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An unusual four-step cascade reaction for accessing furo[3,4-*c*]pyridine-1,4-diones *via* rhodium catalysis†

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The development of efficient cascade reactions is highly important and appealing because of their desirable step-economy and convenience in constructing multiple chemical bonds and complex molecules in one shot. Herein, we report a rare four-step tandem reaction between acrylamides and 4-hydroxy-2-alkynoates to prepare novel furo[3,4-*c*]pyridine-1,4-diones which are difficult to synthesize by traditional methods. This unique domino reaction includes C–H activation, Lossen rearrangement, annulation, and lactonization. Additionally, this protocol features good functional group tolerance, obtainment of products by simple filtration, room temperature, and air compatibility. DFT calculations were conducted to shed some light on the reaction mechanism.

Introduction

The prevalence of heterocycles in natural products and pharmaceuticals has led to the importance and benefits of synthesizing such compounds efficiently. In the past decades, directing group (DG) assisted C–H activation/annulation reactions *via* transition-metal catalysis for the synthesis of heterocycles have achieved tremendous advances.[1,2] DGs play crucial roles in controlling chemical reactivity and regioselectivity in C–H activation reactions. On the other hand, DGs simply adhere to primordial positions and function as auxiliary groups in these reactions without other transformations. Amide-type DGs are frequently applied to C–H activation/annulation reactions for the synthesis of prevalent isoquinolones and 2-pyridones, where DGs remain static in most cases (Scheme 1a).[1,2a–f,3] The rearrangement or migration of DGs in C–H activation reactions provides an intriguing strategy to construct C–C/C–N bonds and also contributes to the synthesis of novel heterocyclic scaffolds.[4,5] Therefore, it is fascinating to apply this emerging strategy to organic synthesis. Nevertheless, the development of this emerging strategy involving DG rearrangement or migration still falls far behind when compared to the numerous reports of static DGs participating in C–H activation reactions.

Even though DGs could improve chemoselectivity and regioselectivity, they may be present as undesired moieties on products at times, and additional steps are required to remove unwanted DGs. If DGs undergo a rearrangement process, it will not only create a new and efficient avenue for synthesizing heterocycles, but also possibly generate novel heterocycles that traditional approaches can hardly furnish. By taking advantage of the strategy of directing group rearrangement, a series of intriguing spirooxindole pyrrolones were synthesized elegantly by Dai's group (Scheme 1b).[6] Acrylamides involving the rearrangement of DGs undergo three processes: C–H activation, directing group rearrangement, and annulation. Recently, we developed an efficient rhodium-catalyzed domino C–H alkenylation, DG migration, and lactonization reaction between *N*-carbamoyl indoles and 4-hydroxy-2-alkynoates for the synthesis of the furan-2(5*H*)-one scaffold (Scheme 1c).[7] Efficient cascade reactions are highly appealing due to their desirable step-economy and convenience in constructing complex molecules with multiple chemical bonds in one shot.[8–11]

To our knowledge, the implementation of a multistep cascade reaction involving four distinct processes of C–H acti-

