followed by a Selectfluor oxidation in a one-pot operation [see (i) and (ii) in Scheme 1]. Notably, the chemoselectivity of the carbonyl-assisted alkene fluorination in step (ii), depicted by state **VII**, is influenced by catalytic amounts of pyridine (Scheme 1).

Among these products, electron-deficient alkenes **7** and **7′** have found widespread use in Diels–Alder reactions and Michael acceptors[10] whereas 4-carbonyl-2-en-1-amides **3** are the key intermediates for naturally occurring ceruleinin, tetrahydroceruleinin and related compounds.[11] 4-Hydroxy-2-en-1-amides **4** were also intermediates for the synthesis of (+)-pinellic acid and (+)-coriolic acid.[12]

Table 1 shows the 1,4-dioxo functionalization of an activated 3-en-1-ynamide **1a**; we employed Selectfluor as the oxidant[13] because of its tolerance of water. In a one-pot operation, 3-en-1-yne **1a** was treated with a catalyst (5 mol%) in CH_3CN/water (3:1) at 50 °C for 0.3–14 h (t_1) to complete an alkyne hydration. To this solution was added Selectfluor (2.0 equiv) to promote an in situ oxidation over a suitable period (t_2 = 1–10 h). For $Zn(OTf)_2$, the hydration was complete within 14 h, giving 3-en-1-amide **2a** in 95% yield (entry 1). A Selectfluor oxidation of this amide in situ for a brief period (t_2 = 1 h), afforded *cis*-4-oxo-2-en-1-amide **3a′** and its *trans* isomer **3a** in 74 and 16% yield, respectively (entry 2). An extended oxidation (t_2 = 12 h, entry 3) gave *trans*-2-en-1,4-dicarbonyl **3a** exclusively in 89% yield. *Cis*-configured alkene **3a′** was evidently the primary product, which was convertible to its *trans*-isomer **3a** under the conditions. We tested the reactions on PPh_3AuOTf, resulting in 3-en-1-amide **2a** in moderate yield (55%) in a brief period (t_1 = 0.5 h, entry 4), further giving *trans*-alkene **3a** in 43% yield after the oxidation (entry 5). IPrAuOTf (IPr = 1,3-bis(di-isopropylphenyl)imidazol-2-ylidene) and $PtCl_2$/CO were



Scheme 1. 1,2- and 1,4-oxo functionalizations.

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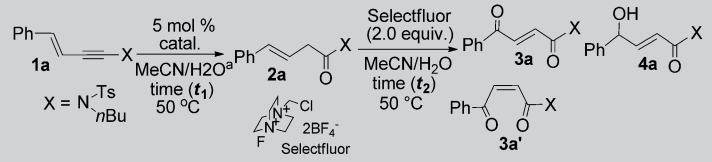
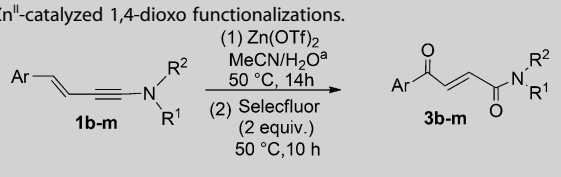
Table 1. Conditions for 1,4-dioxo functionalizations.

