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Ruthenium Complex-Catalyzed Domino Addition/*exo*-Cycloisomerization of Propargylic Alcohols and Tosyl Isocyanate to Form Oxazolidinones

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Abstract: A ruthenium complex with a tetradentate nitrogen–phosphorus mixed ligand is shown to be an efficient catalyst for domino addition/*exo*-cycloisomerization of propargylic alcohols and tosyl isocyanate. In the presence of 2–5 mol% ruthenium complex, a range of terminal propargylic alcohols were reacted with tosyl isocyanate to furnish the corresponding oxazolidinone product exclusively in moderate to excellent yields. Mechanistic studies suggest that propargylic alcohol and tosyl isocyanate undergo addition firstly to generate propargylic carbamate, which is then activated by the ruthenium complex to form an η^2-alkyne complex, rather than the ruthenium vinylidene intermediate, to afford the final oxazolidinone product.

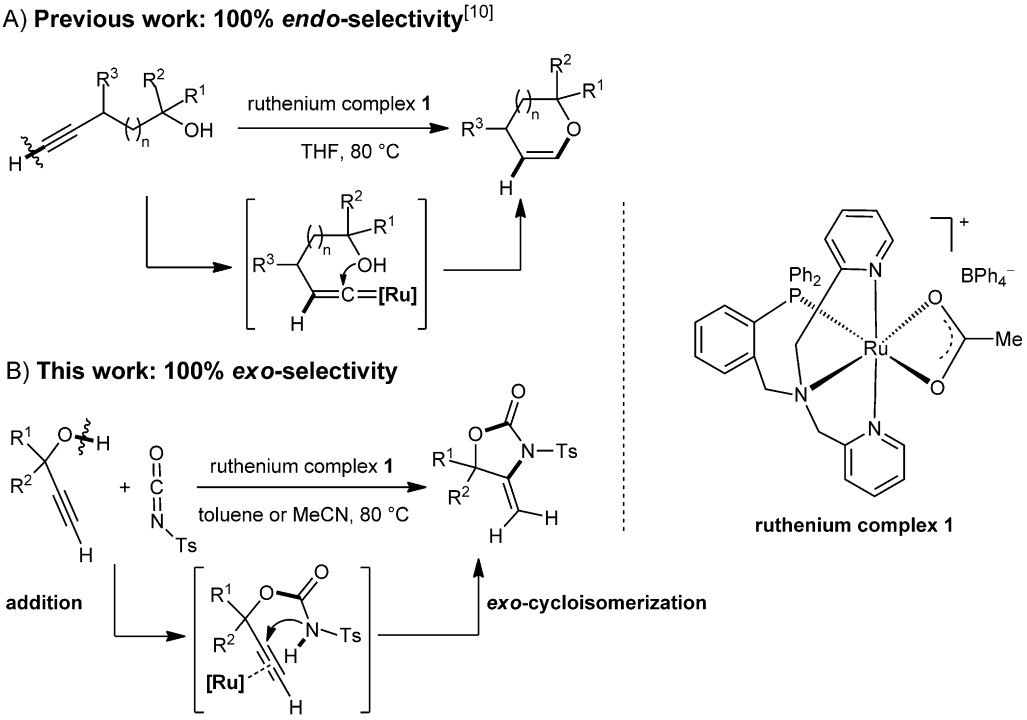
Keywords: addition; cycloisomerization; domino reactions; oxazolidinone; ruthenium

Oxazolidinones are heterocyclic compounds widely used in the pharmaceutical and agricultural industries because of their diverse biological activities as modulators of cytokine activity,[1a] inhibitors of monoamine oxidase,[1b] renin,[1c] sigma receptors,[1d] antibiotics[1e] and antibacterial agents.[1f] As a result, numerous methods have been developed to synthesize these compounds.[2] For example, cycloisomerization of vinyl or propargylic carbamates provides an efficient approach to afford oxazolidinones with the advantage of 100% atom efficiency,[3,4–6] fulfilling the requirements of green chemistry.

