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RESEARCH ARTICLE

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Iron-Catalyzed, Iminyl Radical-Triggered Cascade 1,5-Hydrogen Atom Transfer/(5+2) or (5+1) Annulation: Oxime as a Five-Atom Assembling Unit

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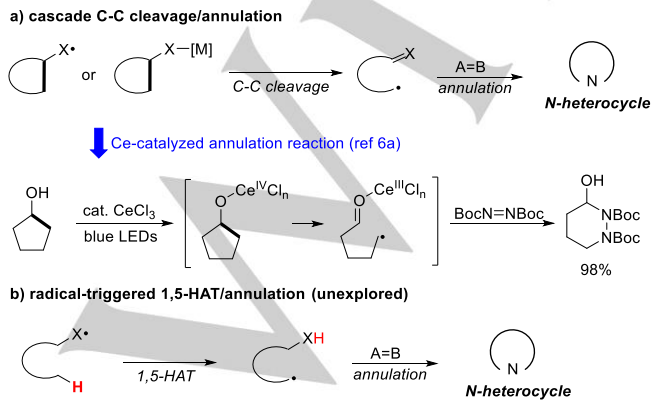
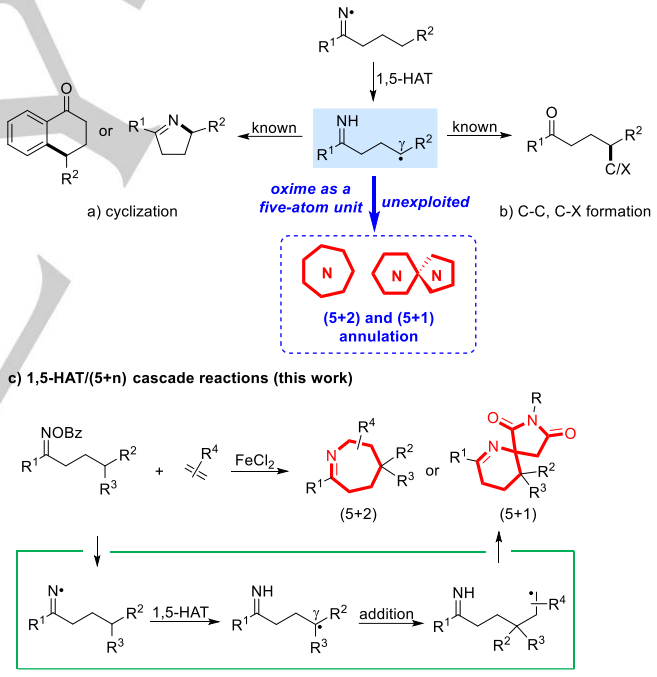
Abstract: By integration of iminyl radical-triggered 1,5-hydrogen atom transfer and (5+2) or (5+1) annulation processes, a series of structurally novel and interesting azepine and spiro-tetrahydropyridine derivatives have been successfully prepared in moderate to good yields. This method utilizes $FeCl_2$ as the catalyst and readily available oximes as five-atom units, and showcases broad substrate scope and good functional group compatibility. The annulation products can be easily converted into many valuable compounds. Moreover, DFT calculation studies are performed to provide some insights into the possible reaction mechanisms for the (5+2) and (5+1) annulations.

Introduction

N-heterocycles are ubiquitous in natural products, pharmaceuticals, agrochemicals, and functional materials.[1] Consequently, a plethora of methods toward these molecules have been developed.[2] Among these methods, radical cyclizations have been emerged as a useful synthetic tool.[3] However, many reactions require the use of potentially toxic and/or explosive compounds as the radical precursors (e.g., organic halides, diazonium salts, and azides), or the use of stoichiometric amounts of radical initiators (e.g., peroxide and Bu_3SnH). Therefore, the development of new and concise synthetic strategy for the synthesis of the N-heterocycles is of high significance. To this end, some interesting protocols involving C-C bond cleavage followed by radical annulation have been recently disclosed (Scheme 1a).[4,5] For example, Zuo realized visible-light-induced, cerium-catalyzed annulations of cycloalkanols with electron-deficient alkenes or di-*tert*-butyl azodicarboxylate.[6] In these reactions, the C-C bonds of unstrained cyclic alcohols can be cleaved by the highly oxidizing Ce^{IV} species. Another fascinating yet unexplored tactic would involve radical-triggered cascade 1,5-hydrogen atom transfer[7,8] (1,5-HAT)/annulation processes. In this scenario, remote C(sp^3)−H bonds can be converted into reactive carbon radicals, which subsequently occur annulation reactions with unsaturated compounds to afford the N-heterocycles (Scheme 1b). Considering the ubiquity of the C(sp^3)−H bonds in organic compounds, the exploration of such a radical-triggered cascade 1,5-HAT/annulation strategy may enable an array of readily available compounds to participate in the synthesis of the N-heterocycles.



