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A rhodium catalyzed cycloisomerization and tandem Diels–Alder reaction for facile access to diverse bicyclic and tricyclic heterocycles†

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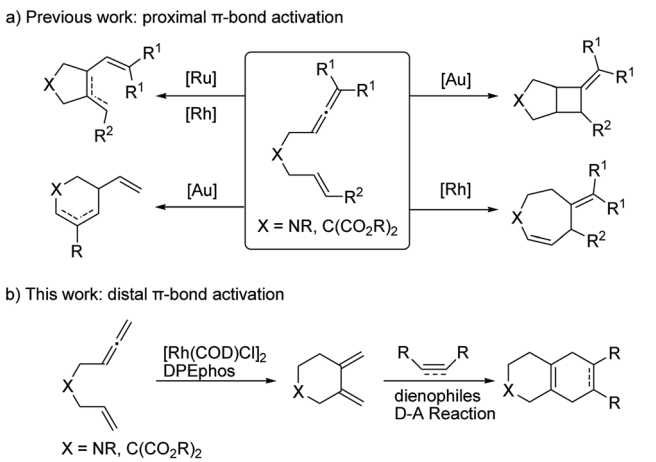
A regioselective distal cycloisomerization of 1,6-allenenes was successfully developed to afford six-membered ring exocyclic 1,3-dienes employing a rhodium/diphosphine catalyst system. Deuterium labelling experiments and DFT calculations were performed to provide insights into the reaction mechanism of this unprecedented transformation. In addition, one-pot tandem Diels–Alder reactions with various dienophiles could readily construct diverse bicyclic and tricyclic nitrogen heterocycles, which are ubiquitous core scaffolds for a variety of natural products and bioactives. High efficiency and exclusive chemo and regioselectivities for a broad substrate scope were achieved under mild conditions using a low catalyst loading of 0.5 mol%.

Transition metal catalyzed cycloisomerization reactions have proved to be synthetically useful and elegant methods to construct structurally diverse all carbon and heterocyclic frameworks with high efficiency and an excellent atom and step economy.[1] In particular, cycloisomerization reactions of linear di-unsaturated systems with a suitable linker chain, such as 1,6-diynes,[2] 1,6-enynes,[3] allenynes,[4] bisallenes,[5] and allenedienes,[6] have been intensely investigated. Furthermore, readily available 1,6-allenenes have attracted extensive synthetic interest and their cycloisomerization has been successfully realized to access diverse heterocycles by employing various transition metal catalysts, including nickel,[7] palladium,[8] ruthenium,[9] rhodium,[10] gold,[11] *etc.* To the best of our knowledge, all the previously reported examples involved a proximal allene π-bond activation and produced five-membered ring dienes as major products (Scheme 1a). In view of diversity-oriented synthesis,[12] it is therefore highly desirable to develop a new versatile catalytic system to furnish alternative cycloisomerization products which enable subsequent multiple functionalizations.

Recently, our group has made significant progress on the development of rhodium catalyzed atom-efficient addition reactions of various pronucleophiles to unactivated allenes and alkynes to provide enantioenriched branched allylic products.[13] To further expand the synthetic potential, we envisioned that 1,6-allenenes would be interesting substrates for cycloisomerization to construct useful cyclic 1,3-dienes by using our rhodium/diphosphine catalytic system. Herein, we present an unprecedented rhodium catalyzed regioselective distal cycloisomerization of 1,6-allenenes to provide six-membered ring exocyclic 1,3-dienes exclusively (Scheme 1b). Based on deuterium labelling experiments and DFT calculations a plausible reaction mechanism could be elucidated. Moreover, a one-pot tandem Diels–Alder reaction with various dienophiles furnished diverse bicyclic and tricyclic nitrogen heterocycles with a high atom- and step-economy.[14] Such fused bicyclic and tricyclic nitrogen containing heterocycles constitute privileged core skeletons of a variety of natural products and drugs as well



Scheme 1 Transition metal catalyzed cycloisomerizations of allenenes.

