Heterocycle Synthesis

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Ruthenium-Catalyzed C–C Bond Cleavage of 2*H*-Azirines: A Formal [3+2+2] Cycloaddition to Fused Azepine Skeletons

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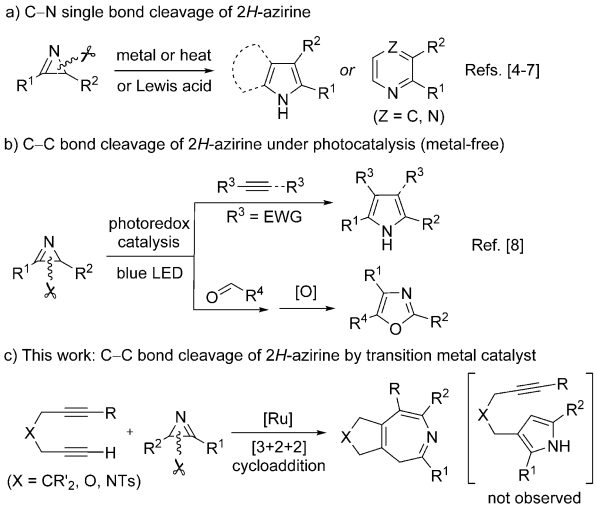
Abstract: *2H-azirines can serve as three-atom synthons by C–C bond cleavage, however, it involves a high energy barrier under thermal conditions (> 50.0 kcal mol^{-1}). Reported is a ruthenium-catalyzed [3+2+2] cycloaddition reaction of 2H-azirines with diynes, thus leading to the formation of fused azepine skeletons. This approach features an unprecedented metal-catalyzed C–C bond cleavage of 2H-azirines at room temperature, and the challenging construction of aza-seven-membered rings from diynes. The results of this study provide a new reaction pattern for constructing nitrogen-containing seven-membered rings and may find applications in the synthesis of other complex heterocycles.*

Transition-metal-catalyzed C–C bond activation represents a straightforward but challenging strategy to discover new transformations and construct complex molecules in modern organic synthesis.[1] In comparison with achievements in C–H bond activation, the development of C–C bond activation still lags behind because of its inert character and poor interaction of the C–C σ bond with transition metals.[2] In contrast, C–C bond activation of small rings has gained considerable attention in the past decade. As a paradigm, 2*H*-azirines can undergo diverse ring-opening reactions by different bond-cleavage modes.[3] To date, the chemistry of 2*H*-azirines mainly focuses on the cleavage of a C–N single bond. For example, 2*H*-azirines can serve as synthetic equivalents of vinyl nitrenes by C–N bond cleavage to construct various N-heterocycles, such as indoles,[4] pyrroles,[5] pyridines[6] and pyrazines[7] (Scheme 1 a). In contrast, reactions of 2*H*-azirines with unsaturated compounds by C–C bond cleavage have been rarely explored.[8–10] Recently, Xiao and Lu disclosed the visible-light-induced C–C bond cleavage of 2*H*-azirines under metal-free conditions, which allowed the divergent synthesis of polysubstituted pyrroles and oxazoles by formal [3+2] cycloadditions (Scheme 1 b).[8] These reactions are initiated by single-electron oxidation of the 2*H*-azirines in the presence of an excited photocatalyst with subsequent homolytic cleavage of the C–C bond. To the best of our knowledge, transition-metal-catalyzed C–C bond cleavage of 2*H*-azirines remains largely unexploited, possibly because of the higher energy barrier.[11]



Scheme 1. Ring-opening reactions of 2*H*-azirines. EWG = electron-withdrawing group, Ts = 4-toluenesulfonyl.

Azepine derivatives are important skeletal motifs which are widely distributed in numerous natural products and pharmaceuticals (Figure 1).[12] Owing to the significant medicinal and bioactive properties of the azepine moiety, many methods for the preparation of azepine-containing heterocycles have been developed in recent decades.[13,14] Particularly, azepine frameworks have been constructed by [4+3], [5+2], and [3+2+2] cycloadditions of unsaturated hydrocarbons with triazoles, aziridines, azomethine imines, cyclopropyl imines, imine esters, and amino ketones.[14] Despite the significant advances made in this subject, there are only limited reports on the preparation of ring-fused azepine derivatives.[13k,14l,m]

