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Zn(II)- or Ag(I)-Catalyzed 1,4-Metathesis Reactions between 3-En-1-ynamides and Nitrosoarenes

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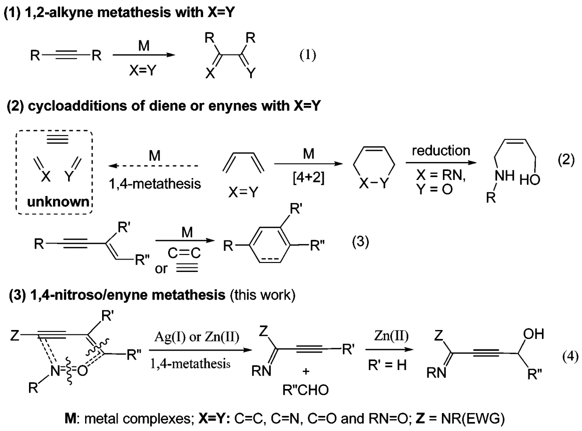
Ⓢ *Supporting Information*

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/alkynation 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 enimine[3] compounds via a 1,2-metathesis route (eq 1). We 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 nitrosoarenes[7] 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.



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

We first tested the reactions of 3-en-1-ynamide **1a** with nitrosobenzene (**2a**) using IPrAuNTf$_2$ (5 mol%, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) and LAuNTf$_2$ (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 AgNTf$_2$, AgOAc, and AgOTs 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 ZnCl$_2$ 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 R^1 substituent (R^1 = 4-bromo- and 4-methoxyphenyl, 2-furanyl, and cyclohexenyl), affording the

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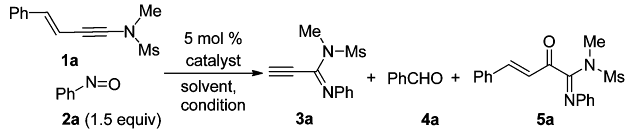
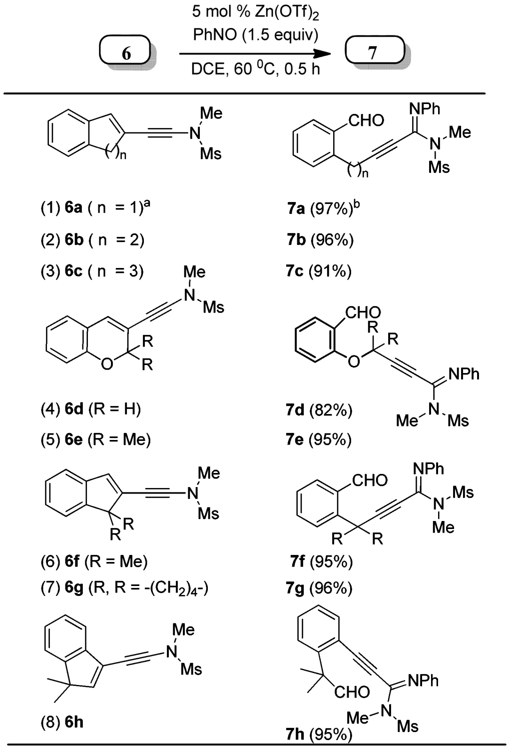
Table 1. 1,2- versus 1,4-Metathesis Reactions



			conditions[b]		products (%)[c]		
entry	catalyst[a]	solvent	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	–	–

[a] IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene), L = $P(tBu)_2$(*o*-biphenyl). [b] [**1a**] = 0.14 M. [c] Product yields are reported after purification from a silica column.

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

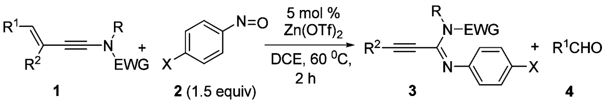


[a] [**6**] = 0.14 M. [b] Product yields are reported after purification from a silica column.

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 (R^2 = 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 = NO_2, 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 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 indenes **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

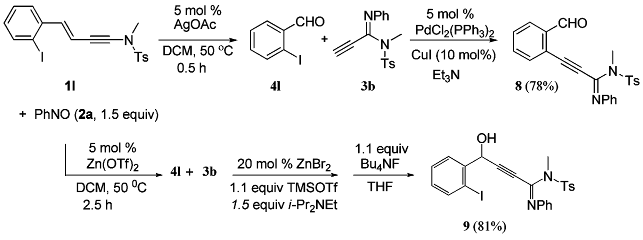


	enyne					products (yield, %)	
entry	1	R^1	R^2	NR (EWG)	nitroso **2** (X)	3	4
1	**1b**	Ph	H	N(Me)Ts	**2a** (H)	**3b** (92)	**4a** (92)
2	**1c**	Ph	H	N(Ph)Ts	**2a** (H)	**3c** (91)	**4a** (91)
3	**1d**	Ph	H	N(*n*Bu)Ts	**2a** (H)	**3d** (98)	**4a** (98)
4	**1a**	4-BrC_6H_4	H	N(Me)Ms	**2a** (H)	**3a** (94)	**4e** (94)
5	**1f**	4-$MeOC_6H_4$	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*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*Pr)	**3m** (95)	**4a** (95)

[a] [**1**] = 0.14 M. [b] Product yields are reported after purification from a silica column.