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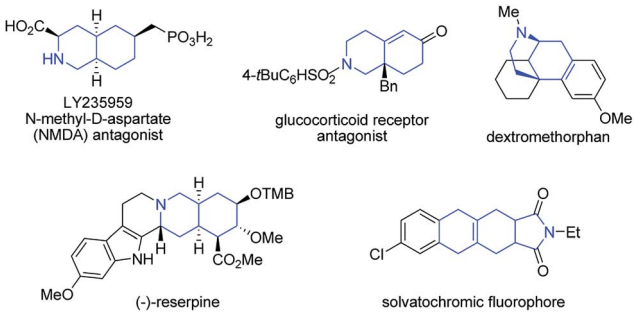


Fig. 1 Selected examples of drugs and natural products containing bicyclic or tricyclic nitrogen heterocycles as core structures.

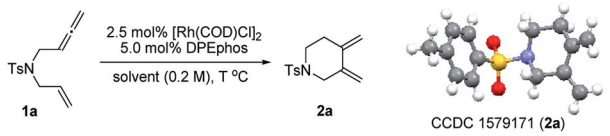
as fluorescent probes (Fig. 1), which highlights the manifold potential applications of this new methodology in medicinal and materials chemistry.[15]

To test our hypothesis, unactivated terminal 1,6-allenene **1a** was chosen as a privileged model substrate for initial reactivity assays. Surprisingly, in contrast to the results reported in the literature, no proximal coupled five-membered ring 1,3-diene product (as shown in Scheme 1a) was detected. Conversely, a completely new kind of six-membered ring exocyclic 1,3-diene was obtained as the sole product with exclusive regioselectivity and in good yield. The molecular structure of product **2a** was unambiguously confirmed by X-ray crystallography analysis. This unexpected preliminary result induced us to systematically optimize the reaction conditions (Table 1). First, several solvents were examined for the new cycloisomerization reaction (Table 1, entries 1–3) with DCE (1,2-dichloroethane) proving to be superior to THF (tetrahydrofuran) and toluene. Further investigations on the reaction temperature revealed that 60 °C was the most suitable temperature for this new transformation. The yield decreased with either higher or lower temperatures (Table 1, entry 5). Finally, the best result (80% yield) was obtained employing a lower substrate concentration of 0.1 M (Table 1, entry 6).

With the optimized reaction conditions in hand, the substrate scope was explored. The results are shown in Table 2. First, substrates having different protecting groups at the nitrogen linker atom were investigated (**2a** to **2g**). Thus, in addition to the sulfonyl groups, easily removable Boc and Cbz carbamates were well tolerated. Second, a variety of allenenes with an all-carbon linker were examined (**2h** to **2n**). In these cases, a slight increase of the reaction temperature to 80 °C was necessary in order to complete the cycloisomerization process. Different ester functions, such as methyl, ethyl and benzyl, were all compatible in this reaction (**2h** to **2j**). Moreover, a group of masked hydroxyl functions were also suitable for the transformation (**2l** to **2n**). It is noteworthy that an interesting diene product **2k** with a spiro ketal structure was obtained in good yield.

To gain deeper insights into the reaction mechanism of this new cycloisomerization reaction, a series of deuterium labelled substrates were prepared and subjected to standard reaction conditions (Scheme 2). The results with substrates **1a-1** and **1a-2** indicated that the deuterium atoms at the terminal positions of alkene and allene completely remained in their original position. Hence, these carbon–hydrogen bonds should not change

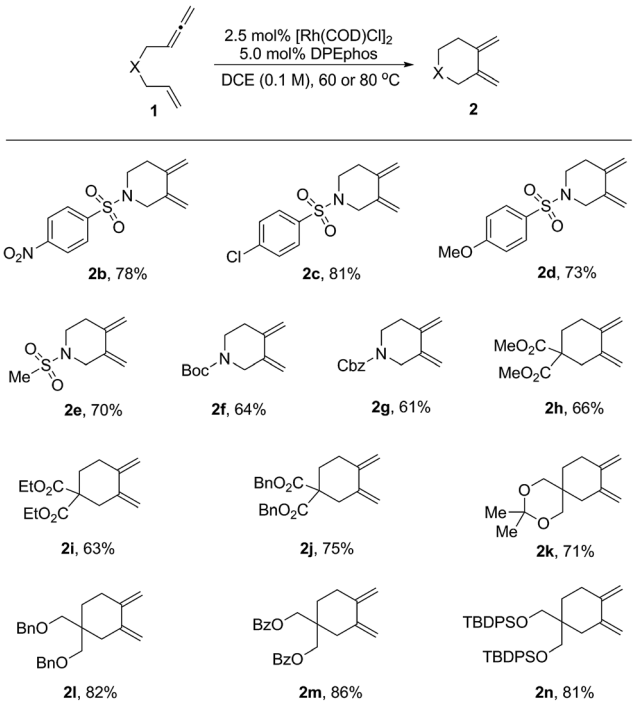
Table 1 Reaction condition optimization for the cycloisomerization to access exocyclic 1,3-dienes[a]



