A Non-Diazo Approach to Functionalized (2-Furyl)-2-pyrrolidines through a Cascade Reaction of Enynal-Derived Zinc Carbenoids with β-Arylaminoketones

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ARTICLE

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This study introduces a cascade approach for synthesizing functionalized (2-furyl)-2-pyrrolidines, showcasing both convergence and remarkable stereoselectivity. This domino process proceeds through an N–H insertion into enynal-derived metal-carbenoid, followed by an intramolecular aldol reaction to provide pyrrolidines with high diastereoselectivity (>98:2). This chemistry utilizes Earth-abundant zinc chloride as a catalyst with loading as low as 1 mol%. This method operates under mild conditions and demonstrates high chemoselectivity by accommodating substrates bearing functionalities such as free alcohols, alkenes, and alkynes.

Introduction

Within *N*-heterocyclic compounds, the pyrrolidine ring stands out as one of the most significant and privileged structures in synthetic and medicinal chemistry. It is the central motif of several natural products and widely utilized organocatalyst proline.[1] Chiral pyrrolidines are also crucial in ligand design for transition metal-mediated processes.[2] Substituted pyrrolidine derivatives show diverse bioactivities, including antibiotic, antibacterial, antifungal, and cytotoxic effects, with potential for therapeutics development (Figure 1).[3]

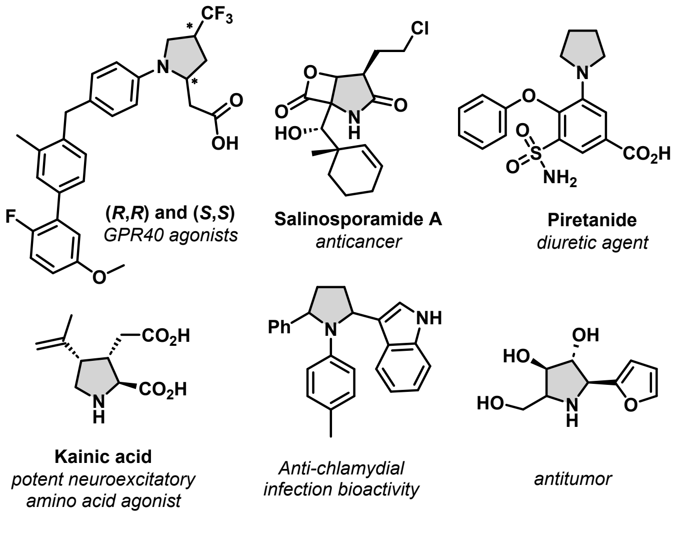

Figure 1. Pyrrolidine natural products.

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Furthermore, several marketed pharmaceuticals contain the pyrrolidine scaffold, emphasizing its importance in drug discovery.[3d] Therefore, synthesizing of functionalized pyrrolidines has been an interest to synthetic chemists. A diverse array of strategies has been developed for the synthesis of pyrrolidines and proline derivatives,[4] including azomethine ylide cycloaddition,[5] alkene hydroamination,[6] iodocyclization,[7] and cycloisomerization.[8]

There have also been cascade approaches involving carbene and metallocarbene intermediates, leading to various functionalized pyrrolidines.[9] Cascade reactions offer several advantages over traditional reactions, such as high efficiency, selectivity, atom economy, and time, including cost-effectiveness with reagents, catalysts, solvents, and waste management. [10] The amalgamation of these benefits renders cascade reactions highly suitable for consideration in green chemistry synthesis.

In this vein, the Moody,[11] Hu,[12] Sun,[13] and Sharma[14] groups developed cascade reactions, utilizing diazo-derived rhodium carbenoids (Figure 2a). Specifically, Moody and Hu groups used Diazo-derived rhodium carbenoids for diverted N–H insertion/aldol cascade to access highly substituted pyrrolidines. The Sharma group applied a similar cascade process involving N-H insertion/aldol/oxy-Cope to access medium-sized azacycles,[14a] which could be easily transformed into functionalized quinolines.[14b]

Despite the broad utilization of diazo-derived metal carbenes, there have been concerns about the safety of diazo compounds due to their potentially explosive nature.[15] Inspired by our work on metal carbene-initiated cascade reactions, we focused on safer carbene precursors. As most cascade reactions involve donor/acceptor (D/A) diazo compounds,[16] we envisioned using enynals, which on activation can generate metal carbenoid analogous to D/A diazos on activation.[17] Notably, enynals and enynones are benchtop stable and do not produce nitrogen gas during the reaction, making them safer

