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A silver-catalyzed domino inverse electron-demand oxo-Diels–Alder reaction of 3-cyclopropylideneprop-2-en-1-ones with 2,3-dioxopyrrolidines *via* cyclobutane-fused furan†

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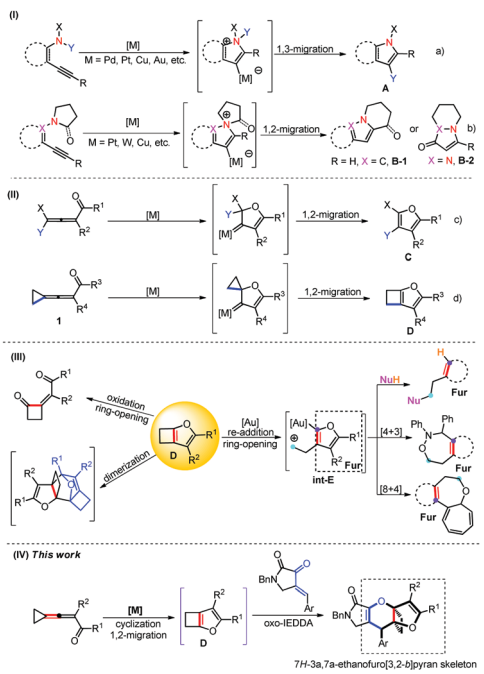
A silver-catalyzed diastereoselective one-pot domino cyclization-migration/inverse electron-demand oxo-Diels–Alder reaction has been disclosed in this communication through the *in situ* generated cyclobutane-fused furan intermediate with 4-vinyl-2,3-dioxopyrrolidine for the construction of 2-oxopyrrolidine-fused tricyclic compounds in moderate to good yields with a broad substrate scope under mild conditions. This new synthetic protocol features good efficiency and atom- and step-economy. A plausible reaction mechanism has also been proposed on the basis of previous reports, NMR tracing and control experiments.

Domino reaction is an ideal process that installs or fragments two or more bonds in a stepwise fashion, and it exhibits striking advantages over multistep reaction because of its high efficiency and atom and step economy.[1] In particular, domino reaction containing sequential units of metal-catalyzed cyclization/migration reaction[2] or Hetero-Diels–Alder (HDA) reactions,[3] which both proceed in a highly atom-economical manner, provide convenient access to complex heterocyclic compounds.[4] The metal-catalyzed sequential cyclization-migration reaction has been well established on the basis of pioneering work in recent years.[5] It is a powerful tool in efficient synthesis of *N*-, *O*-containing heterocycles *via* intramolecular nucleophilic addition of a heteroatom into an activated alkyne or allene by a π-Lewis acidic transition metal catalyst.[6] For example, Yamamoto's group has reported a Pt-catalyzed transformation for the synthesis of 2,3-disubstituted indoles *via* nucleophilic addition of alkynes bearing *N*-functional groups followed by 1,3-migration (Scheme 1, I-a).[7] The complementary cyclization/1,2-migration sequences have been developed by Iwasawa,[8] Zhang[9] and Ueda,[10] using cyclic amines or amides as substrates (Scheme 1, I-b). Moreover, a series of meritorious studies involving the process of oxo-cyclization and 1,2-migration of allenyl ketones and vinylidenecyclopropanes bearing a ketone moiety have been disclosed by Marshall,[11] Hashimi,[12] Gevorgyan,[13] Huang[14] and Ren[15] *etc.*, providing efficient methods for the assembly of the furan derivatives (Scheme 1, II-c and II-d). Notably, among these furan derivatives, the cyclobutane-fused furan **D** has represented multiple reactivities under mild conditions. In this aspect, Huang and co-workers reported the oxidative cycloisomerization of *in situ*



Scheme 1 Metal-catalyzed sequential cyclization-migration reaction and our protocol.

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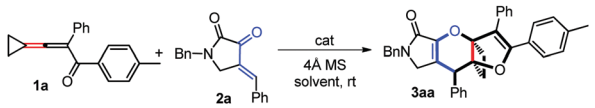
generated furyl intermediate **D** by using Dess–Martin periodinane (DMP) as an oxidant, furnishing highly strained functionalized 2-alkylidenecyclobutanones.[14a] Subsequently, the furyl intermediate **D** also indicated unusual reactivity of self-dimerziation, functioning as a diene and dienophile in one reaction.[14b] Recently, a novel gold-containing 1,4-all carbon dipole Int-**E**, explored by Ren and co-workers, has demonstrated unique reactivities upon trapping with a variety of nucleophiles, furnishing polysubstituted furan derivatives in good yields,[15c] and has been also applied successively to [4+3] cycloaddition[15d] and [8+4] high-order cycloaddition reaction (Scheme 1, III).[15e] Moreover, it is conceivable that this cyclobutane-fused furan **D**, which can be regarded as a furan assembled by electron-rich substituents, should also have potential application in the inverse electron-demand Diels–Alder (IEDDA) reaction.[16]