Entry	Solvent	Temp./°C	Yield[b] [%]
1	DCE	80	65
2	THF	80	58
3	Toluene	80	55
4	DCE	95	51
5	DCE	60	75
6[c]	DCE	60	80

[a] The reactions were carried out on a 0.2 mmol scale of **1a** in the presence of 2.5 mol% of $[Rh(COD)Cl]_2$ and 5.0 mol% of DPEphos in DCE (1.0 mL) at different temperatures for 20 h. [b] Isolated yield. [c] 2.0 mL DCE was used (0.1 M).

Table 2 Substrate scope for the cycloisomerization to access exocyclic 1,3-dienes[a]



[a] The reactions were carried out on a 0.2 mmol scale of **1** in the presence of 2.5 mol% of $[Rh(COD)Cl]_2$ and 5.0 mol% of DPEphos in DCE (2.0 mL) for 20 h. For products **2b** to **2g**, the reactions were performed at 60 °C. For products **2h** to **2n**, the reactions were performed at 80 °C. All the yields were isolated yields.

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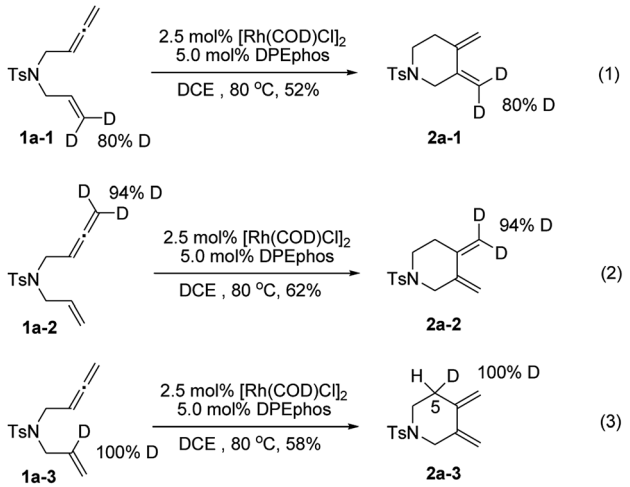
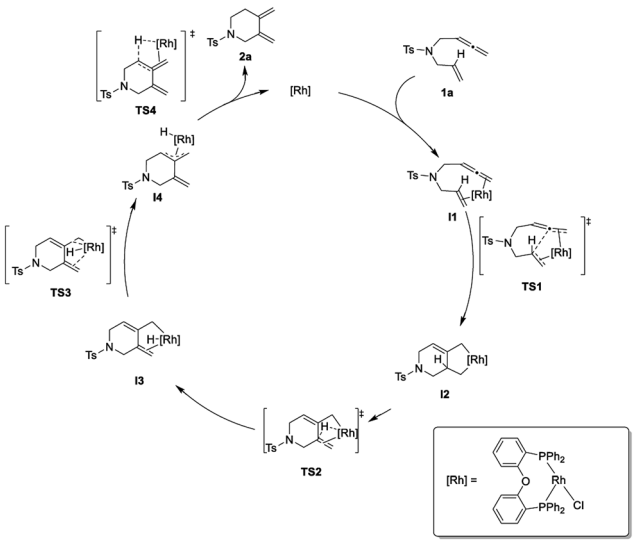


Scheme 2 Deuterium labelling experiments.

during the process (eqn (1) and (2)). However, the deuterium atom at the internal position of the alkene in **1a-3** completely shifted to the 5 position of the piperidine ring (**2a-3**), which indicated that an isomerization step might be involved to form the exocyclic carbon–carbon double bonds (eqn (3)).