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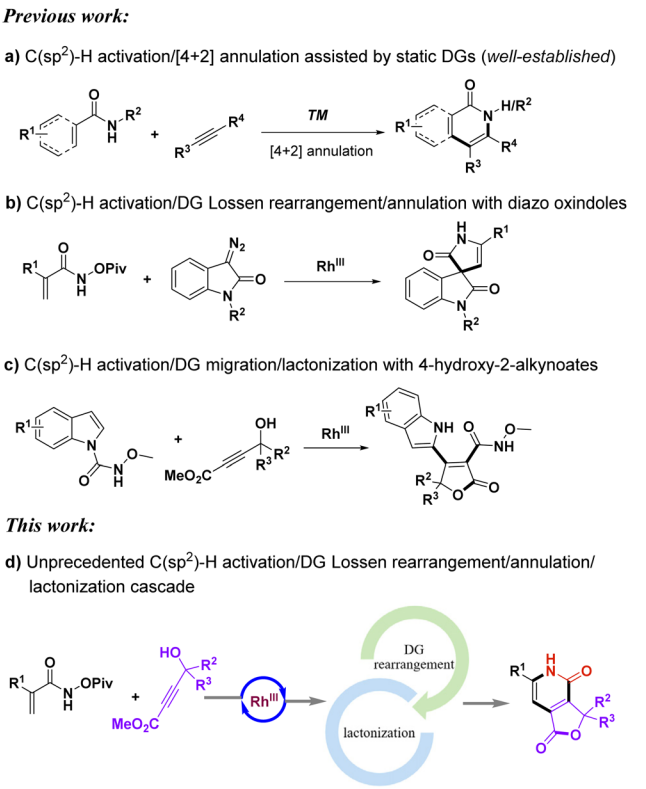
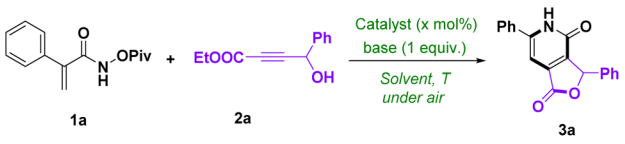


Scheme 1 Transition-metal catalyzed C–H activation/annulation reactions.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Additive	Solvent	Yield[b,c] (%)
1	$MnBr(CO)_5$	NaOAc	TFE	0
2	$[Cp^*IrCl_2]_2$	NaOAc	TFE	6
3	$Cp^*Co(CO)I_2$	NaOAc	TFE	0
4	$[Ru(p\text{-cym})Cl_2]_2$	NaOAc	TFE	0
5	$[Cp^*RhCl_2]_2$	NaOAc	TFE	73 (47)
6	$Pd(OAc)_2$	NaOAc	TFE	0
7	$[Cp^*RhCl_2]_2$	NaOAc	THF	Trace
8	$[Cp^*RhCl_2]_2$	NaOAc	MeOH	15
9	$[Cp^*RhCl_2]_2$	NaOAc	DCE	32
10	$[Cp^*RhCl_2]_2$	NaOAc	CH_3CN	0
11	$[Cp^*RhCl_2]_2$	NaOAc	EA	20
12	$[Cp^*RhCl_2]_2$	Na_2CO_3	EtOH	0
13	$[Cp^*RhCl_2]_2$	Na_2CO_3	TFE	78 (53)
14	$[Cp^*RhCl_2]_2$	K_2CO_3	TFE	19
15	$[Cp^*RhCl_2]_2$	CsOAc	TFE	54 (37)
16	$[Cp^*RhCl_2]_2$	KOAc	TFE	46 (33)
17[d]	$[Cp^*RhCl_2]_2$	—	TFE	0
18[e]	—	Na_2CO_3	TFE	0

