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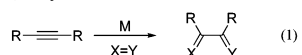
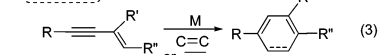
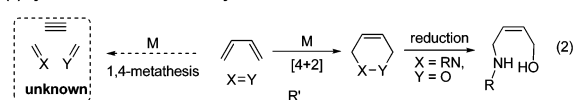
Sagar Ashok Gawade, Deepak B. Huple, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, ROC

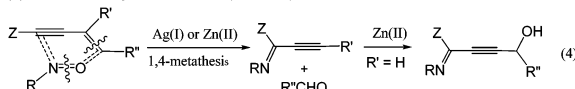
Supporting Information

ABSTRACT: Catalyst-dependent metathesis reactions between 3-en-1-ynamides and nitrosoarenes are described. Particularly notable are the unprecedented 1,4-metathesis reactions catalyzed by Ag(I) or Zn(II) to give 2-propynimidamides and benzaldehyde derivatives. With 3-en-1-ynamides bearing a cycloalkenyl group, 1,4-oxoimination products were produced efficiently. We have developed metathesis/alkynylation cascades for unsubstituted 2-propynimidamides and benzaldehyde species generated *in situ*, to manifest 1,4-hydroxyimination reactions of 3-en-1-ynes. Both 1,4-oxoiminations and 1,4-hydroxyiminations increase the molecular complexity of products.

Metal-catalyzed metathesis reactions represent the practical value of catalytic reactions in the fields of materials science and pharmaceuticals.¹ Metathesis reactions between alkynes and double-bond species $X=Y$ ($C=C$, $C=O$, and $C=N$) are powerful tools to access various diene,¹ enone,² and enimine³ compounds via a 1,2-metathesis route (eq 1). We

(1) 1,2-alkyne metathesis with $X=Y$ (2) cycloadditions of diene or enynes with $X=Y$ 

(3) 1,4-nitroso/enyne metathesis (this work)

M: metal complexes; $X=Y$: $C=C$, $C=N$, $C=O$ and $RN=O$; Z : $NR(EWG)$

disclosed that nitrosoarenes could act as nucleophiles to react with Au(I)- π -alkynes to furnish the first nitroso/alkyne metathesis reactions (eq 1).⁴ Although 1,3-dienes and 3-en-1-ynes are readily available for unsaturated four-carbon motifs, their metal-catalyzed reactions with alkenes, carbonyl, imines, or alkynes occur exclusively with [4+2]-cycloadditions (eqs 2 and 3).^{5,6} Lewis acid-catalyzed [4+2]-cycloadditions of 1,3-dienes with nitrosoarenes⁷ are accessible to N- and O-containing functionalized molecules after cleavage of a N–O bond (eq 2). Our initial task is to achieve new metal-catalyzed

[4+2]-cycloadditions between nitrosoarenes and 3-en-1-ynes. Initial use of Au(I) catalysts affords 1,2-metathesis products,⁴ as depicted in eq 1, but a switch to Zn(II) and Ag(I) catalysts surprisingly implements 1,4-enyne/nitroso metathesis reactions to afford aldehydes and 2-propynimidamides efficiently (eq 4). Herein, a bond order of 2 is increased or decreased between the two neighboring (or interacting) atoms of reactants, thus conforming a metathesis model. Similar 1,4-metathesis reactions were noted between singlet oxygen and a few 3-en-1-ynes, but prolonged photolysis was required to achieve good yields of products (16–64 h).⁸ For the resulting unsubstituted 2-propynimidamides ($R' = H$) and aldehydes, we also accomplish their subsequent alkynations in a one-pot operation to afford alkynol derivatives efficiently, highlighting new hydroxyiminations of 3-en-1-ynes.