Scheme 1. N-heterocycle synthesis through cascade C-C cleavage/annulation and cascade 1,5-HAT/annulation. A=B indicates unsaturated compounds.



Scheme 2. Reactions involving iminyl radical-triggered 1,5-HAT.

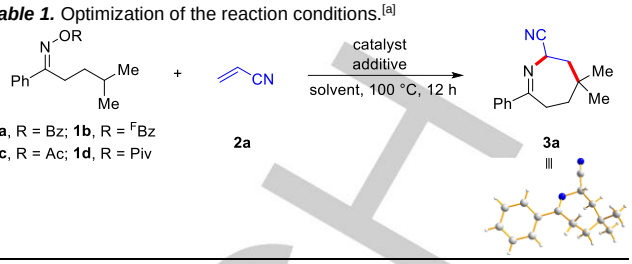
Nitrogen-centered radicals have great capability in the construction of carbon-nitrogen bonds and the N-heterocycles,[9] as exemplified by the well-known Hofmann-Löffler-Freytag reaction[10] that has been applied in the synthesis of various cyclic amines. As one of the most significant classes of nitrogen-centered radicals, iminyl radicals have gained increased attention from synthetic organic chemists in the past few decades. Many synthetic strategies and reactions based on the iminyl radical have been successfully explored, such as cyclization, cycloaddition, and 1,5-HAT.[11] In the field of the iminyl radical-triggered 1,5-HAT, Forrester reported a few seminal works, in which the iminyl radicals were generated by oxidation of phenylalkylideneamino-oxyacetic acids.[12] The resulting iminyl radical species can be transformed into tetralones through tandem 1,5-HAT and intramolecular C−C

bond formation (Scheme 2a). However, elevated temperature and the use of stoichiometric amounts of strong oxidant resulted in poor functional group compatibility and narrow substrate scope. With the advent of new methods toward the formation of the iminyl radicals via cleavage of the oxime N−O bond, including visible-light photoredox catalysis and transition metal catalysis, the iminyl radical-triggered 1,5-HAT has recently achieved remarkable progress. For instance, carbon radicals generated by 1,5-HAT could be trapped by intramolecular imine group to deliver pyrrolines or dihydroimidazoles (Scheme 2a).[13] Besides intramolecular reactions, the carbon radicals could also be intermolecularly captured by some substrates to form C−C, C−N, and C−halide bonds (Scheme 2b).[14] In these reactions, the in situ formed imine group is generally converted into ketone group upon hydrolysis. As such, the intermolecular scenario based on the iminyl radical-triggered 1,5-HAT remains largely restricted to the synthesis of substituted ketones. In considering the synthetic potential of the iminyl radicals and related 1,5-HAT strategies, as well as the importance of the N-heterocycles, it is highly desirable to apply the iminyl radical-triggered 1,5-HAT to the intermolecular annulation reactions to construct the N-heterocyclic compounds.