Cycloadditions involving diynes enable the straightforward construction of medium-sized carbo- or heterocycles with high atom efficiency.[15] Along with our ongoing research interest in the metal-catalyzed cycloaddition reactions by

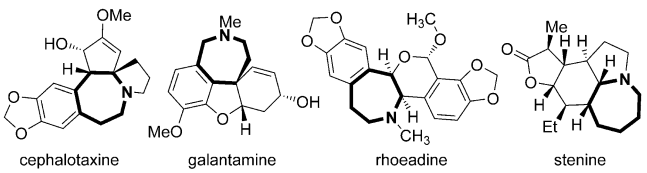


Figure 1. Natural products containing fused azepine skeletons.

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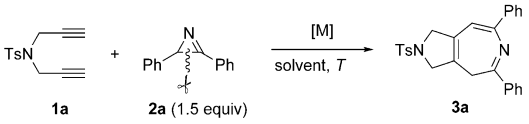
using diynes as C_4 units,[16] we surmized that the azepine framework could be assembled by [3+2+2] cycloaddition of diynes with 2*H*-azirines, in which the 2*H*-azirines would serve as three-atom components. Indeed, examples of the formation of aza-seven-memberd rings from diynes are extremely rare.[17] Our previous studies demonstrated that [3+2] rather than [3+2+2] cycloadducts were preferentially constructed in the reaction of diynes with methyleneaziridines, thus leaving an alkyne unit intact.[16c] To our delight, the reaction of diynes with 2*H*-azirines follows the [3+2+2] pathway by using an appropriate ruthenium catalyst,[18] thus providing the desired azepine architectures (Scheme 1 c). This approach features an unprecedented metal-catalyzed C–C bond cleavage of 2*H*-azirines, and the challenging construction of aza-seven-membered rings from diynes. Herein, we report our preliminary results.

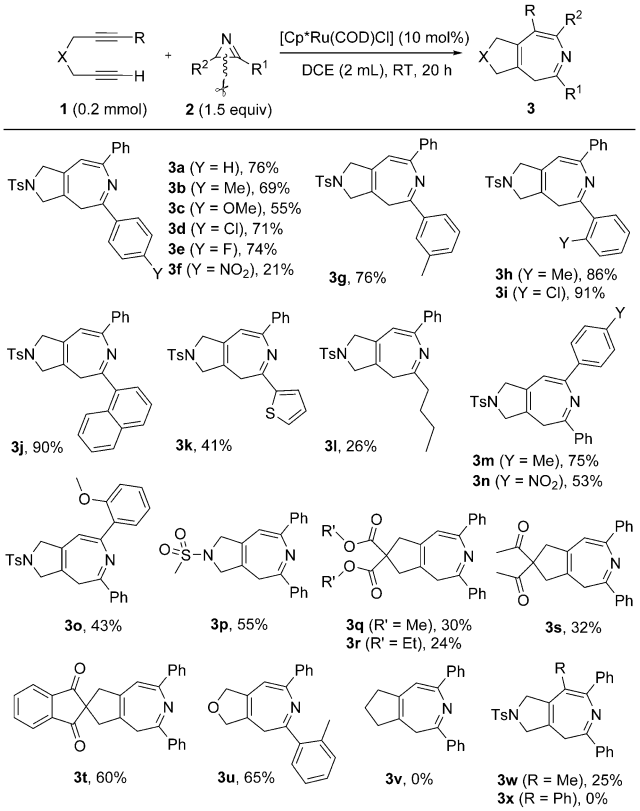
At the outset, the diyne **1a** and 2*H*-azirine **2a** were chosen as model substrates for the optimization of the reaction conditions [Eq. (1)]. The results are summarized in Table S1