The IEDDA reaction, as a significant complementary transformation of Diels–Alder (DA) reaction, has become a valuable synthetic tool for constructing 6-membered cyclic frameworks.[17] Strategies of lowering the LUMO of diene and raising the HOMO of dienophiles have been widely developed to build various heterocyclic compounds.[18] In these protocols, 2,3-dioxopyrrolidines have been widely used in the construction of polycyclic compounds.[19] We envisioned that 2,3-dioxopyrrolidine, an oxo-IED diene, may be able to use as a partner to react with furyl intermediate **D** in an oxo-IEDDA reaction manner to afford polyheterocyclic frameworks. Herein, we wish to report a novel Ag-catalyzed domino cyclization-migration/IEDDA reaction to afford a variety of 2-oxopyrrolidine-fused tricyclic compounds under mild conditions in this communication (Scheme 1, IV-this work).

In the initial examination, 3-cyclopropylideneprop-2-en-1-one **1a** and 1-benzyl-4-benzylidenepyrrolidine-2,3-dione **2a** were used as model substrates to start our investigation. The desired [4+2] cycloadduct **3aa** was produced as a single diastereomer in 94% NMR yield (90% isolated yield) in the presence of 5 mol% of $AgSbF_6$ in anhydrous DCM at room temperature after 10 minutes (Table 1, entry 1). Encouraged by this finding, we attempted to further optimize the reaction conditions, and the results are summarized in Table 1. Using CuCl as a catalyst could give **3aa** in 88% yield (entry 2) and none of **3aa** was formed under gold catalysis if using IPrAuCl as the catalyst, presumably due to re-addition of Au to cyclobutane-fused furan **D** (entry 3).[15c–e] The examination of the counter anion effect of silver salts indicated that $AgSbF_6$ gave the best performance (entries 4–6). A variety of Lewis acid catalysts such as $In(OTf)_3$, $BF_3{\cdot}Et_2O$, $Yb(OTf)_3$, $Y(OTf)_3$ and $Gd(OTf)_3$, were found to be ineffective in delivering **3aa** (entries 7–11), suggesting that this transformation involved a π-Lewis acidic transition metal catalyzed sequential cyclization–migration process. The other solvents were also screened in this reaction with 1,2-DCE, toluene, THF and MeCN, however, these solvents could not further improve the yield of **3aa** (entries 12–15). Finally, a control experiment showed that no reaction occurred in the absence of an Ag catalyst (entry 16). The use of 4Å MS was essential because trace amounts of water could interfere with the formation of intermediate **D**.

With the optimal conditions in hand, we next turned our attention to investigate the substrate scope of this oxo-IEDDA

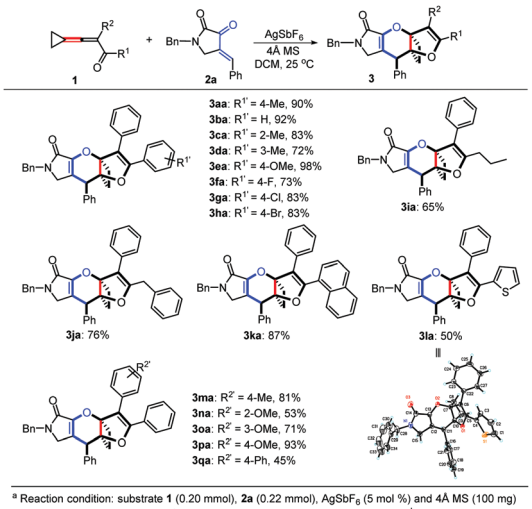
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b]/(%)
1	$AgSbF_6$	DCM	94 (90)[c]
2	CuCl	DCM	88
3	IPrAuCl	DCM	—
4	$AgNTf_2$	DCM	85
5	AgOTf	DCM	91
6	$AgBF_4$	DCM	90
7	$In(OTf)_3$	DCM	—
8	$BF_3{\cdot}Et_2O$	DCM	—
9	$Yb(OTf)_3$	DCM	—
10	$Y(OTf)_3$	DCM	—
11	$Gd(OTf)_3$	DCM	—
12	$AgSbF_6$	1,2-DCE	71
13	$AgSbF_6$	Toluene	61
14	$AgSbF_6$	THF	78
15	$AgSbF_6$	CH_3CN	70
16	—	DCM	—