The construction of seven-membered N-heterocyclic rings is important and desirable due to their interesting biological and pharmaceutical properties.[15] Among the reported approaches toward these compounds, (5+2) annulation reactions are particularly fascinating, because alkenes and alkynes, structurally diverse and readily available compounds, could serve as two-atom units in the transformations. Nonetheless, most of the known (5+2) annulation reactions toward the seven-membered N-heterocycles require the utilization of structurally specific substrates, such as vinylaziridines, pyridinium zwitterions, and oxiranes, which would result in limited molecular diversity.[16] Motivated by the aforementioned work related to the iminyl radical-triggered 1,5-HAT[13,14] and our ongoing research on N−O bond transformations toward the N-heterocycles,[17] we envisaged to develop a new approach involving the iminyl radical-triggered cascade 1,5-HAT/(5+2) annulation for the synthesis of the seven-membered N-heterocyclic rings, in which the oxime serves as a five-atom unit. To our best knowledge, such a protocol remains unexplored. As depicted in Scheme 2c, an iminyl radical induces the formation of a γ-carbon radical via 1,5-HAT. Subsequently, the γ-carbon radical undergoes an addition step to an alkene to deliver a new carbon radical that might be trapped by the intramolecular imine group to form a seven-membered cyclic imine. In addition, a (5+1) annulation process might also occur if the alkene can act as a one-atom unit. These processes appear deceptively simple, but are challenging because some critical problems need to be addressed: 1) inhibition of the γ-carbon radical to take part in intramolecular C−N and C−C bond-forming reactions,[13,18] and 2) suppression of the hydrogen elimination from carbon radicals to yield alkenes.[8a] Herein, we present an iron-catalyzed 1,5-HAT/(5+2) or (5+1) annulation cascade protocol with oximes and alkenes as readily accessible starting materials. This transformation produces various structurally interesting azepine and spiro-succinimide-tetrahydropyridine derivatives, which are the core structures of many natural products and biologically active molecules,[19] and exhibits broad substrate scope and good functional group compatibility.

Results and Discussion

Table 1. Optimization of the reaction conditions.[a]