(1)

in the Supporting Information. Some typical transition-metal catalysts for cycloadditions were first investigated. Unfortunately, no desired product was observed with our previously developed iron catalyst[16a] (Table S1, entry 1). In addition, cobalt,[19a] nickel,[19b] rhodium,[19c] and iridium[19d] catalysts also failed to provide any new products (entries 2–5). However, the possibility that the above systems might be workable could not be completely excluded if an in-depth investigation is done. Gratifyingly, the product 3*H*-azepine **3a** was obtained in 71% yield using 10 mol% [Cp*Ru(COD)Cl] (entry 6; COD = 1,5-cyclooctadiene, Cp* = C_5Me_5). The structure of **3a** was unambiguously confirmed by X-ray crystal diffraction.[20] Various ruthenium (II) catalysts were then evaluated in the reaction, however, none of them led to better results (entries 7–11). Intriguingly, ruthenium(II) complexes lacking either the Cp or Cp* ligand exhibited no appreciable catalytic activity (entries 9–11). Subsequently, a screening of solvents revealed that both DCE and DCM (DCE = 1,2-dichloroethane, DCM = dichloromethane) showed the best performance (entries 12–15). Furthermore, a simple inspection on the reaction temperatures indicated that lowering the temperature to 25 °C can afford a better yield (entry 17). A slight improvement in product yield can be achieved by prolonging the reaction time to 20 hours (80%, entry 19). It is noteworthy that the dimerization of diynes was commonly detected under ruthenium catalysis,[18d,e] thus slightly lowering the yield of **3a**. Remarkably, decreasing the catalyst loading to 5 mol% displayed lower activity (entry 20).

With the optimal reaction conditions secured, we turned our attention to the scope of this reaction. The variations of the R^1 group on the C=N double bond moiety of 2*H*-azirines were first examined. As highlighted in Scheme 2, both



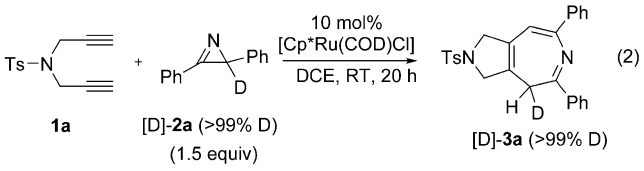
Scheme 2. Substrate scope. Yields of isolated products are given.

electron-donating and electron-withdrawing groups on the phenyl ring could be successfully introduced, thus providing the corresponding polysubstituted azepines (**3b–e**, **3g–i**) in moderate to excellent yields. The R^1 group is placed near to the methylene unit (CH_2) in the product, as identified by the X-ray crystal diffraction of **3g**.[20] However, the 2*H*-azirine **2f**, bearing a strong electron-withdrawing aryl group, provided **3f** in low yield. 2*H*-azirines bearing an *ortho*-substituted phenyl ring (**2h**, **2i**) or 1-naphthyl group (**2j**) reacted smoothly to afford the corresponding azepines in high yields, thus suggesting that steric hindrance is well tolerated (**3h–j**). Moreover, the 2-thienyl group was tolerated and provided the desired product **3k** albeit with moderate yield. Replacement of the aryl group with an alkyl substituent also led to the effective formation of the corresponding apezine (**3l**), although a much lower yield was observed. Notably, the reaction was sensitive to the electronic and steric effect of the R^2 substituent. 2*H*-azirine, having an electron-donating group (Me) on the *para* position of the phenyl ring (**2m**), showed higher reactivity than that bearing an electron-withdrawing group (NO_2, **2n**). When a sterically more demanding 2-methoxyphenyl-substitued 2*H*-azirine (**2o**) was employed, a satisfactory yield can still be achieved.

Next, the reactions of various terminal diynes with 2*H*-azirines were investigated. The sulfonamide-based diynes (**1a**, **1p**) could undergo this cyclization and be transformed into the corresponding cycloadducts in moderate yields. However, malonate-tethered terminal diynes were found to be less effective, thus affording the azepines in 30 and 24% yield,

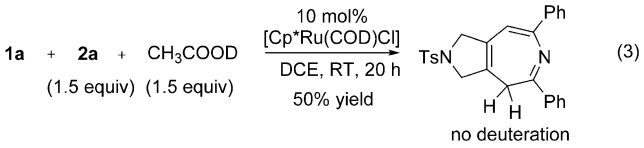
respectively (**3q** and **3r**). Interestingly, ketones, which are unsaturated groups that also undergo cycloadditions with diynes,[18f] did not interfere with the reaction involving the azirines (**3s** and **3t**). In addition, the O-tethered diyne **1u** reacted with 2*H*-azirine **2h** to deliver **3u** in moderate yield. Unfortunately, unlike our previous observation in the ruthenium-catalyzed [2+2+2] cycloaddition,[16b] the methylene-linked diyne was completely unreactive, thus indicating that the Thorpe–Ingold effect[21] was crucial for this transformation (**3v**). Furthermore, when the unsymmetrical diyne **1w**, bearing a methyl group at one alkyne terminus, was subjected to the reaction, the azepine compound **3w** was obtained albeit with low yield. However, the diyne **1x**, with a phenyl group at one alkyne terminus, showed no reactivity under the optimized reaction conditions, probably because of steric hindrance.[22]