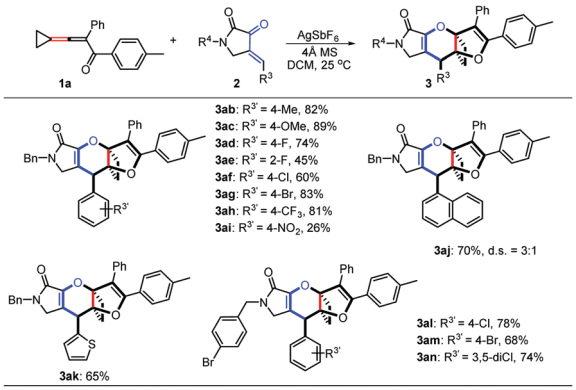
[a] Unless otherwise stated, the reaction was carried out using **1a** (0.20 mmol), **2a** (0.22 mmol), 100 mg of 4 Å MS and 5 mol% of catalyst in solvent (2.0 mL) under an Ar atmosphere for 10 minutes. [b] Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield.

reaction, and the results are shown in Schemes 2 and 3, respectively. A range of allenyl ketones **1** could be successfully employed. When R^1 was an aromatic group, regardless of whether they had electron-donating or -deficient substituents, the reactions proceeded smoothly, giving the corresponding products **3ba–3ha** in good yields ranging from 72% to 98%. In addition, when R^1 was a *n*-propyl, a benzyl, a 1-naphthyl or a 2-thiophenyl group, the reaction was also compatible, affording the desired oxo-IEDDA reaction products **3ia-3la** in 65%, 76%, 87% and 50% yields, respectively. Furthermore, as for an R^2 group in substrate **1**, it could be a variety of aromatic groups, furnishing the desired products **3ma–3qa** in moderate to good



[a] Reaction condition: substrate **1** (0.20 mmol), **2a** (0.22 mmol), $AgSbF_6$ (5 mol %) and 4Å MS (100 mg) in 2.0 mL anhydrous DCM at 25 °C under argon atmosphere for 5 to 60 minutes. [b] Isolated yield.

Scheme 2 Substrate scope of cyclopropyl allenyl ketones[a,b].



[a] Reaction condition: substrate **1a** (0.20 mmol), **2** (0.22 mmol), $AgSbF_6$ (5 mol %) and 4Å MS (100 mg) in 2.0 mL anhydrous DCM at 25 °C under argon atmosphere for 5 to 60 min. [b] Isolated yield.

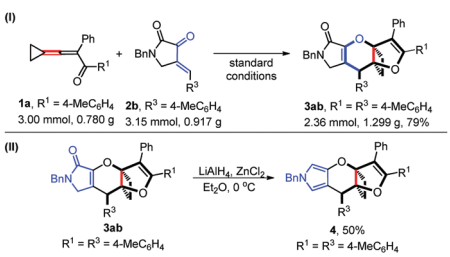
Scheme 3 Substrate scope of 4-vinyl-2,3-dioxopyrrolidine **2**[a,b].

yields. Noticeably, the structure of **3la** has been unambiguously determined by X-ray diffraction and the CIF data are presented in the ESI.†

Next, we attempted to explore the substrate scope of 4-vinyl-2,3-dioxopyrrolidine **2**, and the results are summarized in Scheme 3. As can be seen, the R^3 moiety of substrates **2** could be electron-rich or electron-poor aromatic rings, giving the desired products **3ab-3ai** in moderate to good yields ranging from 26% to 89%. In the case of an aromatic R^3 group bearing a 4-NO_2 substituent, the poor solubility of substrate **2i** might lead to the lowest yield in this reaction, giving **3ai** in 26% yield. Moreover, the reaction of **1a** with **2j**, in which the R^3 group was a 1-naphthyl moiety rather than a phenyl ring, provided **3aj** in 70% yield as a pair of rotamers with 3 : 1 d.s. value due to its steric bulkiness. Heteroaromatic 2-thiophenyl group containing **2k** was also tolerated, furnishing the desired product **3ak** in 65% yield. Introducing a substituent on the phenyl ring of the benzyl R^4 moiety did not affect the yield of **3**, providing **3al–3an** in 68–78% yield.