To shed further light on the mechanism of this new cycloisomerization reaction, DFT computations were performed.[16] Based on the labeling experiments and the DFT calculations the mechanism depicted in Scheme 3 is proposed. Starting from a monomeric [ClRh(DPEphos)] complex ([Rh]) the substrate **1a** could coordinate to form the chelate intermediate **I1**. An oxidative coupling *via* **TS1** furnishes the σ-allyl intermediate **I2**. This is followed by a β-hydride elimination (**TS2**) to give the σ-allyl hydride complex **I3**. Isomerization to the π-allyl intermediate **I4** (*via* **TS3**) and reductive elimination (*via* **TS4**) deliver product **2a** and regenerate the rhodium catalyst.



Scheme 3 Proposed mechanism for the rhodium-catalyzed cycloisomerization of 1,6-allenenes to six-membered exocyclic 1,3-dienes.

Fig. 2 displays the energy profile of the reaction. The highest energetic barriers are the oxidative coupling to form a five-membered metallacycle (**TS1**) with a ΔG of 14.6 kcal mol^{-1} (M06/def2SVP) and the reductive elimination step (**TS4**) with a ΔG of 14.5 kcal mol^{-1} (M06/def2SVP). The calculated reaction mechanism is in accord with the results of the deuterium labelling experiments. Furthermore, calculations of the complete catalytic cycle for the traditional 5-membered ring cycloisomerization were performed. However, the energy barrier of the rate determining step was found to be significantly higher and is therefore unfavored.[16]

Considering that exocyclic 1,3-dienes **2** are potentially good reaction partners in Diels–Alder reactions, we anticipated that in the presence of suitable dienophiles, a one-pot tandem cycloisomerization/Diels–Alder reaction could be developed. This could become an efficient synthetic method to prepare diverse bicyclic and tricyclic nitrogen heterocycles.[16] Indeed, as summarized in Table 3, we found that a wide range of 1,6-allenenes reacted smoothly in the presence of the rhodium catalyst and *N*-phenyl maleimide to furnish the desired tricyclic heterocycles **4** in good yields along with exclusive regio- and diastereoselectivities. The constitution and relative configuration of **4c** were determined by X-ray crystallography analysis, while the others were assigned by analogy. For the protected amide allenenes (**4a–4g**), as low as 0.5 mol% of the rhodium catalyst was sufficient to achieve full conversion. Comparable yields showed that the protecting groups on the nitrogen atom exhibited negligible influences on the reaction. For carbon-linked allenene substrates (**4h–4o**) a slightly increased catalyst loading of 1 mol% was needed to allow for smooth and complete transformation. Various functional groups, such as ester, ketone, ketal and ethers, were all well tolerated.

Next, the scope of dienophiles for the rhodium catalyzed domino cycloisomerization/Diels–Alder reaction was evaluated. As illustrated in Table 4, a wide range of symmetrical dienophiles proved suitable, providing the desired tricyclic and bicyclic heterocycles in good to high yields.

Thus, a series of *N*-aryl maleimides with either electron poor or electron rich aryl substituents behaved well and provided the tandem products in good to high yields (**6a–6n**). A variety of aryl halides including F, Cl, Br and even I were well tolerated enabling subsequent derivatization through diverse cross-coupling methods (**6e–6h**). Other well behaving dienophiles were benzoquinone (**6o**), the diphenyl ketone derived from fumaric acid (**6p**), dimethyl fumarate (**6q**), *trans*-dicyano ethylene (**6r**), acetylene dicarboxylate (**6s**), tetra-cyano ethylene (**6f**) and azo dicarboxylate (**6u**).

The obtained fused tricyclic heterocyclic products contain an internal tetra-substituted alkene function, which permits a variety of functionalization reactions. Towards this goal the tricyclic products **4a** and **4h** were selected for preliminary studies (Scheme 4).