1a, R = Bz; **1b**, R = ^{F}Bz
1c, R = Ac; **1d**, R = Piv

2a

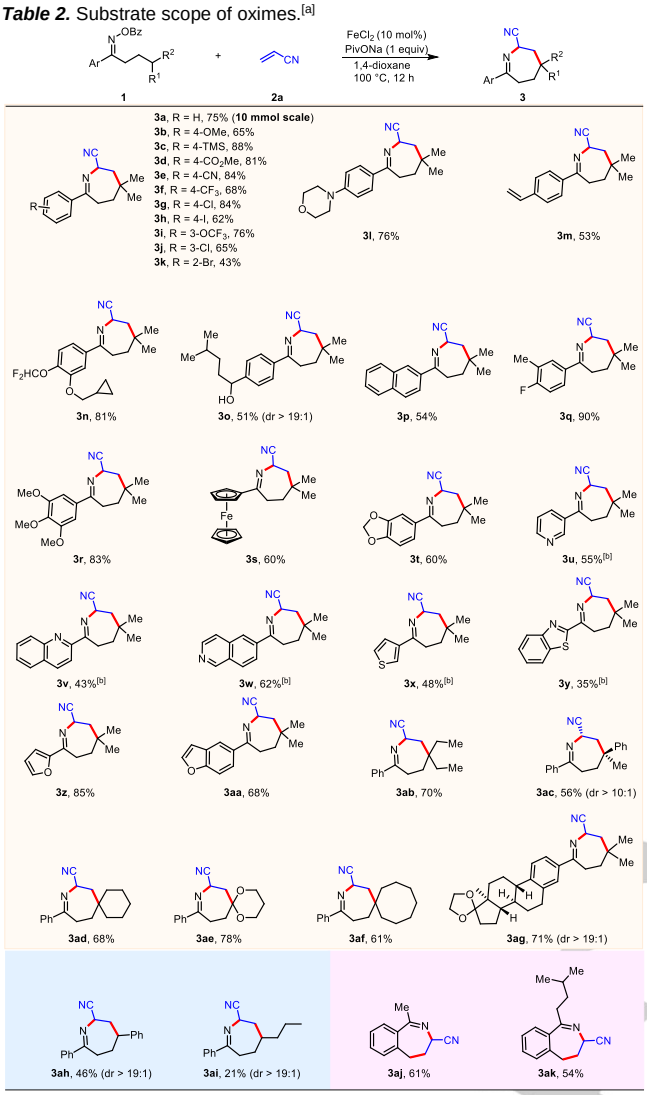
3a

Entry	R	Catalyst	Additive	Solvent	Yield [%][b]
1	Bz	CuBr	none	THF	0
2	Bz	$NiCl_2$	none	THF	0
3	Bz	$CoCl_2$	none	THF	0
4	Bz	$FeCl_3$	none	THF	20
5	Bz	$Fe(acac)_3$	none	THF	26
6	Bz	$Fe(OAc)_2$	none	THF	21
7	Bz	$FeCl_2$	none	THF	28
8	Bz	$FeCl_2$	none	1,4-dioxane	33
9	Bz	$FeCl_2$	none	MeCN	trace
10	Bz	$FeCl_2$	none	toluene	14
11	Bz	$FeCl_2$	none	DMSO	6
12	Bz	$FeCl_2$	$PhCO_2Na$	1,4-dioxane	52
13	Bz	$FeCl_2$	AcONa	1,4-dioxane	63
14	Bz	$FeCl_2$	PivONa	1,4-dioxane	82
15	^{F}Bz	$FeCl_2$	PivONa	1,4-dioxane	58
16	Ac	$FeCl_2$	PivONa	1,4-dioxane	51
17	Piv	$FeCl_2$	PivONa	1,4-dioxane	53
18	Bz	none	PivONa	1,4-dioxane	0

[a] Reaction conditions: oxime **1** (0.1 mmol), acrylonitrile **2a** (0.2 mmol), catalyst (10 mol%), additive (0 or 1 equiv), solvent (1 mL), 100 °C, 12 h, in a sealed tube, under Ar. Abbreviation: ^{F}Bz = pentafluorobenzoyl. [b] Isolated yields.

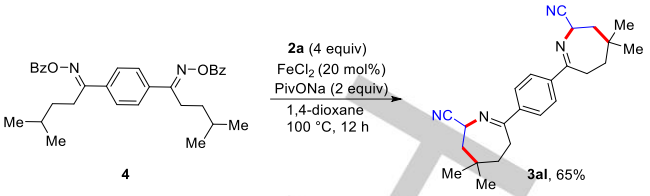
We commenced our investigation by choosing oximes (**1a**) and acrylonitrile (**2a**) as model substrates to develop an effective catalytic system to realize the (5+2) annulation reaction. Considerable experimentation has been conducted, and some important results are shown in Table 1.[20] Among different kinds of transition metals,[21] including copper, nickel, cobalt, and iron salts, $FeCl_2$ exhibited the best catalytic reactivity toward **3a** formation (entries 1−7). The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction.[22] The reaction afforded **3a** in 33% yield with 1,4-dioxane as the solvent (entry 8), while showed significantly lower yields in MeCN, toluene, and DMSO (entries 9−11). A further improvement was achieved by using 1 equiv of sodium pivalate as an additive (82%, entry 14). Considering the influence of the oxime group on the transformation, several *O*-substituted oximes were studied (entries 15−17); however, all the reactions produced the target product in moderate yields. A control experiment demonstrated that catalytic amount of $FeCl_2$ was indispensable, because **3a** cannot be observed in its absence (entry 18). Thus, the optimal reaction conditions were concluded to be the following: $FeCl_2$ (10 mol%) as the catalyst, PivONa (1 equiv) as the additive, and 1,4-dioxane as the solvent at 100 °C for 12 h.

Table 2. Substrate scope of oximes.[a]



[a] Reaction conditions: oxime **1** (0.2 mmol), acrylonitrile **2a** (0.4 mmol), $FeCl_2$ (10 mol%), PivONa (0.2 mmol), 1,4-dioxane (2 mL), 100 °C, 12 h, in a sealed tube, under Ar. [b] $FeCl_2$ (20 mol%) was used.