To explore the reaction mechanism, the reaction of **1a** with deuterated 2*H*-azirine, [D]-**2a**, was first investigated [Eq. (2)]. As expected, the desired product [D]-**3a** was



(2)

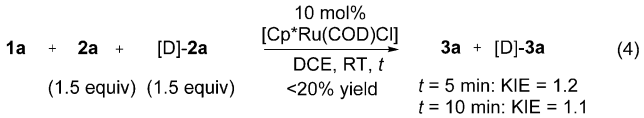
obtained with more than 99% deuterium incorporation. This observation reveals that a 1,5-sigmatropic hydrogen shift occurs in the reaction. Additionally, the reaction of **1a** and **2a** in the presence of CH_3COOD did not provide any deuterated product [Eq. (3)], thus indicating an intramolecular proton-



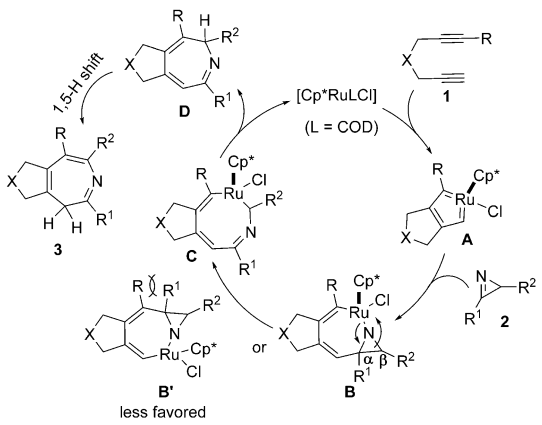
(3)

transfer process and an irreversible C–H functionalization. Under this premise, kinetic isotope effect (KIE) studies were performed. The intermolecular competitive reactions between **2a** and [D]-**2a** with **1a** gave a KIE value of approximately 1.0 at 5 minutes (or 10 min) on the basis of ^{1}H NMR analysis [Eq. (4)]. These data suggest that the C–H bond cleavage is not involved in the rate-determining step.

Consequently, a plausible mechanism was outlined (Scheme 3) on the basis of the present results. The catalytic cycle starts with the oxidative cyclization of the diyne **1** on the ruthenium center to form the ruthenacyclopentatriene inter-



(4)



Scheme 3. Proposed mechanism.

mediate **A**.[18] Then, the insertion of the imine moiety on 2*H*-azirine **2** into the intermediate **A** affords either the intermediate **B** or **B′**. The intermediate **B′** is less favored as a result of the steric repulsion between R^1 and R. Subsequently, β-carbon elimination[23] results in C–C bond cleavage. The bicyclic [5.1.0] skeleton of **B** is expanded with the release of the strain of three-membered aziridine ring to give the eight-membered ruthenacycle intermediate **C**. The reductive elimination of **C** provides the 2*H*-azepine **D** and regenerates the catalyst. Finally, 1,5-H shift of **D** provides the thermodynamically stable product 3*H*-azepine **3**.[24] In the case of unsymmetrical diynes **1w** and **1x**, the steric repulsion between R and R^2 may cause the diminished yields in products.[25]

In summary, we have successfully developed a formal [3+2+2] approach to construct seven-membered heterocycles through the ruthenium-catalyzed cycloaddition of diynes with 2*H*-azirines under mild reaction conditions, in which 2*H*-azirines undergo the cleavage of C–C single bond. This transformation provides a facile and straightforward method for the synthesis of fused azepine derivatives with broad substrate scope and a wide range of functional groups. We expect that these results may provide new insight into the chemistry of 2*H*-azirines and find applications in the synthesis of complex heterocycles.

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Keywords: alkynes · C–C activation · cycloaddition · heterocycles · ruthenium

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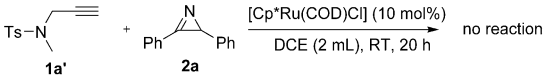

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