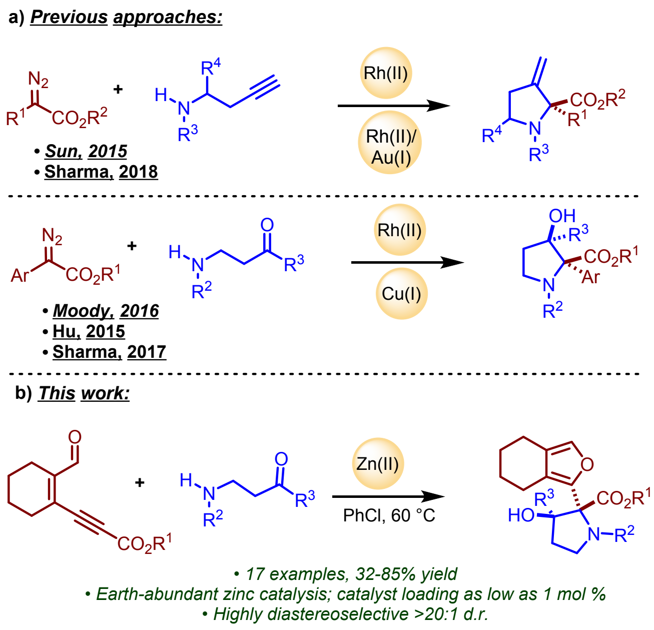


Figure 2. Synthetic approaches towards pyrrolidines.

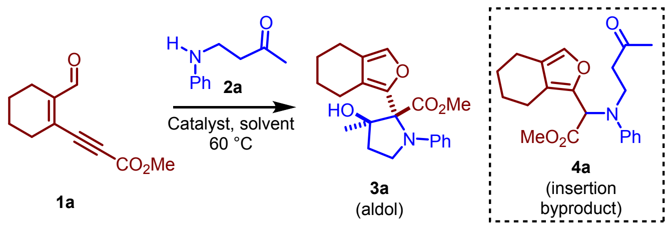
substitutes for diazo compounds. Of significant importance, these carbene precursors can be activated under mild conditions using readily available Earth-abundant metals such as zinc and copper.[18]

The enyn-al/-one-derived metal carbenes have been utilized in various transformations, including N–H, O–H, S–H, and Si–H insertion reactions,[19] and successful cyclopropanations.[20] Despite the similar reactivity to diazo compounds,[21] the utilization of these precursors in cascade reactions has been limited. Recently, the Hu group reported a rhodium-catalyzed domino sequence involving O-H insertion to enynal-derived rhodium carbenes followed by trapping with an imine.[22] This study presents a cascade reaction of enynal-based zinc carbenoids featuring a novel N–H insertion/aldol cascade process to synthesize highly substituted (2-furyl)-2-pyrrolidines (Figure 2b).

Results and Discussion

Our endeavor to develop a novel N–H insertion/aldol reaction commenced with synthesizing benchtop stable enynal donor **1a** on a large scale (5g) using the reported protocol.[23] Our objective was to optimize the reaction conditions by identifying the most suitable components in each category, including the catalyst and solvent. As a starting point, we chose aminoketone **2a** as the model substrate (Table 1). To test our hypothesis, we began our optimization with rhodium (II) salts as described in the literature.[11, 22] To our satisfaction, the desired product **3a** was obtained, albeit with a yield of 43%, at room temperature using methylene chloride (CH_2Cl_2) as the solvent (entry 1). Increasing the temperature to 60 °C led to increased product formation (59%, entry 2). Other rhodium (II) catalysts, however, did not improve the yield of the reaction (entries 3–6). Subsequently, we shifted our focus to Earth-abundant catalysts. We were delighted that zinc (II) chloride ($ZnCl_2$) known to activate enynals, provided the desired aldol product at room temperature (entry 7). The yield of the aldol product further improved when the temperature was raised to 60 °C (entry 8). In contrast, other catalysts, such as copper or iron, produced the desired aldol product but with lower yields (entries 9, 10). Following that, our focus shifted towards optimizing the solvent for the reaction with $ZnCl_2$ as the catalyst. Pleasantly, changing the solvent to chlorobenzene[22] resulted in a further increase in the yield of the aldol product, reaching 75% (entry 11). A similar outcome was observed when trifluorotoluene was used as the solvent (entry 12). However, using 1,2-dichloroethane (DCE) and toluene yielded the desired product with slightly lower yields (entries 12, 13). Next, we explored other zinc (II) -salts. Zinc (II) bromide and zinc (II) trifluoromethanesulfonate also showed potential in providing the aldol product, albeit with slightly lower yields (entries 14, 15). Notably, zinc (II) iodide exhibited results similar to $ZnCl_2$ (entry 16). However, $ZnCl_2$ proves to be more cost-effective when compared to ZnI_2, prompting us to select it as the preferred catalyst.