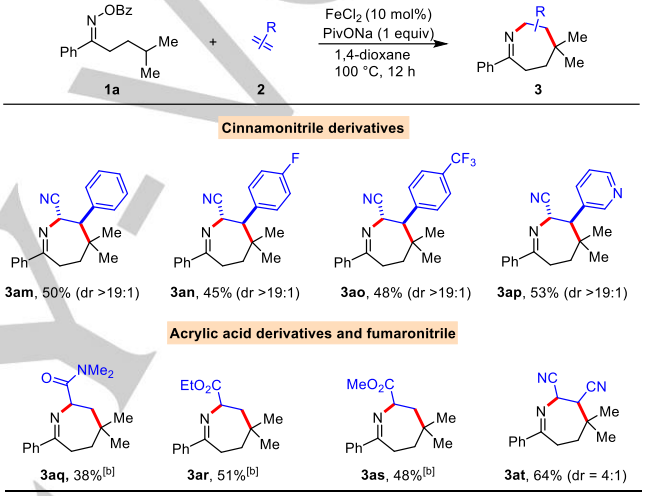
After identifying the optimal reaction conditions, we surveyed the substrate scope with respect to oximes (Table 2). Substrate **1** reacted well with acrylonitrile, giving rise to the corresponding products in 43−90% yields (**3b**−**3r**), with tolerance of a series of functional groups, including methoxy (**3b** and **3r**), trimethylsilyl (**3c**), ester (**3d**), cyano (**3e**), trifluoromethyl (**3f**), trifluoromethoxy (**3i**), difluoromethoxyl (**3n**), chloro (**3g** and **3j**), iodo (**3h**), bromo (**3k**), fluoro (**3q**), morpholino (**3l**), olefinic (**3m**), cyclopropyl (**3n**), hydroxyl (**3o**), and naphthyl groups (**3p**). An oxime with a ferrocene functionality displayed moderated reactivity in the transformation, which produced **3s** in 60% yield. Our approach was also amenable to several heterocycle-derived oximes, which include the ones derived from benzodioxole (**3t**), pyridine (**3u**), quinoline (**3v**), isoquinoline (**3w**), thiophene (**3x**), benzothiazole (**3y**), furan (**3z**), and benzofuran (**3aa**). In terms of the substituents (R^1 and R^2) at the γ position of the oxime moiety, they can be ethyl/ethyl (**3ab**), phenyl/methyl (**3ac**). The substituents can also be cyclic moieties. As such, the annulation method can furnish structurally interesting spiro-azepine derivatives in moderate yields (**3ad**−**3af**). Furthermore, the newly developed approach was suitable for the estrone-derived oxime, and the corresponding product **3ag** was obtained in 75% yield. The iminyl radical-triggered 1,5-HAT was also suitable for the generation of secondary (**3ah** and **3ai**) and primary carbon radicals (**3aj** and **3ak**), which can take part in the annulation reactions to deliver the target products. Note that, when an



Scheme 3. A two-fold annulation reaction.

oxime bears two potentially reactive sites for 1,5-HAT, the reaction preferred to occur at the methyl group (**3ak**), probably due to the relatively high stability of the benzylic carbon radical. Our method can be scaled up to 10 mmol scale with a slightly lower yield (75% yield). Interestingly, a two-fold annulation reaction between bis-oxime **4** and **2a** readily provided the target product **3al** in 65% yield (Scheme 3).

Table 3. Substrate scope of alkenes.[a]

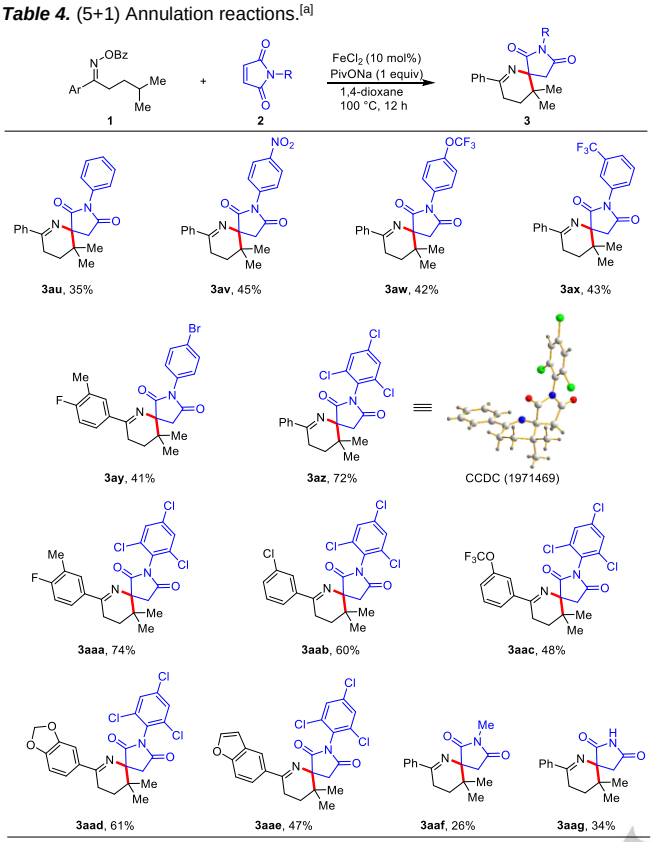


[a] Reaction conditions: oxime **1a** (0.2 mmol), alkene **2** (0.24 mmol), $FeCl_2$ (10 mol%), PivONa (0.2 mmol), 1,4-dioxane (2 mL), 100 °C, 12 h, in a sealed tube, under Ar. [b] Alkene (0.4 mmol) was used.