A perhaps more challenging reaction is cycloisomerization of alkynyl amides, which can lead to either *endo*- or *exo*-cyclic enamides.[7] Much effort has been spent developing efficient and selective catalytic systems for the transformation.[8,9] The following have been shown to efficiently generate *exo*-cyclic enamides: Cr, Mo, W,[8a] Et_2Zn,[8b] Ru,[8c] Pt,[8d] $Hg(OTf)_2$,[8e] while Cu[8f] can produce *endo*-cyclic enamides such as indoles and isoquinolin-1(2*H*)-ones. Phase-transfer catalysts,[9a] I_2,[9b] Pd,[9c,d] organic superbase P_4-*t*-Bu,[9e] the Brønsted base 1,5,7-triazabicyclo[4.4.0]dec-1-ene,[9f] the base $LiN(TMS)_2$,[9g,h] and *t*-BuOK[9i] efficiently generate *exo*-cyclic enamides.

The first efficient method for preparing oxazolidinones by *exo*-cycloisomerization of propargylic carbamates was base-catalyzed.[4] Then an N-heterocyclic carbene was shown to catalyze the same reaction after propargylic alcohols and benzoyl isocyanates were mixed to generate propargylic carbamates *in situ*.[5] More recent work has focused on transition metal catalysts for *exo*-cycloisomerization of propargylic carbamates to afford oxazolidinones,[6] specifically Cu[6a] and Au.[6b,c] In 2014, Bäckvall reported the Pd-catalyzed intramolecular hydroamination of propargylic carbamates and carbamothioates.[6d]

As part of the continuing efforts in heterocycle construction,[10] our previous work suggests that Ru may also be useful in efficiently and selectively generating oxazolidinones.[11] We synthesized a novel ruthenium complex **1** containing a tetradentate nitrogen–phosphorus mixed ligand and showed that it efficiently catalyzed the *endo*-cycloisomerization of alkynols.[11a] Mechanistic studies showed that the catalytic cycle involves a vinylidene intermediate, which guarantees the *endo*-selectivity of the reaction (Scheme 1, A).[11b] As the first ruthenium-catalyzed reaction for producing oxazolidinones, here we show that the same ruthenium complex **1** efficiently catalyzes a domino reaction involving addition and *exo*-cycloisomerization of propargylic alcohol and tosyl isocyanate. The propargylic alcohol adds to tosyl isocyanate to generate the corresponding carbamate *in situ*, which surprisingly undergoes *exo*-cycloisomerization exclusively to



Scheme 1. Cycloisomerization catalyzed by ruthenium complex **1**.

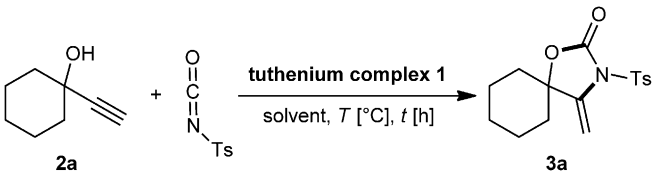
afford oxazolidinone products in good to excellent yield (Scheme 1, B).

We began our studies with the cycloaddition of 1-ethynylcyclohexanol **2a** and 4-methylbenzenesulfonyl (tosyl) isocyanate in the presence of 2 mol% ruthenium complex **1** in THF at 80 °C (Table 1). Unexpectedly, the *exo*-cyclic product 4-methylene-3-tosyl-1-oxa-3-azaspiro[4.5]decan-2-one **3a** was obtained in 77% yield (entry 1), and its structure was fully consistent with published data from ^{1}H and $^{13}C\{^{1}H\}$ NMR and mass spectrometry.[6d] Screening solvents showed that 1,4-dioxane and 1,2-DCE gave the product **3a** in 19% and 64% yields, respectively (entries 2 and 3). Performing the reaction in boiling CH_2Cl_2 for 12 h led to similarly low yield (entry 4). Using MeCN as solvent dramatically increased the yield of **3a** to 88% (entry 5). In the end, toluene was found to be the best choice, affording **3a** in 90% isolated yield (entry 6). Testing other ruthenium compounds such as $[CpRuCl(PPh_3)_2]$, $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2(PPh_3)_3]$ showed that little product **3a** formed (entries 7–9). Changing the reaction temperature did not improve the yield of **3a** (entries 10 and 11), while decreasing the loading of ruthenium complex **1** to 1 mol% reduced the yield of **3a** (entry 12). Conducting the reaction in the absence of ruthenium complex **1** yielded only a trace of product (entry 13). Interestingly, the addition of a catalytic amount of base such as Et_3N and DBU reduced the reaction time with maintained yields for the formation of product **3a** (entries 14 and 15). The results demonstrated that the bases may act as proton shuttles in the catalytic cycle to enhance the reaction rates,[6c] as a support for the mechanism. The addition of pyridine led to a lower 82% yield, due to its coordination property with ruthenium catalyst to inhibit the transformation (entry 16).