We first tested the reactions of 3-en-1-ynamide **1a** with nitrosobenzene (**2a**) using IPrAuNTf₂ (5 mol%, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) and LAuNTf₂ (5 mol%, L = P(*t*Bu)₂(*o*-biphenyl)) in dichloroethane (DCE, 28 °C), from which we isolated a 1,2-metathesis product (**5a**) in good yields (81–90%) together with a 2-propynimidamide (**3a**) and benzaldehyde (**4a**) in 3–5% yields (Table 1). Astonishingly, silver salts (5 mol%) like AgNTf₂, AgOAc, and AgOTf gave 1,4-metathesis products **3a** and **4a** in high yields (88–95%, entries 3–5) in DCE (28 °C), with AgOAc being the most effective. Cheap zinc catalysts Zn(OTf)₂ and ZnCl₂ were also active catalysts for such a 1,4-enyne/nitroso metathesis in DCE at 60 °C (2–3 h) to give **3a** and **4a** in 90–98% yields. For AgOAc, the reactions were compatible with various solvents, including dichloromethane (DCM), MeCN, and THF, giving **3a** and **4a** in 85–92% yields. No reactions occurred in the absence of a metal catalyst, even though the starting mixture was heated in DCE (60 °C) for 10 h; UV irradiation of the same reagents alone in DCE (0 °C, 10 h) gave complicated mixtures of products.

We examined the reactions of various 3-en-1-ynamides **1** and nitrosoarenes **2** to assess the scope of applicable substrates. The 1,4-metathesis reactions were performed with Zn(OTf)₂ (5 mol %) in DCE (60 °C, 2 h). For 3-en-1-ynamides **1b–1d** bearing different sulfonamides (NR(EWG) = NMeTs, NPhTs, and N(*n*Bu)Ts), their resulting products **3b–3d** and benzaldehyde **4a** were obtained with yields exceeding 91% (Table 2, entries 1–3). We tested the reactions on other 3-en-1-ynamides **1e–1h** bearing a varied R¹ substituent (R¹ = 4-bromo- and 4-methoxyphenyl, 2-furanyl, and cyclohexenyl), affording the

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Table 1. 1,2- versus 1,4-Metathesis Reactions

entry	catalyst ^a	solvent	conditions ^b		products (%) ^c		
			T (°C)	t (h)	3a	4a	5a
1	IPrAuCl/AgNTf ₂	DCE	28	15	5	5	81
2	LAuCl/AgNTf ₂	DCE	28	0.5	3	3	90
3	AgNTf ₂	DCE	28	20	88	88	—
4	AgOAc	DCE	28	5	95	95	—
5	AgOTs	DCE	28	8	92	92	—
6	Zn(OTf) ₂	DCE	60	2	98	98	—
7	ZnCl ₂	DCE	60	3	90	90	—
8	AgOAc	DCM	28	2	92	92	—
9	AgOAc	MeCN	28	3.5	88	88	—
10	AgOAc	THF	28	3.5	85	85	—
11	—	DCE	60	10	10	—	—

^aIPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, L = P(*t*Bu)₂(*o*-biphenyl). ^b[1a] = 0.14 M. ^cProduct yields are reported after purification from a silica column.

desired 2-propynimidamide 3a and aldehydes 4e–4h in 83–97% yields (entries 5–7). These Zn(II)-catalyzed reactions were extensible to enyne substrates 1i–1k bearing an alkyl or phenyl substituent (R² = methyl, isopropyl, and phenyl), giving 2-propynimidamides 3i–3k and benzaldehyde 4a in 87–94% yields (entries 8–10). This synthetic method was applicable to additional nitrosoarenes 2b,2c (X = NO₂, isopropyl), giving desired 3l,3m and benzaldehyde 4a in 91–95% yields (entries 10–12).

To demonstrate the feasibility of a new 1,4-oxoimination of 3-en-1-ynes with nitrosobenzene 2a, we prepared cyclic alkenes bearing an ethynylamide group, 6a–6h; the resulting products 7a–7h would hence contain both oxo and imine functionalities (Table 3). Such 1,4-oxoiminations were implemented by Zn(OTf)₂ (5 mol%) and 2a (2.0 equiv) in hot DCE (60 °C, 0.5 h). Entries 1–3 show the efficient productions of desired