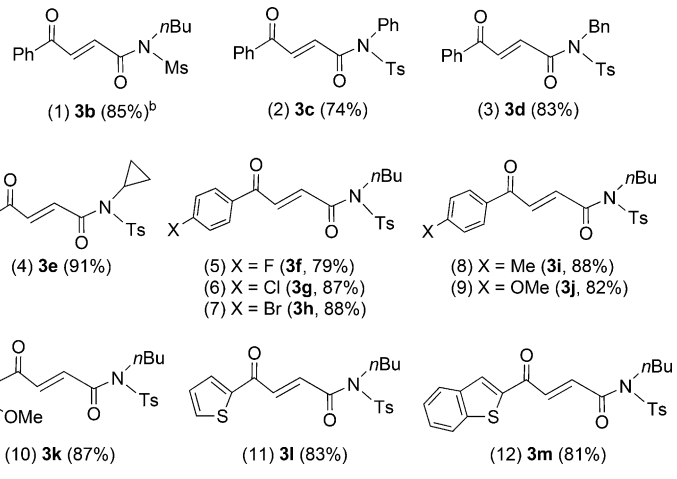


	Catalyst	t_1 [h]	t_1 [h]	Compounds [%][b]			
				2a	**3a′**	**3a**	**4a**
1	$Zn(OTf)_2$	14	0	95	–	–	–
2	$Zn(OTf)_2$	14	1	–	74	16	–
3	**$Zn(OTf)_2$**	**14**	**12**	**–**	**–**	**89**	**–**
4	PPh_3AuOTf	0.5	0	55	–	–	–
5	PPh_3AuOTf	0.5	1	–	–	43	–
6	IPrAuOTf	2	0	91	–	–	–
7	IPrAuOTf	2	5	–	49	23	–
8	$PtCl_2$/CO	0.3	0	98	–	–	–
9	$PtCl_2$/CO	0.3	5	–	14	42	5

[a] $MeCN/H_2O$ = 3:1, [**1a**] = 0.07 M. [b] Product yields are reported after separation on a silica-gel column.

Table 2. Zn^{II}-catalyzed 1,4-dioxo functionalizations.





[a] $MeCN/H_2O$ = 3:1. [1] = 0.07 M, 5 mol% $Zn(OTf)_2$. [b] Product yields are reported after separation on a silica-gel column.

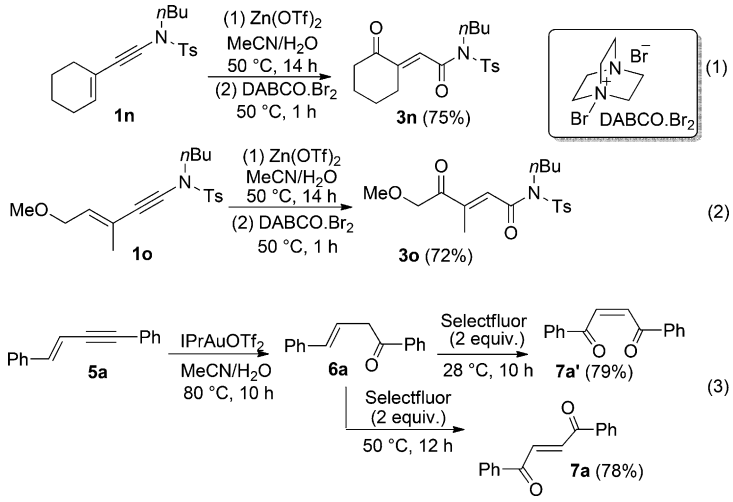
excellent hydration catalysts (t_1 = 0.3–3 h) to give 3-en-1-amide **2a** in 91–98% yield (entries 6 and 8). Upon Selectfluor oxidations, IPrAuOTf gave desired compounds **3a** and **3a′** in 23 and 49% yield, respectively (entry 7), whereas $PtCl_2$/CO gave three products, including **3a** (42%), **3a′** (14%) and 4-hydroxy-2-en-1-amide **4a** (5%, entry 9). Although $Zn(OTf)_2$ catalyzed the alkyne hydration slowly, it gave the best yield (**3a**, 89%) over the entire sequence.