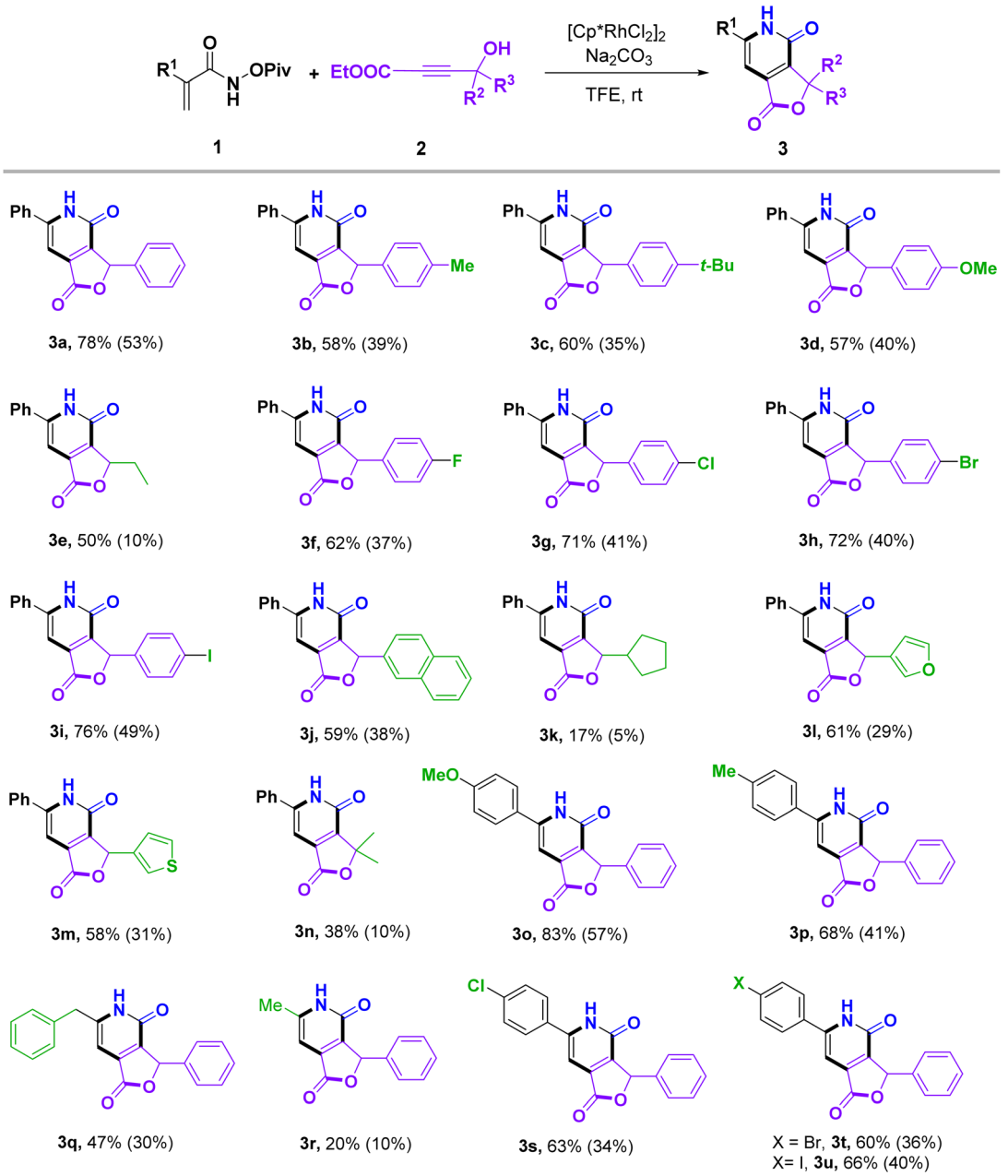
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (3 mol%), additive (0.2 mmol), under air, solvent (1.0 mL), room temperature, 6 h. [b] Total isolated yield. [c] Isolated yields obtained by simple filtration are shown in parenthesis. [d] Na_2CO_3 was not used. [e] $[Cp^*RhCl_2]_2$ was not used.

vation, directing group rearrangement, annulation, and lactonization has yet to be documented. In this study, we report a rare four-step tandem reaction between acrylamides and 4-hydroxy-2-alkynoates[12] to prepare novel furo[3,4-*c*]pyridine-1,4-diones which are difficult to synthesize by traditional methods. The four-step tandem reaction involves C–H activation, DG Lossen rearrangement, [4 + 2] annulation, and lactonization. The method can tolerate a variety of functional groups. Furthermore, the products can be easily purified by filtration and the reaction is compatible with both room temperature and air. These features contribute to the practicality and versatility of the protocol.