Using these optimized reaction conditions, we explored the substrate scope (Table 2). First, we examined disubstituted propargylic alcohols with substitutions at propargylic positions R^1 and R^2. Six- or five-membered spiro-propargylic alcohols were reacted with 4-methylbenzenesulfonyl isocyanate to afford the desired spiro-oxazolidinones **3a** and **3b** in, respectively, 90% and 92% yields. Likewise, propargylic alcohols disubstituted with methyl or benzyl groups gave the corresponding products **3c** and **3d** in, respectively, 87% and 90% yields. Propargylic alcohols disubstituted with different substitutions also participated in the reaction, giving oxazolidinones **3e** and **3f** in good yields.

We next studied the reactivity of propargylic alcohols monosubstituted at R^1 (with $R^2 = H$). The domino reaction proceeded smoothly with various such substrates to furnish the corresponding oxazolidinones in moderate to good yield, although the reaction time had to be extended to 24 h and the catalyst loading increased to 5 mol%. Propargylic alcohols carrying an alkyl or styryl substituent gave the corresponding products **3h–j** in 55–73% yield. In order for the reaction to proceed efficiently with aryl-monosubstituted propargylic alcohols, the solvent had to be

Table 1. Optimization of the domino addition/*exo*-cycloisomerization catalyzed by ruthenium complex **1**.[a]