First, the palladium catalyzed diastereoselective hydrogenation delivered the saturated azatricyclic **7** as a single diastereomer in high yield. By treatment with a suitable bromination reagent (PyH^*Br_3) in DCM, the dibrominated product **8** was obtained as a mixture of diastereomers. Epoxidation with *m*-

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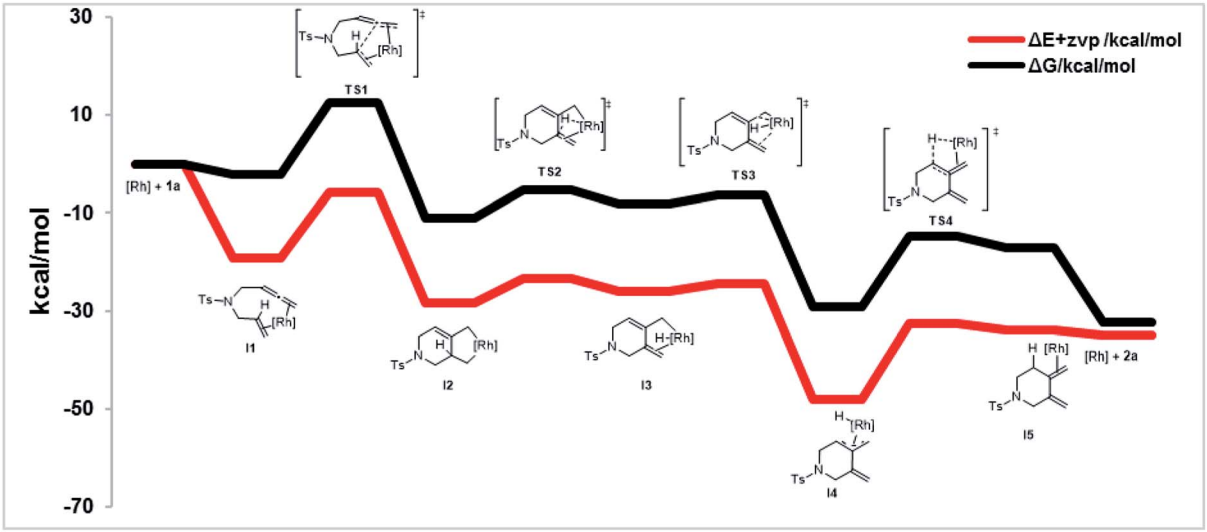
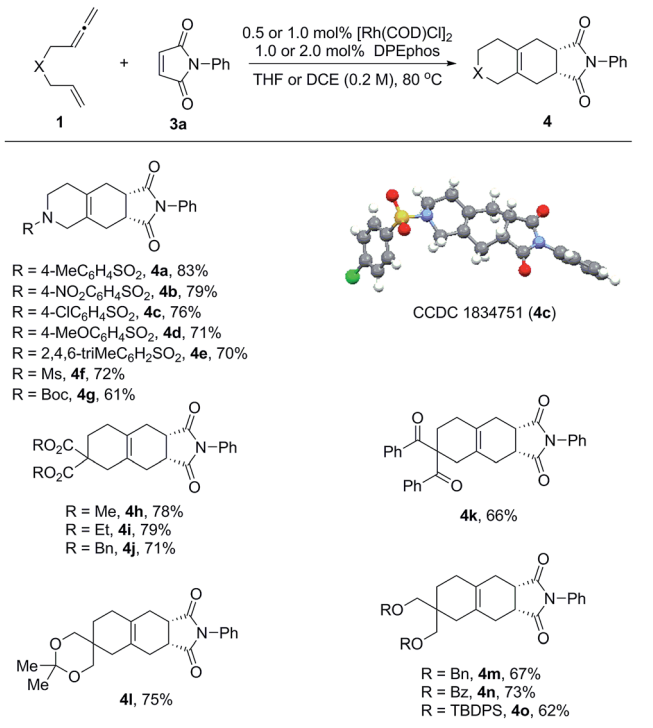


Fig. 2 Computed catalytic cycle of the Rh catalyzed cycloisomerization of 1,6-allenenes to six-membered exocyclic 1,3-dienes. All energies (PCM-M06/def2SVP//BP86/def2SVP) are given with respect to the energies of the [ClRh(DPEphos)] complex and the substrate.