Table 1. Optimization table for the N-H insertion.



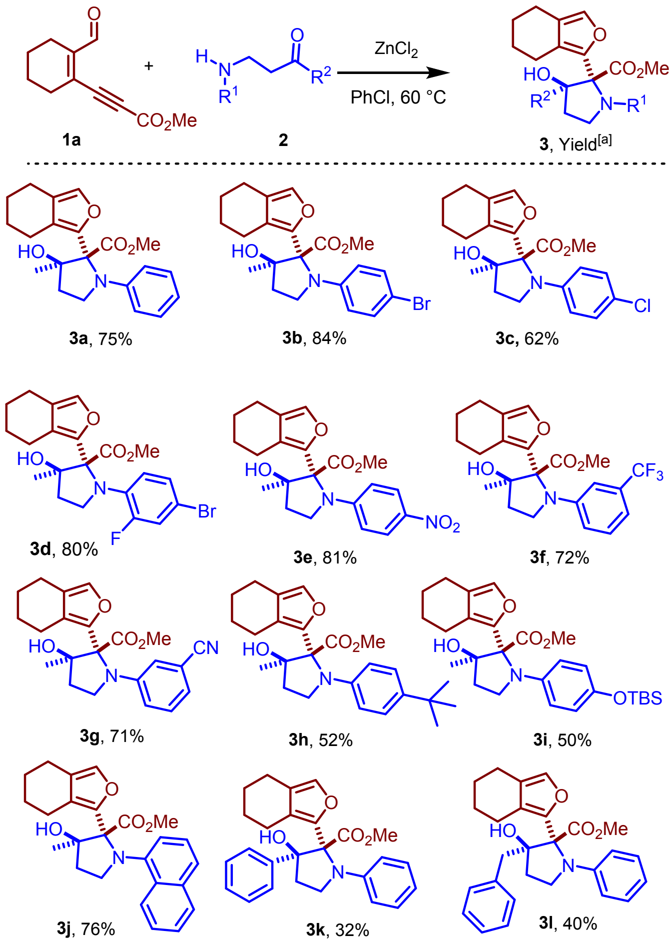
Entry[a]	Catalyst (mol%)	Solvent	Time	Yield (3a)[b]	Yield (4a)[b]
1[c]	$Rh_2(OAc)_4$ (10)	CH_2Cl_2	16 h	43	23
2	$Rh_2(OAc)_4$ (10)	CH_2Cl_2	8 h	59	18
3	$Rh_2(esp)_2$ (10)	CH_2Cl_2	8 h	45	13
4	$Rh_2(TFA)_4$ (10)	CH_2Cl_2	8 h	54	9
5	$Rh_2(TPA)_4$ (10)	CH_2Cl_2	8 h	0	0
6	$Rh_2(HFB)_4$ (10)	CH_2Cl_2	8 h	19	16
7[c]	$ZnCl_2$ (20)	CH_2Cl_2	16 h	40	33
8	$ZnCl_2$ (20)	CH_2Cl_2	8 h	65	11
9	$[CuOTf]_2$•tol (20)	CH_2Cl_2	8 h	49	7
10	$Fe(BF_4)_2$ (20)	CH_2Cl_2	8 h	31	6
11	$ZnCl_2$ (20)	DCE	6 h	69	10
12	**$ZnCl_2$ (20)**	**PhCl**	**6 h**	**75**	**11**
13	$ZnCl_2$ (20)	Toluene	6 h	70	16
14	$ZnCl_2$ (20)	$PhCF_3$	6 h	75	17
15	$ZnBr_2$ (20)	PhCl	6 h	72	0
16	ZnI_2 (20)	PhCl	6 h	75	0
17	$Zn(OTf)_2$ (20)	PhCl	6 h	71	0
18	-	PhCl	3 d	26	0

[a] Reaction conditions: **1a** (85 µmol), **2a** (50 µmol), catalyst, solvent (1.5 mL), temperature (60 °C). [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxy benzene as an internal standard. [c] Room temperature.