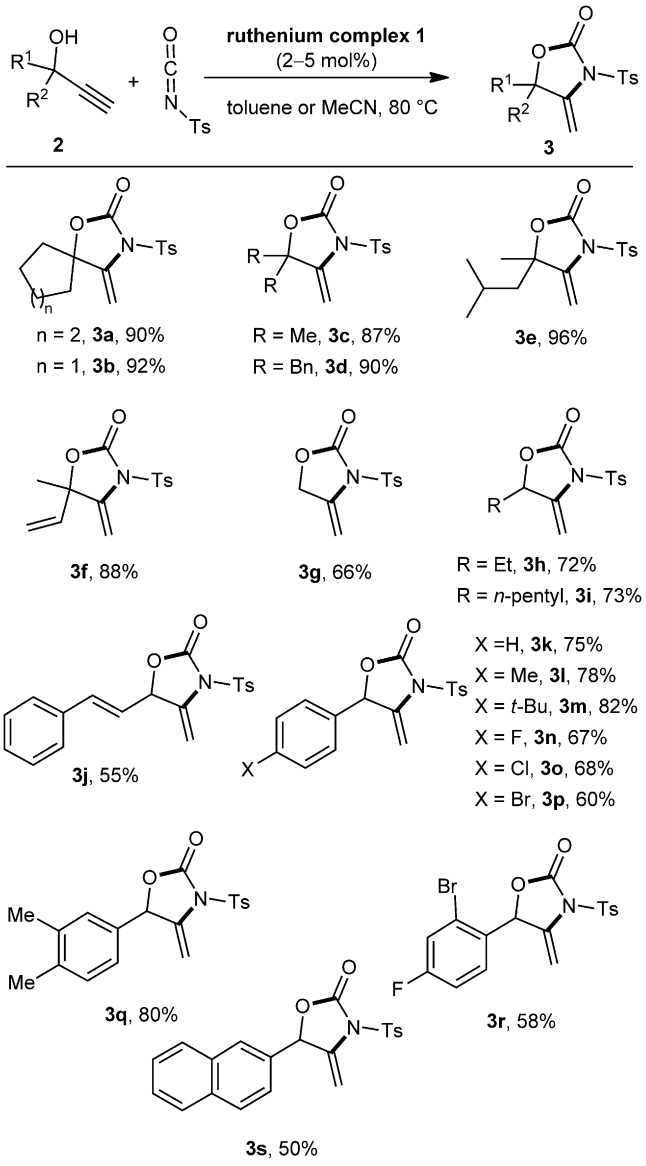


2a **3a**

Entry	Solvent	T [°C]	t [h]	Yield of **2a** [%][b]
1	THF	80	4	77
2	1,4-dioxane	80	4	19
3	1,2-DCE	80	4	64
4	CH_2Cl_2	50	12	10
5	CH_3CN	80	4	88
6	toluene	80	4	92 (90)[c]
7[d]	toluene	80	4	7
8[e]	toluene	80	4	2
9[f]	toluene	80	4	10
10	toluene	110	4	87
11	toluene	50	12	11
12[g]	toluene	80	12	60
13[h]	toluene	80	12	trace
14[i]	toluene	80	2	91
15[j]	toluene	80	2	92
16[k]	toluene	80	2	82

[a] *Reaction conditions:* **2a** (0.5 mmol), 4-methylbenzenesulfonyl isocyanate (0.5 mmol) and ruthenium complex **1** (0.01 mmol) in solvent (1.5 mL) under a nitrogen atmosphere, unless otherwise noted.
[b] Determined from ^{1}H NMR spectra using $PhSiMe_3$ as internal standard.
[c] Isolated yield.
[d] $[CpRuCl(PPh_3)_2]$ (0.01 mmol) was used.
[e] $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol) was used.
[f] $[RuCl_2(PPh_3)_3]$ (0.01 mmol) was used.
[g] Ruthenium complex **1** (0.005 mmol) was used.
[h] Without ruthenium complex **1**.
[i] Et_3N (0.05 mmol) was added.
[j] DBU (0.05 mmol) was added.
[k] Pyridine (0.05 mmol) was added.

Table 2. Substrate scope of domino addition/*exo*-cycloisomerization catalyzed by ruthenium complex **1**.[a,b,c]



[a] *Reaction conditions:* **2** (0.5 mmol), 4-methylbenzenesulfonyl isocyanate (0.5 mmol) and ruthenium complex **1** (0.01 mol) in toluene (1.5 mL) at 80 °C for 4 h under a nitrogen atmosphere. Isolated yields are shown.
[b] For products **3g–s**, ruthenium complex **1** (0.025 mmol) was used, and the reaction time was extended to 24 h.
[c] MeCN was used as solvent in reactions to generate **3k–s**.

switched to MeCN. This is likely due to inadequate solubility of the substrates in toluene. Single-crystal X-ray diffraction analysis of product **3k** confirmed that the domino reaction was producing oxazolidinones with complete *exo*-selectivity (Figure 1).[12] Aryl-monosubstituted propargylic alcohols carrying electron-donating groups such as methyl and *tert*-butyl on the benzene ring gave the oxazolidinones **3l** and **3m** in good yield. Halogen-substituted propargylic alcohols gave the corresponding oxazolidinones **3n–p** in 60–68% yield.

The domino reaction yielded a more complicated array of products when the propargylic alcohols carried either electron-donating substituents (MeO, Me_2N, pyrrolidinyl) or electron-withdrawing substituents (NO_2, CN) on the benzene ring. Nevertheless, propargylic alcohols carrying multiple substitutions on the benzene ring gave the desired products **3q** and **3r** in good yield. When 1-(naphthalen-2-yl)prop-2-yn-1-ol was used in the reaction, the corresponding oxazolidinone **3s** was obtained in only 50% yield. Unfortunately, propargylic alcohols containing heteroaromatic rings such as thiophene and furan did not participate in the reaction, even under harsh conditions (110 °C, 48 h). Internal propargylic alcohols such as 1-(phenyl-