Table 3. Zn-Catalyzed 1,4-Oxoimination of 3-En-1-ynamides

entry	product	yield (%)
(1) 6a (n = 1) ^a	7a	97%
(2) 6b (n = 2)	7b	96%
(3) 6c (n = 3)	7c	91%
(4) 6d (R = H)	7d	82%
(5) 6e (R = Me)	7e	95%
(6) 6f (R = Me)	7f	95%
(7) 6g (R, R = -(CH ₂) ₄ -)	7g	96%
(8) 6h	7h	95%

^a[6] = 0.14 M. ^bProduct yields are reported after purification from a silica column.

benzaldehyde derivatives 7a–7c with yields >91% from cyclic alkene derivatives 6a–6c of various sizes (n = 1–3). These 1,4-oxoimination reactions were also applicable to oxacyclic alkene derivatives 6d,6e (R = H, Me), giving desired products 7d,7e in 82–95% yields (entries 4 and 5). For disubstituted indenenes 6f,6g bearing a 2-ethynylamide, 7f,7g were produced with 95–96% yields (entries 6 and 7). For the 3-indenyl ethynylamide analogue 6h, the same reaction afforded an aliphatic aldehyde (7h) in 95% yield (entry 8).

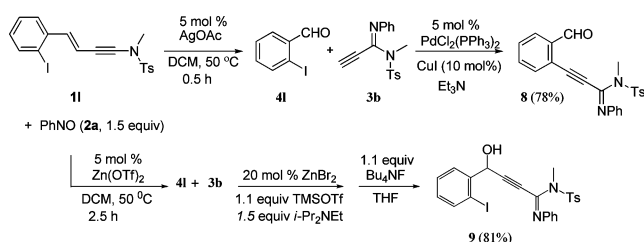
Table 2. Scope for 1,4-Nitroso/Enyne Metathesis

entry	enyne				nitroso 2 (X)	products (yield, %)	
	1	R ¹	R ²	NR (EWG)		3	4
1	1b	Ph	H	N(Me)Ts	2a (H)	3b (92)	4a (92)
2	1c	Ph	H	N(Ph)Ts	2a (H)	3c (91)	4a (91)
3	1d	Ph	H	N(<i>n</i> Bu)Ts	2a (H)	3d (98)	4a (98)
4	1a	4-BrC ₆ H ₄	H	N(Me)Ms	2a (H)	3a (94)	4e (94)
5	1f	4-MeOC ₆ H ₄	H	N(Me)Mb	2a (H)	3a (97)	4f (97)
6	1g	2-furanyl	H	N(Me)Ms	2a (H)	3a (83)	4g (83)
7	1h	cyclohexenyl	H	N(Me)Mb	2a (H)	3a (93)	4h (93)
8	1i	PH	Me	N(Me)Ms	2a (H)	3i (94)	4a (94)
9	1j	Ph	<i>i</i> Pr	N(Me)Ms	2a (H)	3j (90)	4a (90)
10	1k	Ph	Ph	N(Me)Ms	2a (H)	3k (87)	4a (87)
11	1a	Ph	H	N(Me)Ms	2b (NO ₂)	3l (91)	4a (91)
12	1a	Ph	H	N(Me)Ms	2c (<i>i</i> Pr)	3m (95)	4a (95)

^a[1] = 0.14 M. ^bProduct yields are reported after purification from a silica column.

Simultaneous production of unsubstituted 2-propynimides and aldehydes allows their further elaborations with catalytic formation of a carbon–carbon bond. Scheme 1 depicts