It is noteworthy to mention that, for the practical purpose of weighing, we used 20 mol% of $ZnCl_2$. In the absence of the

$ZnCl_2$, heating the reaction with chlorobenzene for 3 days resulted in a 26% yield of the desired aldol product (entry 18). We selected $ZnCl_2$ as the catalyst of choice and chlorobenzene as the appropriate solvent for further explorations.

Having established the optimized reaction conditions, we explored the substrate scope of the cascade reaction involving enynal **1a** and various phenyl-substituted aminoketones **2** (Scheme 1). We successfully obtained a series of corresponding products **3** in moderate to high yields. Notably, halogen substitution at the *para*-position of the phenyl group led to high yields of the aldol products (**3b**, **3c**). Moreover, halogen substitution at the *ortho* and *para* positions exhibited similar reactivity, resulting in the corresponding aldol products with high yields (**3d**). We observed that electron-withdrawing substitutions on the phenyl ring facilitated a clean reaction, leading to the desired aldol products. Specifically, *para*-substitution with *-nitro* showed high efficiency, affording the aldol product with an excellent yield (**3e**).

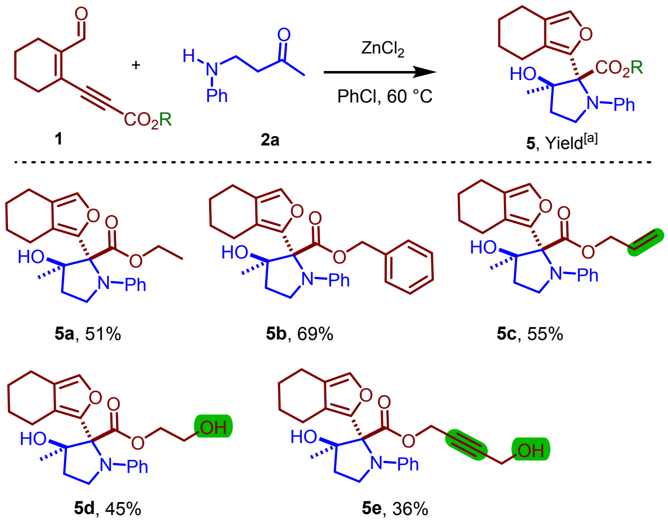


Scheme 1. The scope of N-H insertion/aldol cascade reaction of aminoketones **2**. [a] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxy benzene as an internal standard.

Both *meta*-substituted *-trifluoromethyl* and *-cyano* aminoketones were also amenable to this transformation, yielding the corresponding aldol products with slightly decreased yields (**3f**, **3g**). Furthermore, aminoketones bearing electron-donating groups were also compatible with high reactivity, albeit affording marginally lower yields (**3h**, **3i**). Likewise, substituting the *N*-phenyl with a naphthyl group did not significantly influence the reaction, resulting in the corresponding aldol product with a comparable yield (**3j**).

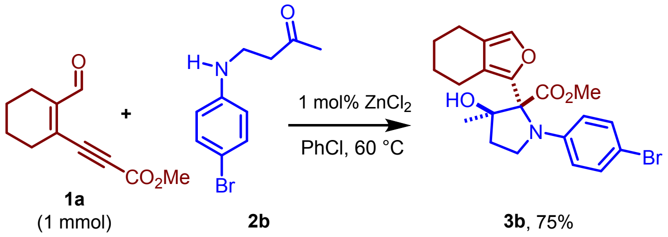
Next, we examined the influence of electronic and steric factors on ketone functionality in β-aminoketones by replacing the methyl with phenyl and benzyl groups. In both cases, we obtained a reduced yield of the corresponding aldol products (**3k**, **3l**) along with insertion and some unidentified byproducts.