We prepared additional *E*-configured 3-en-1-ynamides **1b–m** to assess the substrate scope (Table 2). In a one-pot operation, 3-en-1-ynes **1** were heated with $Zn(OTf)_2$ catalyst in $MeCN/H_2O$ (3:1) at 50 °C for 14 h; to this solution, Selectfluor (2 equiv) was added before additional heating for 10 h. Entries 1–4 show the generality of this 1,4-dioxo reaction to various sulfonamide groups including NR^1R^2 = NMs(*n*Bu), NTs(Ph), NTs(benzyl), NTs(cyclopropyl), giving desired 4-oxo-2-en-1-amides **3b–e** in satisfactory yields (74–91%, entries 1–4). These catalytic 1,4-difunctionalizations were further extendable to substrates **1f–h** bearing electron-deficient phenyl substituents X = F, Cl, and Br; their 1,4-dicarbonyl products **3f–h** were obtained in good yields (79–88%, entries 5–7). The same reactions also worked for 3-en-1-ynamides **1i** and **j** bearing a varied electron-rich phenyl group (X = Me, OMe), giving compounds **3i** and **j** in 82–88% yield (entries 8 and 9). For substrate **1k** bearing an *ortho*-methoxy substituent, its resulting product **3k** was obtained in 87% yield. The reactions were applicable to 2-thiophene and 2-benzothiophene derivatives **1l** and **m** delivered 4-oxo-2-en-1-amides **3l** and **m** in 81–83% yield.

We prepared additional 3-en-1-yn-1-amides **1n** and **o** bearing an aliphatic group to expand the reaction scope, but the use of Selectfluor failed to promote a clean oxidation sequence. With water soluble DABCO.Br_2 (*bis*-bromine-1,4-diazabicyclo-[2.2.2]octane), the desired 4-oxo-2-en-1-amides **3n** and **o** were obtained in 75 and 72% yield respectively [Eq. (1), (2)].

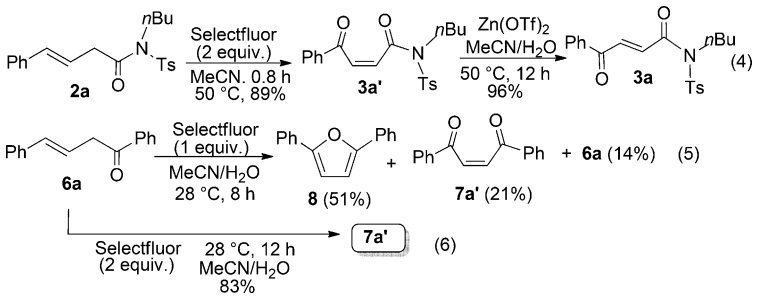
We tested the reaction on an unactivated 3-en-1-yne **5a** to enhance its synthetic utility [Eq. (3)]; IPrAuOTf (5 mol%, IPr = 1,3-bis(di-isopropylphenyl)-imidazol-2-ylidene) replaced $Zn(OTf)_2$ to attain an effective alkyne hydration. The hydration for 3-en-1-yne **5a** was complete in CH_3CN/H_2O (3:1, 80 °C) for 10 h; the treatment of this resulting solution in-situ with Selectfluor (2 equiv) at 28 °C (10 h), afforded only *cis*-4-oxo-2-en-1-one **7a′** in 79% yield. If the Selectfluor oxidation was performed in CH_3CN/H_2O (3:1, 50 °C) for 12 h, *trans*-alkene **7a** was obtained with 78% yield. Herein, the hydration product **6a** was isolated for spectral characterization.

Table 3 shows the generalization of one-pot syntheses of *cis*-4-oxo-2-en-1-ones **7b′–k′** using unactivated 3-en-1-ynes **5b–k** and IPrAuOTf (5 mol%) in $MeCN/H_2O$ (3:1). The *cis*-olefin configurations are revealed by the proton coupling constants J = 11–12 Hz; the time t_1 and t_2 referred to complete consumption of 3-en-1-ynes **5** and their hydration intermediates **6**, respectively. For substrates **5b** and **c** bearing alterable styryl Ar^1 groups (X = OMe and Me), their corresponding products **7b′** and **c′** were obtained in 81–86% yield (entries 1 and 2). The reactions were extendable to their electron-deficient styryl analogues **5d** and **e** (X = F and CF_3), giving desired products **7d′** and **e′** in 72–73% yield (entries 3 and 4). These hydrative oxidations also worked for enynes **5f–h** bearing variable alkynyl Ar^2 substituents (Y = OMe, Me and F), affording compounds **7b′**,**c′**, and **d′** in 71–74% yield (entries 5–7). The reactions were also applicable to *cis*-4-oxo-2-en-1-ones **7i′** and **j′** bearing 4-methoxy- or 4-



fluorophenyl groups; the yields were 76–84% (entries 8 and 9). A heteroaryl group as in species **7k**′ was compatible with this reaction providing the product in 54% yield.