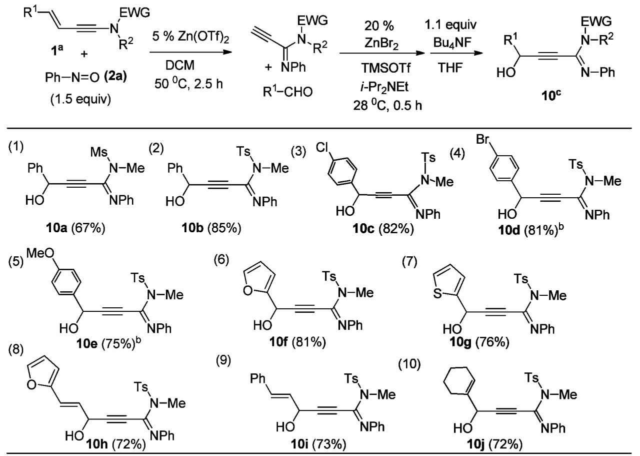
Simultaneous production of unsubstituted 2-propynimidamides and aldehydes allows their further elaborations with catalytic formation of a carbon−carbon bond. Scheme 1 depicts two one-pot cascade reactions between 3-en-1-ynamide **1l** and nitrosobenzene **2a** (2 equiv) under optimized conditions. Treatment of these reactants with AgOAc (5 mol%) in DCM (50 °C, 0.5 h) delivered 2-iodobenzaldehyde (**4l**) and a 2-propynimidamide **3b** efficiently; to this solution were added $PdCl_2(PPh_3)_2$, CuI (10 mol%), and Et_3N (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 alkynylation[10] *in situ* of aldehyde **4l** with $ZnBr_2$ (20 mol%), TMSOTf (1.1 equiv), and iPr$_2$NEt (1.5 equiv) in the same solution. A final workup with Bu_4NF in THF afforded alkynol derivative **9** in 81% yield.

Scheme 1. Two One-Pot Cascade Reactions



The formation of an alkynol product like **9** from 3-en-1-ynamide **1l** 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 additional examples. In entries 5−7, external aldehydes R^1CHO (R^1 = 4-$MeOC_6H_4$, 2-furyl, and 2-thienyl, 0.5 or 1.0 equiv) were added before the alkynation because of their lower reactivity. These one-pot reactions were accessible to alkynols **10a**,**10b** bearing various sulfonamides (NR^2EWG = NMeMs, NMeTs); the yields were 67−85% (entries 1 and 2). The reactions were applicable to 3-en-1-ynamides bearing different styryl groups (R^1 = XC_6H_4, 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** (R^1 = 2-furanyl 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).

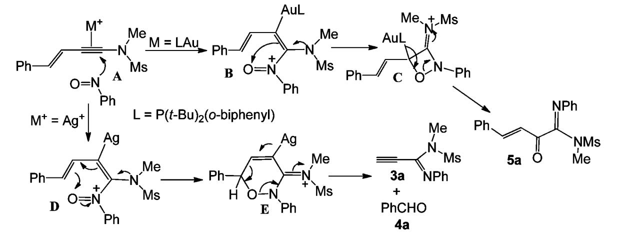
Table 4. One-Pot Metathesis/Alkynylation Cascades



[a] [1] = 0.14 M TMSOTf (1.0 equiv), iPr$_2$NEt (1.5 equiv). [b] External 4-$MeOC_6H_4CHO$ (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. [c] Products are reported efter separation from a silica column.

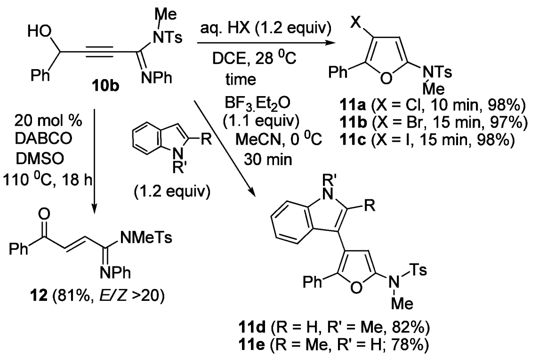
Shown in Scheme 2 is a plausible mechanism to rationalize catalyst-dependent chemoselectivity of 1,2- versus 1,4-metathesis reactions; we envisage that both reactions proceed via an initial attack of nitrosobenzene at metal π-alkyne species **A**. In recent work, we demonstrated that LAu^+ (L = P(tBu)$_2$(o-biphenyl)) 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(tBu)$_2$(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, dienylsilver 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.

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



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 $BF_3{\cdot}Et_2O$ (1.1 equiv) afforded aminofurans **11d**,**11e** of the same type; the

Scheme 3. Synthetic Applications of 3-Imidoylalkynol 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-ynamides[14] with nitrosoarenes. LAuNTf$_2$ (L = P(*t*Bu)$_2$(*o*-biphenyl) catalyzed 1,2-metathesis reactions, whereas AgNTf$_2$ 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 alkynation between unsubstituted 2-propynimidamides and benzaldehyde derivatives generated *in situ*. The feasibility of such metathesis/alkynation 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.

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Notes

The authors declare no competing financial interest.

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