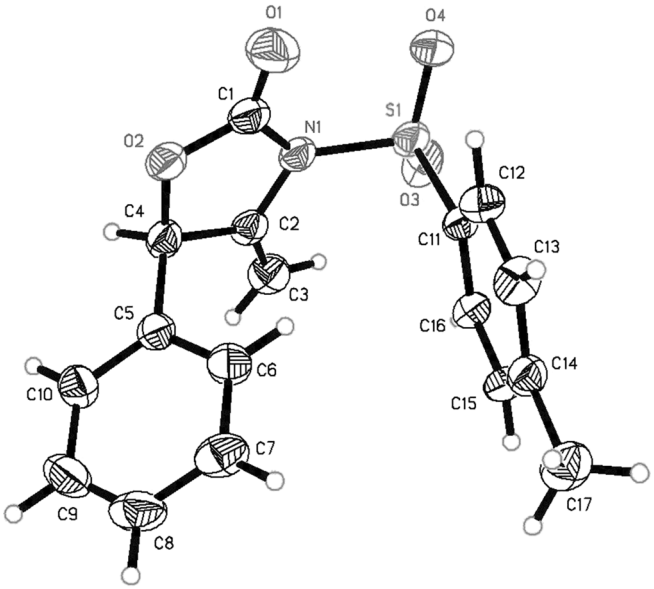
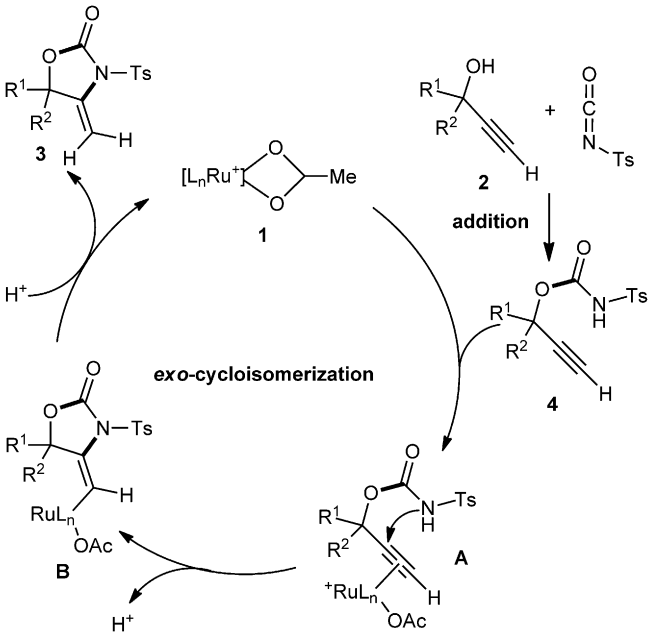


Figure 1. ORTEP diagram of product **3k**.

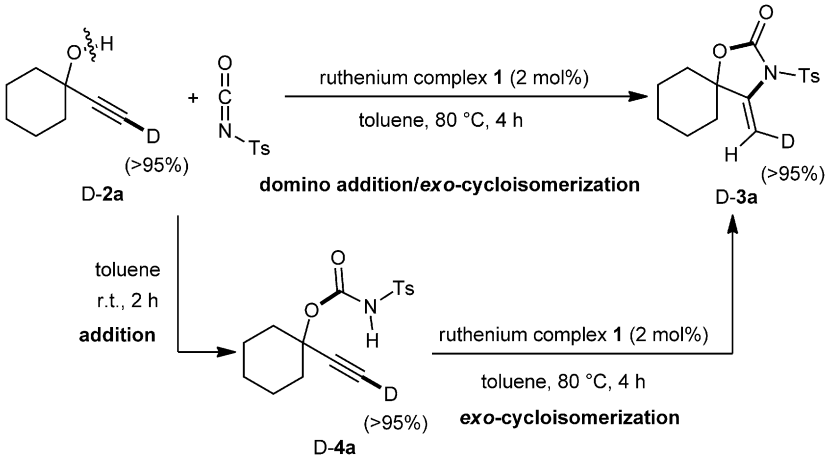
ethynyl)cyclohexanol and but-2-yn-1-ol also failed to react efficiently, perhaps due to the steric effect. Similarly, homopropargylic alcohols such as but-3-yn-1-ol did not undergo the transformation to generate the 6-*exo* cyclization product. It is also noteworthy that the other isocyanates, such as benzoyl isocyanate, ethyl carbonisocyanatidate, 1-chloro-4-isocyanatobenzene or 1-isocyanatopropane, could not react with **2a** to afford the oxazolidinone products under the present conditions. To evaluate the applications of this approach, we performed the reaction using 10 mmol (1.24 g) of 1-ethynylcyclohexanol **2a**. In the presence of 2 mol% of ruthenium complex **1** in toluene, the reaction gave the cyclized product **3a** in 82% isolated yield (2.64 g).