We performed control experiments to elucidate the mechanism of 1,4-dioxo functionalizations [Eq. (4)]. Treatment of 3-en-1-amide **2a** with Selectfluor (2 equiv) in MeCN (50 °C, 0.8 h) gave *cis*-4-oxo-2-en-1-amide **3a**′ in 89% yield exclusively; $Zn(OTf)_2$ was unnecessary herein. *cis*-Alkene **3a**′ is readily converted to its *trans* isomer **3a** with $Zn(OTf)_2$ in MeCN/H_2O (3:1) at 50 °C (12 h). Structural analysis of *cis*-olefin **3a**′ led us to postulate that an aminofuran species is a likely precursor that is prone to Selecfluor oxidation to give **3a**′. With 3-en-1-one **6a**, its oxidation with Selectfluor (1.0 equiv) in MeCN/H_2O (3:1) allowed the isolation of a furan derivative **8** in 51% yield [Eq. (5)]. When Selectfluor was used in sufficient proportion (2 equiv), *cis*-4-oxo-2-en-1-one **7a**′ was obtained in 83% yield [Eq. (6)]. We are aware of no precedent for electrophile-induced cyclizations of 3-en-1-carbonyl species to form furan derivatives.[14–16]

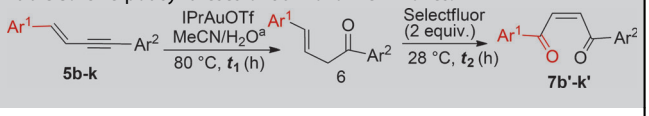


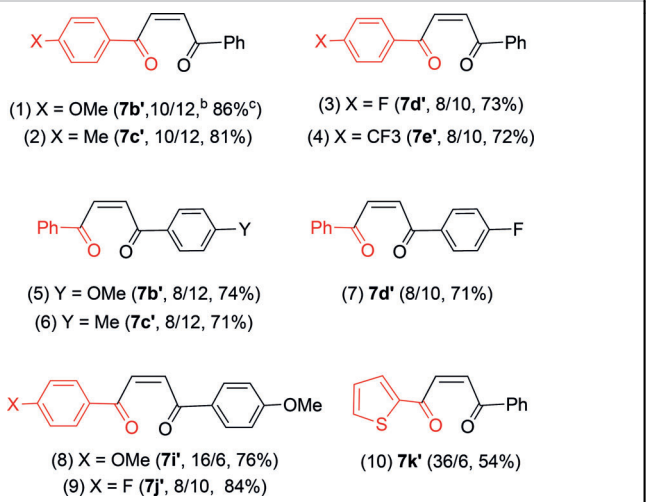
Accordingly, we propose a mechanism in Scheme 2 involving a carbonyl-assisted alkene fluorination as represented by species **B**. To rationalize the intermediacy of 2-aminofuran **8**′, we envisage that Selectfluor attacks the olefin of intermediate **2a** to form F^+-coordinated alkene[10] **A** with a positive character at its benzylic carbon, further inducing an amide attack to form an oxonium species **B**.[13,17] After delivering an "fluorinum" ion, the remaining [*N*]=1,4-diazabicyclo-[2,2,2]octanium, acted as a base to facilitate the deprotonation of this oxonium species to give 4-fluoro-dihydrofuran **C**. A subsequent loss of HF from species **C** is expected to occur readily because aromatic aminofuran **8**′ is formed. A subsequent Selectfluor oxidation on this furan afforded cis-4-oxo-2-en-1- amide **3a**′ via intermediates **D** and **E**.