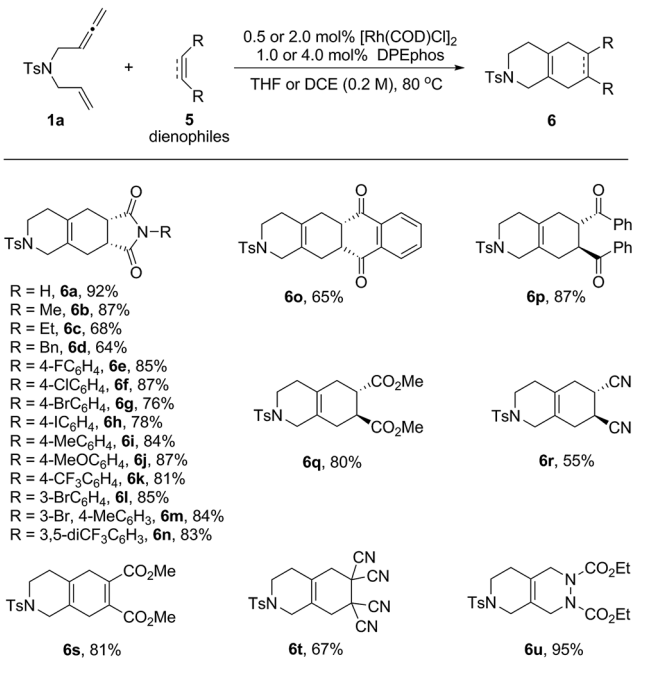
CPBA furnished the epoxide **9** as a single diastereomer. A dihydroxylation yielded the vicinal diols **10a** and **10h** as single diastereomers from **4a** and **4h**, respectively. These diols could be oxidatively cleaved to give the ten-membered diketones **11a** and **11h**. Alternatively, the tricyclic product **4h** could be directly transformed into **11h** *via* ozonolysis. It is noteworthy that such medium-sized fused bicyclic structures are difficult to access by other methods, highlighting the significance of this new

Table 3 Substrate scope for the cycloisomerization and tandem Diels–Alder reaction[a]



[a] The reactions were carried out on a 0.2 mmol scale of **1** with 1.0 equivalent of **3a** at 80 °C for 20 h. For products **4b** to **4g**, the reactions were performed in THF (1.0 mL) using 0.5 mol% of $[Rh(COD)Cl]_2$ and 1.0 mol% of DPEphos. For products **4h** to **4o**, the reactions were performed in DCE (1.0 mL) using 1.0 mol% of $[Rh(COD)Cl]_2$ and 2.0 mol% of DPEphos. All the yields were isolated yields.

Table 4 Substrate scope for various dienophiles[a]



[a] The reactions were carried out on a 0.2 mmol scale of **1a** with 1.0 equivalent of **5** in the presence of 0.5 mol% of $[Rh(COD)Cl]_2$ and 1.0 mol% of DPEphos in THF (1.0 mL) at 80 °C for 20 h. For products **6s** to **6u**, the reactions were performed in DCE (1.0 mL) using 2.0 mol% of $[Rh(COD)Cl]_2$ and 4.0 mol% of DPEphos and the dienophiles were added after the first cycloisomerization step was completed. All the yields were isolated yields.

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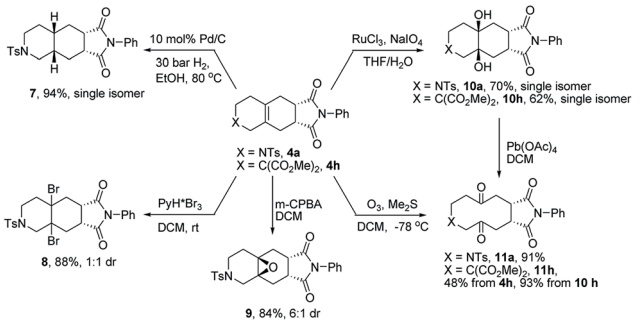

Scheme 4 Diverse synthetic transformations of **4a** and **4h**.

method for potential application in the synthesis of natural products and medicinal chemistry.

Conclusions

In conclusion, a novel regioselective cycloisomerization of 1,6-allenenes was successfully developed to generate six-membered ring exocyclic 1,3-dienes by using a rhodium/diphosphine catalyst system. Based on labelling experiments corroborated by DFT computations a plausible reaction mechanism could be suggested. Moreover, one-pot tandem Diels–Alder reactions with various dienophiles led to the efficient and rapid construction of diverse bicyclic and tricyclic nitrogen heterocycles. The new method displays a high efficiency, broad substrate scope, complete atom and step economy, low catalyst loading of 0.5 mol%, and excellent chemo-, regio-, and diastereoselectivity. Further studies on the application of this new method are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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