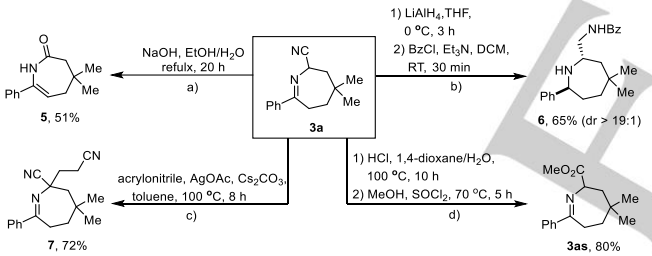
Subsequently, we turned our attention to evaluate the substrate scope of alkenes (Table 3). Cinnamonitriles participated in the annulation reactions to generate the desired products in moderate yields (**3am**−**3ap**). In addition, acrylamides, acrylates, and fumaronitrile can react with **1a** to give rise to the final products in synthetically useful yields (**3aq**−**3at**). Unfortunately, other alkenes, such as styrene and methyl cinnamate were unreactive in the transformation.

Interestingly, when maleimides were utilized as the substrates, the (5+1) annulation products, spiro-succinimide-tetrahydropyridine derivatives, were observed (Table 4). A series of N-aryl maleimides with different functionalities on the aryl ring, including nitro (**3av**), trifluoromethoxy (**3aw**), trifluoromethyl (**3ax**), fluoro (**3ay**), bromo (**3ay**), and chloro groups (**3az**),[23] were amenable to the reaction, affording the corresponding products in moderate yields. In addition, the reactions betwen N-(2,4,6-trichlorophenyl)maleimide and various oximes can also generate the desired products (**3aaa**−**3aae**). Besides N-aryl maleimides, N-Me maleimide (**3aaf**) and NH-maleimide (**3aag**) can take part in the reactions to deliver the target products in synthetically useful yields.

Table 4. (5+1) Annulation reactions.[a]

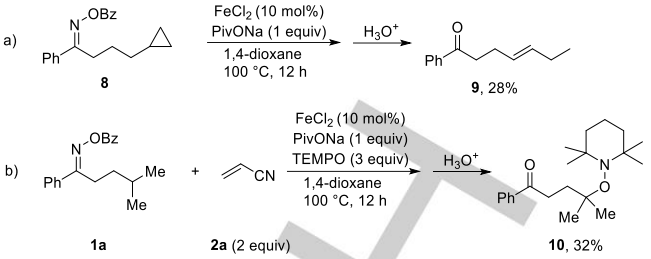


[a] Reaction conditions: oxime **1a** (0.2 mmol), alkene **2** (0.24 mmol), $FeCl_2$ (10 mol%), PivONa (0.2 mmol), 1,4-dioxane (2 mL), 100 °C, 12 h, in a sealed tube, under Ar.