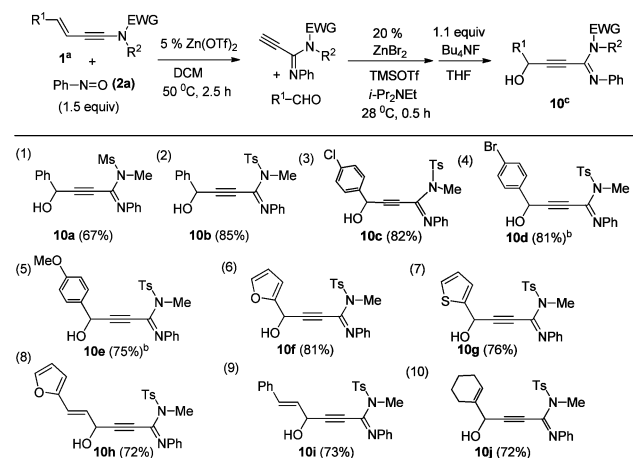
Scheme 1. Two One-Pot Cascade Reactions



two one-pot cascade reactions between 3-en-1-ynamide **11** and nitrosobenzene **2a** (2 equiv) under optimized conditions. Treatment of these reactants with AgOAc (5 mol%) in DCM (50 °C, 0.5 h) delivered 2-iodobenzaldehyde (**4l**) and a 2-propynimide **3b** efficiently; to this solution were added PdCl₂(PPh₃)₂, CuI (10 mol%), and Et₃N (15 equiv) to effect an *in situ* Sonogashira reaction,⁹ giving a desired coupling product **8** in 78% yield. Alternatively, we employed Zn(OTf)₂ (5 mol%) to catalyze the initial metathesis reaction in a sealed flask (DCM, 50 °C, 2.5 h), followed by a reported alkynylation¹⁰ *in situ* of aldehyde **4l** with ZnBr₂ (20 mol%), TMSOTf (1.1 equiv), and *i*-Pr₂NEt (1.5 equiv) in the same solution. A final workup with Bu₄NF in THF afforded alkynol derivative **9** in 81% yield.

The formation of an alkynol product like **9** from 3-en-1-ynamide **11** is synthetically interesting because this transformation represents a novel 1,4-hydroxyimination of a 3-en-1-yne. Table 4 shows the generalization of such reactions with

Table 4. One-Pot Metathesis/Alkynylation Cascades



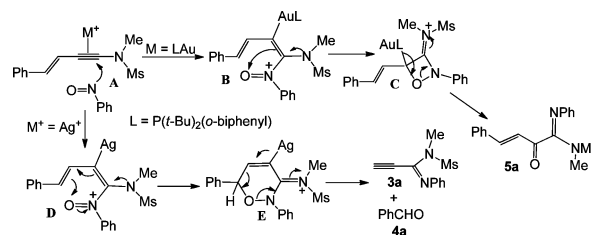
^a[1] = 0.14 M TMSOTf (1.0 equiv), *i*-Pr₂NEt (1.5 equiv). ^bExternal 4-MeOC₆H₄CHO (1.0 equiv) was added in entry 5, and 2-furyl- and 2-thienyl aldehydes (0.5 equiv) were added in entries 6 and 7 before their alkynylations. ^cProducts are reported after separation from a silica column.

additional examples. In entries 5–7, external aldehydes R¹CHO (R¹ = 4-MeOC₆H₄, 2-furyl, and 2-thienyl, 0.5 or 1.0 equiv) were added before the alkynylation because of their lower reactivity. These one-pot reactions were accessible to alkynols **10a**, **10b** bearing various sulfonamides (NR²EWG = NMeMs, NMeTs); the yields were 67–85% (entries 1 and 2). The

reactions were applicable to 3-en-1-ynamides bearing different styryl groups (R¹ = XC₆H₄, X = Cl, Br, and MeO, entries 3–5), giving desired alkynols **10c**–**10e** in 75–82% yields. These zinc-catalyzed reactions were amenable to the synthesis of heteroaryl-substituted alkynols **10f**, **10g** (R¹ = 2-furyl and 2-thienyl) with satisfactory yields (76–81%, entries 6 and 7). For 3-en-1-ynamides bearing varied alkenyl substituents, the related 4-en-1-yn-3-ols **10h**–**10j** were produced efficiently (72–73%, entries 8–10).