Interestingly, nitrogen-base additives altered the oxidation chemoselectivity as depicted in Table 4. Our vigorous trials indicated performing the reaction with an initial treatment of 3-en-1-ynamide **1a** with a mixture of Selectfluor (2.0 equiv) and additives (10 mol%) in MeCN/H_2O (50 °C, 3:1) for 16–20 h.[15] Et_3N and DBU, with 10 mol% loading, led to formation of *E*-configured 4-hydroxy-2-en-1-amide **4a** in 47–58% yield (entries 1–2) whereas undesired 4-oxo-2-en-1-amides **3a**′ and **3a** were also present in significant portions (12–18%). Gratifyingly, the use of pyridine (10 mol%) gave desired **4a** with 83% yield (entry 3). We tested the reaction with $PtCl_2$/CO because of its hydration activity; Amide **4a** was formed in low yield (23%). The structure of this amide was carefully determined by ^1H NOE-effect.

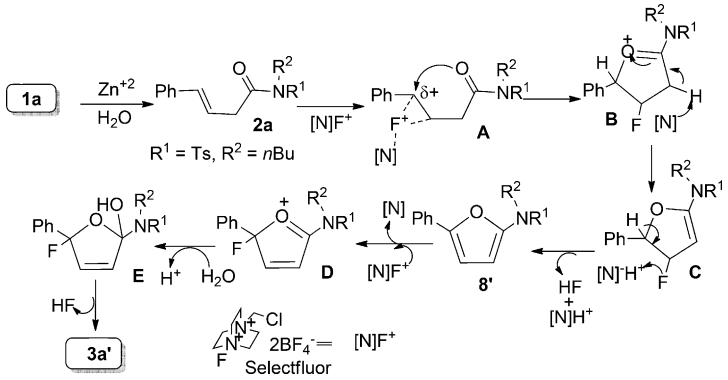
We assess the generality of this Zn^{II}-catalyzed 4-hydroxy-1-oxo functionalization using the same 3-en-1-ynamides **1b–m** (see Table 2). As shown in Table 5, this altered chemoselectivity arose from added pyridine (10 mol%). In some instances (entries 1, 4, 6, and 7), we obtained 4-oxo-2-en-1-amides **3** and **3**′ with minor proportions (5–9%). The reaction was tolerant of modifications to the sulfonamide group, giving *E*-configured 4-hydroxy-2-en-1-amides **4b–e** in 65–74% yield. The reactions worked well for 3-en-1-ynamides **1f–k** bearing an electron-deficient and -rich phenyl group, giving desired products **4f–k** with 73–83% yield (entries 5–10). For heteroaryl derivatives **1l**

Table 3. One-pot syntheses of *cis*-4-oxo-2-en-1-ones.





[a] MeCN/H_2O=3:1. [b] These values refer to t_1(h)/t_2(h). [c] Product yields are reported after a silica-gel column.



Scheme 2. A mechanism for 1,4-dioxo reaction.

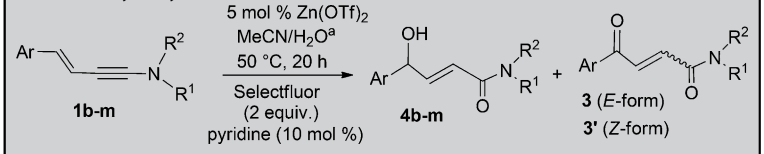
and **m**, resulting products **4l** and **m** were produced with 76–77% yield.