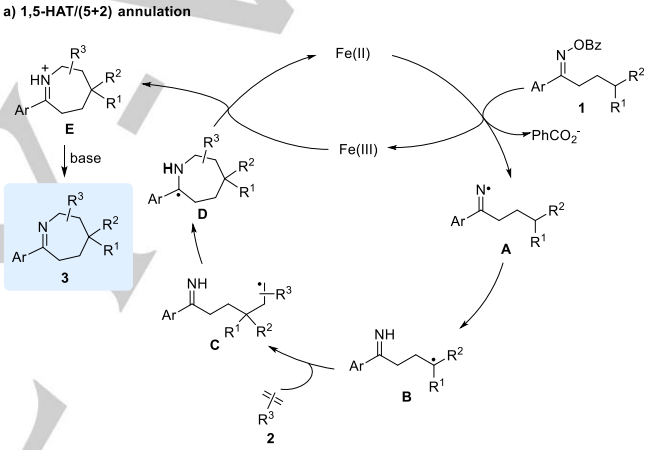
Scheme 4. Synthetic transformations. Reaction conditions: a) **3a** (0.1 mmol), NaOH (0.3 mmol), EtOH (1 mL), H_2O (1 mL), reflux, 10 h. b) 1) **3a** (0.1 mmol), $LiAlH_4$ (0.4 mmol), THF (2 mL), 0 °C, 5 h; 2) BzCl (0.15 mmol), Et_3N (0.2 mmol), DCM (5 mL), RT, 2 h. c) **3a** (0.1 mmol), acrylonitrile (0.2 mmol), AgOAc (0.01 mmol), Cs_2CO_3 (0.02 mmol), toluene (1 mL), reflux, 8 h. d) 1) **3a** (0.1 mmol), conc. HCl (1 mL), 1,4-dioxane (2 mL), H_2O (1 mL), 100 °C, 10 h; 2) $SOCl_2$ (0.5 mmol), MeOH (5 mL), 70 °C, 5 h.

Besides the structural importance of the azepine derivatives, their synthetic utility would also be attractive. As illustrated in Scheme 4, **3a** was converted into a cyclic enamide **5** in 51% yield under basic conditions (Scheme 4a). Through sequential reduction by lithium aluminum hydride and acylation by benzoyl chloride, **3a** can be transformed into an azepane **6** in 65% yield (Scheme 4b). In addition, a Michael addition reaction between **3a** and acrylonitrile furnished the corresponding product **7** in 72% yield (Scheme 4c). The CN group of **3a** can also be efficiently converted into an ester group upon hydrolysis and esterification (Scheme 4d).



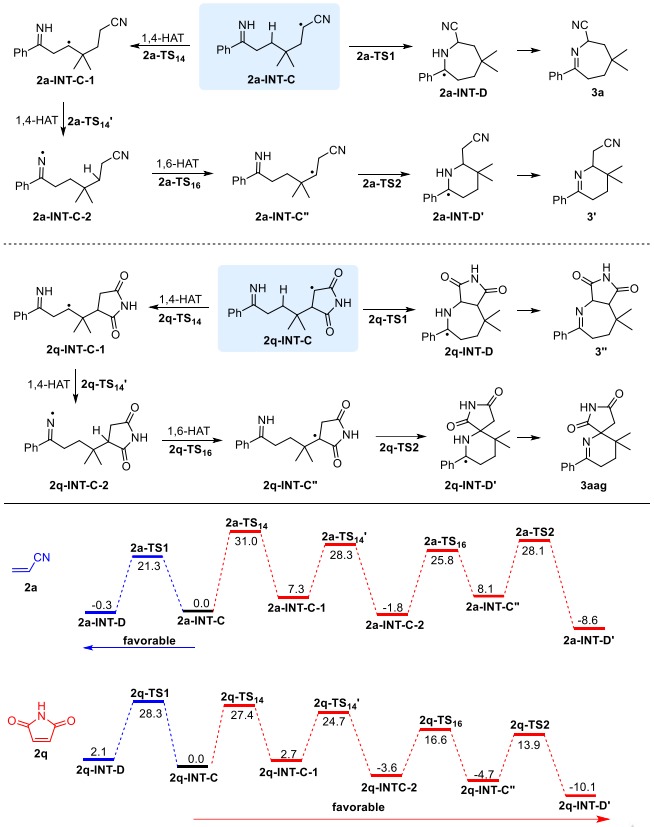
Scheme 5. Mechanistic investigations.

To gain insights into the reaction mechanism, some experiments were conducted (Scheme 5). A radical clock reaction was performed with oxime **8** as the substrate (Scheme 5a). Under the standard reaction conditions, the reaction produced a ring-opening product **9** in 28% yield. In addition, the addition of 3 equiv of radical scavenger TEMPO into the model reaction totally inhibited the formation of seven-membered product **3a**, and significant amounts of radical-trapping product **10** was observed (Scheme 5b). These results supported the involvement of a γ-carbon radical in the (5+2) annulation reaction.



Scheme 6. Proposed mechanism for cascade 1,5-HAT/(5+2) annulation.