A gram-scale synthesis of **3ab** was then carried out to examine the practicality of this methodology. As shown in Scheme 4, the reaction of 3.00 mmol of **1a** with 3.15 mmol of **2b** produced 1.299 g of **3ab** in 79% yield under the standard conditions (Scheme 4, I). It was also worth noting that the cascade reduction and dehydration-aromatization of **3ab** could be achieved upon treating with $LiAlH_4$ and $ZnCl_2$ in ether at 0 °C, furnishing pyrrole-fused tetrahydropyran derivative **4** in 50% yield (Scheme 4, II).

Then, the ^{1}H NMR spectroscopic tracing and control experiments were conducted to verify the reaction mechanism. In the



Scheme 4 Gram-scale synthesis and synthetic application.

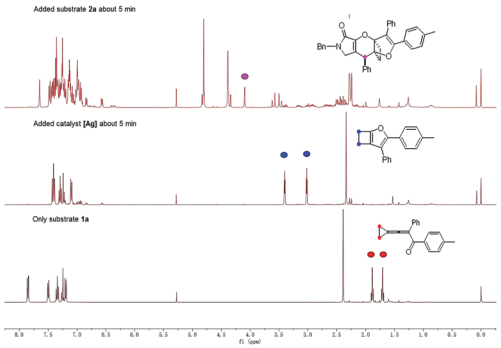
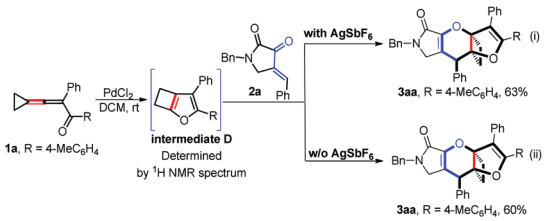
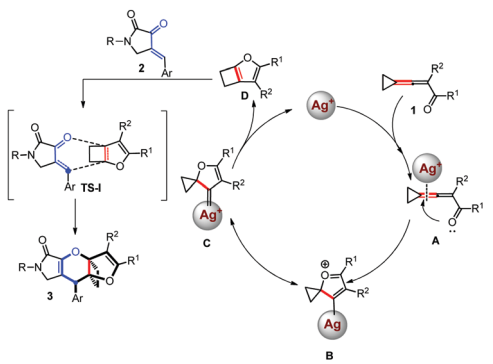


Fig. 1 ^{1}H NMR spectra of tracing experiments.



Scheme 5 Control experiments.



Scheme 6 Proposed reaction mechanism.

^{1}H NMR tracing experiments, the formation of cyclobutane-fused furan **D** (Fig. 1, middle) was identified and monitored by comparing with the original ^{1}H NMR spectrum of **1a** (Fig. 1, bottom). Subsequently, the signals of cyclobutane-fused furan **D** immediately disappeared along with the addition of **2a**, and the signals of the desired product **3aa** appeared (Fig. 1, top). These results indicated that the reaction proceeded through a sequential reaction pathway of cyclization-migration and IEDDA. Furthermore, the control experiments confirmed that cyclobutane-fused furan **D** could be transformed to **3aa** in 63% yield in the presence of $AgSbF_6$ and in 60% yield in the absence of $AgSbF_6$ (Scheme 5, i and ii), suggesting that the oxo-IEDDA reaction was a catalyst-free process.

On the basis of Huang[14] and Ren's[15] reports and our own examinations, a plausible reaction mechanism has been outlined in Scheme 6. Initially, the nucleophilic attack of the carbonyl

oxygen atom to the silver(I)-coordinated allene moiety of **1** affords spirocyclic oxonium ion **B**, which undergoes isomerization to give the more stabilized silver carbenoid intermediate **C**. Then, cyclobutane-fused furan **D** can be provided through a ring-expansion process along with the metal elimination. In this process, the regenerated silver(I) cation will take part in the next catalytic cycle. Finally, the oxo-IEDDA of **D** with substrate **2** occurs smoothly, affording the desired product **3**.

In conclusion, a novel Ag-catalyzed diastereoselective one-pot domino cyclization-migration/inverse electron-demand oxo-Diels–Alder reaction has been disclosed in this paper. The reaction proceeds through an *in situ* generated cyclobutane-fused furan intermediate, which serves as an electron-rich dienophile for the oxo-IEDDA reaction with 4-vinyl-2,3-dioxopyrrolidine, allowing efficient and diastereoselective construction of 2-oxopyrrolidine-fused tricyclic compounds in moderate to good yields with a broad substrate scope under mild conditions. This new synthetic protocol features the use of readily available starting materials, proceeding through a one-pot domino procedure, with good yields and atom- and step-economy. Further investigations on expanding the applications of this synthetic method in the preparation of more complex molecules are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts of interest to declare.

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