After successfully exploring the substrate scope of aminoketones, our attention turned to the N–H insertion/aldol reaction involving various ester-substituted enynal (Scheme 2). We observed that replacing the methyl ester with bulkier groups decreased product yield (**5a**, **5b**). However, we were delighted to discover that esters bearing alkene and alkyne functionalities were well-tolerated, providing the products with good yields (**5c**, **5d**). Notably, even in the presence of free alcohols, the N–H insertion proceeded smoothly, forming the corresponding aldol products in good yields (**5d**, **5e**). The high chemoselectivity of the insertion/aldol reaction with alkene, alkyne, and free alcohol underscores the robustness of the cascade approach under the developed protocol.



Scheme 2. The scope of N-H insertion/aldol cascade reaction of enynal **1**. [a] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxy benzene as an internal standard.

To demonstrate the applicability of this approach, we performed the reaction on a 1 mmol scale. In assessing the catalytic efficiency of $ZnCl_2$ in facilitating the N–H insertion/aldol cascade reaction, we reduced the catalyst loading to 1 mol%. To our delight, the reaction proceeded smoothly with only a slight decrease in yield (75%, Scheme 3).



Scheme 3. Application to large-scale synthesis.

The structure of the aldol product was unequivocally determined through single crystal X-ray analysis of compound **3b** (CCDC 2285842)[24] (Figure 3). Notably, the study revealed that in the aldol product, the newly formed alcohol and the ester group consistently remained on the same side of the pyrrolidine ring, thus providing only *cis*-diastereomer. The formation of the *cis*-isomer is in accordance with the findings of the Moody and Hu group under Rh (II)-catalyzed conditions.[11-12] This intriguing observation strongly implies a well-organized transition state during the formation of the aldol product, which provides essential insights into the reaction mechanism and the stereochemical outcome.

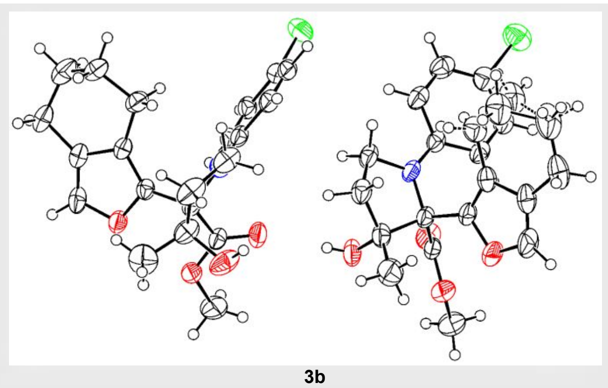
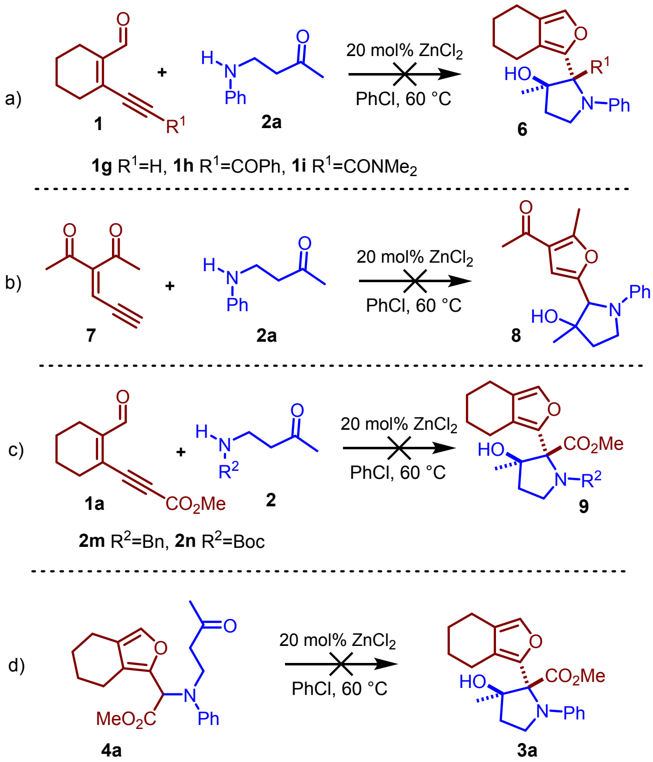


Figure 3. Single crystal X-ray structure of pyrrolidine **3b**.