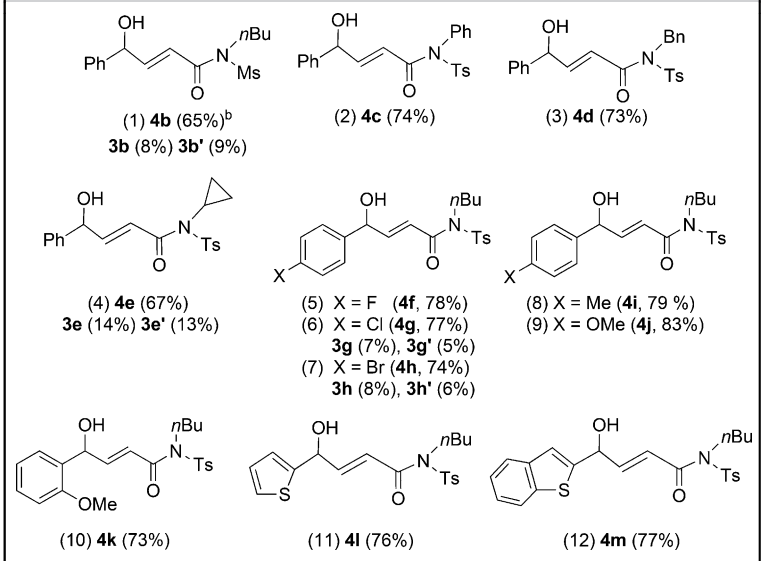
As shown in Scheme 3, pyridine alone (10 mol%) impeded the oxidation of 3-en-1-amide **2a**, leading to 63% recovery, with no olefin isomerization occurring for species **2a** (entry 1). Notably, $Zn(OTf)_2$ promoted this oxidation to afford the desired **4a** in 78% yield together with **3a**/**3a**′ in 6–8% yield. The Selectfluor oxidation of starting **2a** in $MeCN/H_2O$* (3:1, O* = 23% ^{17}O) gave ^{17}O-enriched **4a**, of which the ^{17}O NMR revealed two major peaks, assignable to C=O ($\delta = 377$ ppm) and C–OH ($\delta = 29$ ppm). Under the Zn^{II}/pyridine conditions, there is no oxygen exchange between water and this ^{17}O-enriched **4a**. Mass-spectral analysis revealed that ^{17}O-enriched **4a** contained one ^{17}O atom according to its H_2O* isotope source.

The effect of $Zn(OTf)_2$ is rationalized in a proposed mechanism (Scheme 4). In the absence of Zn^{2+}, pyridine likely reacted with water to generate hydroxide to decompose Selectfluor. Before the C(3)-H deprotonation of oxonium species **B** with [*N*] = 1,4-diazabicyclo[2,2,2]octanium, as shown by the **B**→**C** conversion (Scheme 2), water might attack this oxonium species rapidly through two paths (i) or (ii) according to our ^{17}O labeling results. In the presence of Selectfluor and $Zn(OTf)_2$, such an acidic medium inhibits a proton loss of species **F** and **H**, thus inhibiting the **F**→**G** and **H**→**I** transformations. In the presence of pyridine, $Zn(OTf)_2$ would form a complex $(TfO)_2Zn(py)_2$ to activate the protonation of **F** and **H**, ultimately giving 4-hydroxy-2-en-1-amide **4a** through a loss of HF from key intermediate **I**. An alternative route involving an allylic oxidation of isomerization alkene **2a**′ is excluded according to a control experiment (Scheme 3, entry 1).

In summary, new 1,4-oxo functionalizations of 3-en-1-ynes have been developed based on a hydrative oxidation approach. The one-pot dioxo reactions were applicable to various 3-en-1-ynes including unactivated 3-aryl-3-en-1-ynes, giving *Z*- or *E*-configured 2-en-1,4-dicarbonyl compounds selectively. Our mechanistic analysis supported an initial formation of furan intermediates, generated from carbonyl-assisted alkenyl fluorinations of hydration intermediates. The addition of pyridine altered the oxidation selectivity to give *E*-4-hydroxy-2-en-1-amides instead. A cooperative action of pyridine and Zn^{II} was suggested to mediate the hydrolysis of key oxonium intermediates **B**. This work reports the first successful 1,4-oxo functionalization of readily available 3-en-1-ynes to form highly functionalized alkenes.