To clarify how ruthenium complex **1** catalyzes this domino addition/*exo*-cycloisomerization, we tested the reaction of D-**2a** with tosyl isocyanate under the optimal reaction conditions (Scheme 2). The resulting product D-**3a** contained a completely deuterated alkenyl hydrogen, suggesting that domino cyclization does not involve C–D cleavage of terminal alkyne D-**2a**. Consistent with this idea, reacting deuterated propargylic alcohol D-**2a** and tosyl isocyanate in the absence of ruthenium complex **1** gave the corresponding deuterated addition product D-**4a**. Using the addition product D-**4a** directly in the domino reaction under optimal conditions led to deuterated product D-**3a**.

These results lead us to propose a tentative mechanism for ruthenium-catalyzed domino addition/*exo*-cycloisomerization (Scheme 3). First, addition of propar-



Scheme 3. Proposed mechanism for the domino addition/*exo*-cycloisomerization catalyzed by ruthenium complex **1**.



Scheme 2. Mechanistic studies of the domino addition/*exo*-cycloisomerization catalyzed by ruthenium complex **1**.

gylic alcohol **2** and tosyl isocyanate gives the propargylic carbamate **4**. The alkyne group of intermediate **4** is activated by the ruthenium complex **1** to form an η^2-alkyne complex **A**, which rapidly undergoes intramolecular nucleophilic attack to give the ruthenium complex **B**. Subsequently, Protonation of the metal–carbon bond simultaneously releases oxazolidinone **3** and regenerates ruthenium complex **1**. Comparing with the hydroxy group of alkynols in the *endo*-cycloisomerization,[11] the nucleophilic group *N*-tosylamide demonstrates a much larger steric hindrance effect, which is unfavorable for the addition to a ruthenium vinylidene intermediate. Moreover, *N*-tosylamide possesses a stronger nucleophilicity to fulfil an intramolecular nucleophilic attack to the η^2-alkyne complex **A**. Both factors may result in the *exo*-selectivity of the current reaction.

In summary, we have developed the first ruthenium complex-catalyzed protocol for producing oxazolidinones in good to excellent yield *via* domino addition/*exo*-cycloaddition between propargylic alcohol and tosyl isocyanate. Mechanistic studies suggest that during the reaction, propargylic alcohol and tosyl isocyanate first undergo addition, generating propargylic carbamate, which undergoes *exo*-cycloisomerization exclusively to afford the oxazolidinone. The *exo*-selectivity of complex **1** in the cycloisomerization of propargylic carbamates contrasts with its *endo*-selectivity in the cycloisomerization of alkynols, which demonstrates the diverse catalytic abilities of ruthenium complex **1**. We hope our work will open the door to an even broader array of catalytic applications of ruthenium complex **1** in organic reactions.

Experimental Section

Typical Procedure for Ruthenium Complex 1-Catalyzed Domino Addition/*exo*-Cycloisomerization

4-Methylbenzenesulfonyl isocyanate (0.5 mmol) was added to a solution of propargylic alcohol **2** (0.5 mmol) in toluene or MeCN (1.5 mL, as indicated in Table 2). After the reaction mixture had been stirred for 10 min at room temperature, the ruthenium complex **1** (0.01 or 0.025 mmol as indicated in Table 2) was added and the temperature was increased to 80 °C. After stirring for 4–24 h, the reaction mixture was concentrated and purified by flash column chromatography on silica gel using petroleum ether-EtOAc as eluent (in ratios ranging from 10:1 to 3:1), giving the desired product **3**.

Acknowledgements

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[12] CCDC 1032121 contains the supplementary crystallographic data for **3k** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