Shown in Scheme 2 is a plausible mechanism to rationalize catalyst-dependent chemoselectivity of 1,2- versus 1,4-metathesis reactions;

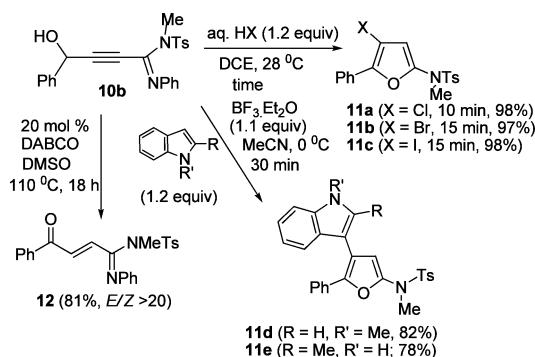
Scheme 2. A Plausible Mechanism for 1,2- and 1,4-Metathesis Reactions



thesis reactions; we envisage that both reactions proceed via an initial attack of nitrosobenzene at metal π -alkyne species **A**. In recent work, we demonstrated that LAu⁺ (L = P(*t*-Bu)₂(*o*-biphenyl)) is more electron-rich than Ag⁺ to direct a 1,2-shift of the neighboring group through a hyperconjugation effect.¹¹ For LAu (L = P(*t*-Bu)₂(*o*-biphenyl)), the alkenylgold C=C bond of intermediate **B** is thus highly electron-rich and nucleophilic to attack the oxygen of the nitrosonium moiety to generate species **C**, of which the weak N–O bond is readily cleaved by LAu to give 1,2-metathesis product **5a**. In contrast, diensilver species **D** behaves like normal dienes to undergo a well-known [4+2]-cycloaddition,⁷ giving a cycloadduct intermediate, **E**. We envisage that its weak N–O bond is the major reason for molecular fragmentation to generate the terminal 3-iminoalkyne **3a** and benzaldehyde, rather than giving a [4+2]-nitroso cycloadduct through a protodemetalation.

We have developed new synthetic use of an alkynol derivative, **10**. As depicted in Scheme 3, treatment of an alkynol **10b** with aqueous HX (1.2 equiv, X = Cl, Br, and I) in DCE (28 °C, 10–15 min) delivered highly substituted aminofurans **11a**–**11c** in excellent yields (97–98%). We have determined their structures with ¹H NOE spectra. Likewise, treatment of this alkynol with indoles (1.2 equiv) and BF₃·Et₂O (1.1 equiv) afforded aminofurans **11d**, **11e** of the same type; the

Scheme 3. Synthetic Applications of 3-Imidoalkynol **10b**



corresponding yields were 78–82%. The molecular structure of **11e** was confirmed by X-ray diffraction.¹² The mechanism of these new cyclizations is provided in the Supporting Information. Alkynol **10b** was transformed into an *E*-configured enone **12** according to a reported DABCO-catalyzed rearrangement;¹³ its structure is distinct from that of the enone **5a** given from a 1,2-nitroso/alkyne metathesis reaction (Table 1).

In summary, we report catalyst-dependent chemoselectivities in the metathesis reactions of 3-en-1-ynamides¹⁴ with nitrosoarenes. LAuNTf₂ (L = P(*t*Bu)₂(*o*-biphenyl)) catalyzed 1,2-metathesis reactions, whereas AgNTf₂ or Zn(OTf)₂ implemented unprecedented 1,4-metathesis reactions. Before this work, metal-catalyzed metathesis reactions were strictly limited to a 1,2-metathesis mode, whereas 1,3-dienes and 3-en-1-ynes exclusively undergo metal-catalyzed [4+2]-cycloadditions with double bond species. We prepared cycloalkene derivatives of 3-en-1-ynamides in a series to achieve new 1,4-oxoimination reactions of 3-en-1-ynes. We have developed one-pot cascade reactions to activate an alkylation between unsubstituted 2-propynimidamides and benzaldehyde derivatives generated *in situ*. The feasibility of such metathesis/alkylation cascades is manifested with sufficient examples, further highlighting novel 1,4-hydroxyiminations of 3-en-1-ynes. These alkynol products are readily transformed into substituted aminofurans or functionalized enones. The focus of this work is not only on the discovery of 1,4-metathesis reactions, but also includes the development of their new synthetic utility.

■ ASSOCIATED CONTENT

■ Supporting Information

X-ray crystallographic data of **11e**; experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

rsliu@mx.nthu.edu.tw

Notes

The authors declare no competing financial interest.

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