Based on the aforementioned results and the previous work on iminyl radical transformations, a plausible reaction mechanism is illustrated for the cascade 1,5-HAT/(5+2) annulation reactions (Scheme 6). Single electron transfer from Fe(II) to the oxime results in N−O bond cleavage to generate Fe(III) and an iminyl radical **A**.[14e,21g-i] The latter undergoes 1,5-HAT to form an alkyl carbon radical **B**. Through the addition of the γ-carbon radical to the alkene, a new carbon radical **C** can be produced. The carbon radical would add to the intramolecular imine group to give rise to an intermediate **D**,[24] which could be oxidized by the Fe(III) to form an iminium ion **E** with concurrent regeneration of the Fe(II) catalyst. After deprotonation, the azeping derivative **3** would be generated. Fe(III) salts can also induce the reaction (entries 4 and 5, Table 1), and a possible reason might be that the Fe(III) salts were firstly reduced to Fe(II) species under the reaction conditions (e.g., 1,4-dioxane).[18]



Scheme 7. Energy profile of annulation reactions with relative Gibbs free energies [kcal/mol].

Next, we sought to use density functional theory (DFT) calculations at B2PLYP/def2-TZVPPD/SMD//M06-2X/def2-TZVP level to understand the chemoselectivity for the formation of seven-membered and six-membered rings (Scheme 7).[25] After 1,5-HAT and the addition to the alkene, a key intermediate **INT-C** was formed. The seven-membered ring could be generated by intramolecular cyclization of the **2a-INT-C** for acrylonitrile **2a**. After proposing and calculating four different pathways, the computational results suggested that the **2q-INT-C** would produce the six-membered ring via sequentially 1,4-HAT, 1,4-HAT, 1,6-HAT and intramolecular cyclization for NH-maleimide **2q** (see Scheme S4 in the Supporting Information for the details).[26] The energy barriers of the annulation reactions of **2a** and **2q** were calculated. The highest energy barrier (**2a-TS$_{14}$**) among the process to produce six-membered ring was 9.7 kcal/mol higher than that of **2a-TS1**, suggesting the formation of seven-membered ring from **2a** was more favorable. On the other side, for the substrate **2q**, the energy of **2q-INT-D** was slightly higher (2.1 kcal/mol) than **2q-INT-C**, while the energies of **2q-INT-C'' ** and **2q-INT-D'** were 4.7 and 10.1 kcal/mol lower than **2q-INT-C**, respectively. Moreover, the energy barrier of **2q-TS1** was 0.9 kcal/mol higher than the highest energy barrier (**2q-TS$_{14}$**) among the process to produce six-membered ring. These results implied that the reaction of **2q** was favorable to form the six-membered ring.

Conclusion

We have successfully exploited oximes as five-atom units for the iminyl radical-triggered cascade 1,5-HAT/(5+2) or (5+1) annulation reactions with various electron-deficient alkenes, which allow for the rapid assembly of over 50 examples of structurally new and interesting azepine and spiro-tetrahydropyridine derivatives as potentially attractive privileged scaffolds in drug discovery. The method exhibits broad substrate scope and good functional group compatibility. The survey of more iminyl radical-triggerred cascade 1,5-HAT/(5+n) annulation reactions with the oximes as the five-atom units to access N-heterocycles is ongoing in our group.

Acknowledgements

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Keywords: oximes • *N*-heterocycles • cascade reaction • iron catalysis • synthetic methods

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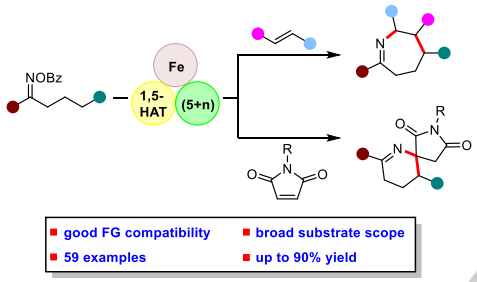

With readily available oximes as five-atom units, a variety of azepine and spiro-tetrahydropyridine derivatives have been synthesized through the iminyl-radical triggered 1,5-hydrogen atom transfer/(5+2) or (5+1) annulation cascade protocol. This method exhibits broad substrate scope and good functional group compatibility.