The ester functionalities in the donor proved crucial for advancing the aldol pathway. Without the ester moiety, no aldol product was obtained. The enynal donors **1g** decomposed under the reaction conditions, rendering the aminoketone **2a** unreactive (Scheme 4a). This outcome aligns with the characteristics of the D/A diazo compound utilized for the cascade reactions, as opposed to the donor/donor (D/D), or acceptor/acceptor (A/A) diazo counterparts. Furthermore, we investigated the influence of the ketone (**1h**) and amide (**1i**) groups by replacing the ester in the enynal **1a** (Scheme 4b). Surprisingly, no desired aldol product was produced. The enynal with phenyl-ketone **1h** led to a Michael addition reaction with **2a**, whereas the enynal with methyl amide **1i** only resulted in insertion product. We also investigated dicarbonyl en-yn-ones (**7**) as carbene precursor, but did not observe any insertion or aldol product in this reaction (Scheme 4b). Additionally, substituting the aromatic amine **2** with benzyl- or Boc-protected amines did not undergo any reaction with the enynal **1a** under the optimized conditions (Scheme 4c). We also employed insertion product **4a** under the optimized conditions to gain further insight into the reaction mechanism. However, the reaction did not proceed to yield the aldol product (Scheme 4c). This experiment suggests the involvement of a metal-bound zwitterionic intermediate, which is crucial for the subsequent progression of the aldol step.



Scheme 4. Control experiments.

Based on the above results, control experiments, and observations, we have formulated a plausible mechanism for the zinc-catalyzed N–H insertion/aldol cascade reaction, as illustrated in Figure 4. Initially, $ZnCl_2$ activates the alkyne moiety in enynal **1a**. Subsequently, the aldehyde group within the enynal unit attacks the activated alkyne in a 5-*exo*-dig cyclization manner. This process is followed by the back donation from zinc, leading to the gain of the furan aromaticity, thereby generating the zinc carbenoid intermediate **A**, which has similar reactivity to D/A diazo-derived metal carbenoids. Next, the N–H insertion to the carbene leads to the formation of intermediate **B**. The generated intermediate **B** undergoes an intramolecular attack on the ketone through a fused five-six-membered transition state, leading to the formation of the desired pyrrolidine product **3** in a *cis*-diastereomeric fashion. However, it is important to note that intermediate **B** also has the potential to undergo protodemetalation, leading to the formation of the N–H insertion byproduct **4**.

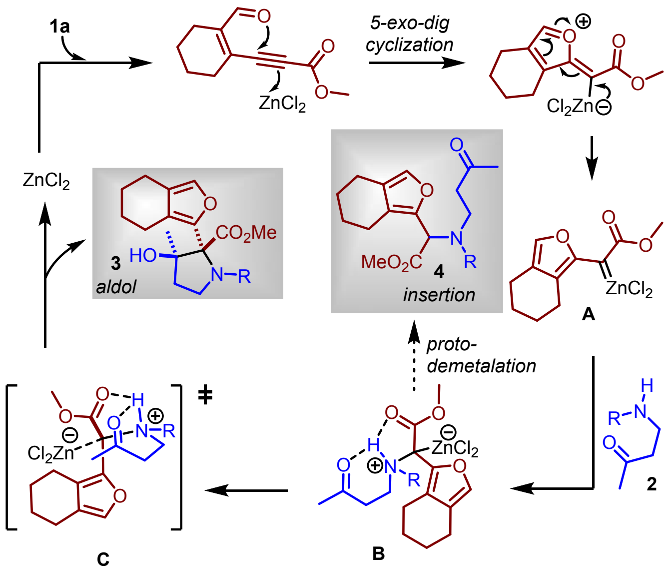


Figure 4. Plausible mechanism.

Conclusion

In conclusion, we have successfully established a strategy for the stereoselective synthesis of highly substituted (2-furyl)-2-pyrrolidines through an N–H insertion/aldol cascade. This efficient method utilizes Earth-abundant zinc (II) catalyst and exhibits remarkable chemoselectivity towards a diverse range of β-arylaminoketones and enynal-esters featuring free alcohols, alkenes, and alkynes. Furthermore, the catalyst loading can be minimized to as low as 1 mol%. The observed high stereoselectivities in the pyrrolidine formation can be rationalized by proposing a mechanistic pathway involving a fused five-six-membered transition state for the intramolecular aldol reaction. These mechanistic insights contribute to the understanding of the enynal's reactivity and will enable their application to other cascade processes to access biorelevant scaffolds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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24. *CCDC 2285842 (3b) contains the supplementary crystallographic data for this paper. These data can be obtained free of chargefrom the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/).*