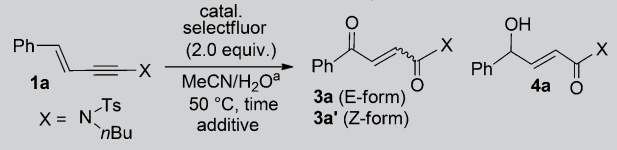
Table 5. 4-Hydroxy-1-oxo functionalizations.





[a] $MeCN/H_2O = 3:1$, [1] = 0.07 M. [b] product yields are reported after separation on a silica-gel column.

Table 4. Additive effects on chemoselectivity.



	5 mol% cat.	10 mol% additive	*t* [h]	Compound [%][b] **3a**′	**3a**	**4a**
1	$Zn(OTf)_2$	Et_3N (10)	20	14	12	47
2	$Zn(OTf)_2$	DBU (10)	20	18	15	58
3	$Zn(OTf)_2$	Pyridine (10)	18	3	4	83
4	$PtCl_2$/CO	Pyridine (10)	16	12	34	23

[a] $MeCN/H_2O = 3:1$, [1a] = 0.07 M. [b] Product yields are reported after separation on a silica-gel column.

Acknowledgements

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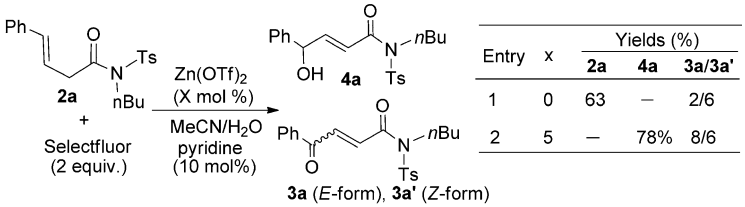
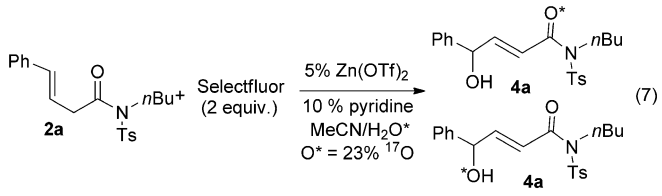
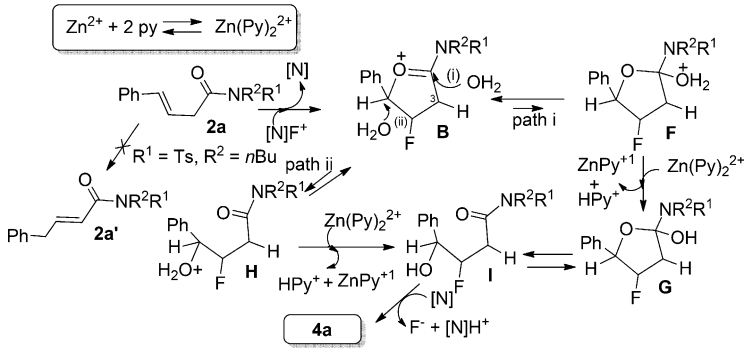


Entry	x	Yields (%) 2a	4a	3a/3a'
1	0	63	–	2/6
2	5	–	78%	8/6



Scheme 3. The effect of $Zn(OTf)_2$ and pyridine.



Scheme 4. A mechanism for alkene oxidation.

Keywords: 1,4-enediones · 1,4-oxohydroxy · 3-en-1-ynes · hydrative oxidations · regioselective difunctionalizations

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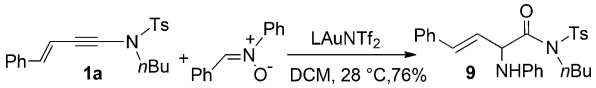

[8] Besides 1,2-oxo reactions on 3-en-1-ynamide,[7] a gold-catalyzed oxoamination reaction occurred with a 1,2-addition mode. The spectral data of compound **9** is provided in the Supporting Information.

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