Results and discussion

We embarked on our studies with the optimization of the reaction conditions for the cyclization between acrylamide **1a** and ethyl 4-hydroxy-4-phenylbut-2-ynoate **2a**. No desired product **3a** was obtained when catalyzed by $MnBr(CO)_5$, $[RuCl_2(p\text{-cym})]_2$, $Cp^*Co(CO)I_2$ and $Pd(OAc)_2$, respectively (Table 1, entries 1–6). Switching to $[Cp^*IrCl_2]_2$ led to only 6% yield (entry 2). In contrast, the yield of **3a** was improved to 73%, and 43% of the product could be obtained by simple filtration when using $[Cp^*RhCl_2]_2$ (entry 5). The structure of **3a** was confirmed using 1D-NMR and NOESY experiments as well as mass spectra. Solvent screening revealed that TFE outperformed other common solvents, such as THF (only trace), MeOH (15% yield), DCE (32% yield with 40% substrate not being consumed) and EA (20% yield) (entries 7–11). When using ethanol and adding Na_2CO_3 as a base, the yield of **3a** was 0% (entry 12). After extensive screening of additives, such as Na_2CO_3, K_2CO_3, CsOAc, and KOAc, Na_2CO_3 was identified as the optimal one (entries 13–16). The control experiments confirmed that no desired reaction occurred in the absence of an additive or rhodium (entries 17 and 18).

With the optimal conditions in hand, we next examined the scope of this cyclization reaction (Scheme 2). Aryl-substituted propynol bearing electron-donating groups are all tolerated in this system, such as CH_3, *t*-Bu, OMe, and CH_2CH_3, and the corresponding products can be obtained in high yields by direct filtration (**3a–3e**). To our delight, electron-withdrawing groups including F, Cl, Br, and I were also tolerated well with the isolated yields ranging from 62% to 72% (**3f–3i**). Although the yield of the product dropped dramatically when the group was changed to cyclopentyl (**3k**), the reaction was compatible with other different rings (naphthalene, furan, and thiophene) and afforded the products smoothly (**3j**, **3l**, and **3m**). We also explored tertiary alkynol and obtained the desired product in a moderate yield (**3n**). Next, we investigated R^1 of acrylamide **1** bearing electron-donating and electron-withdrawing groups at the *para* position of the phenyl group, and the reactions proceeded well to generate the corresponding products. In comparison, when the phenyl group was changed to the benzyl

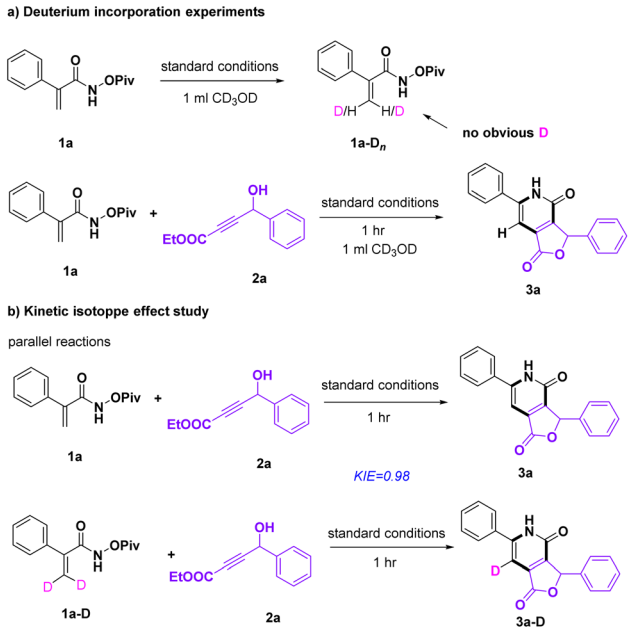


Scheme 2 Substrate scope. Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (3 mmol%), Na_2CO_3 (0.2 mmol), under air, trifluoroethanol (1.0 mL), rt, 6–12 h. Total yields are shown, and yields obtained by simple filtration are shown in parentheses.

and methyl group, the yield dropped to 47% and 20%, respectively (**3o–3u**). Additionally, the structures of **3h**, **3n**, **3p**, and **3q** were further confirmed by NOESY experiments.

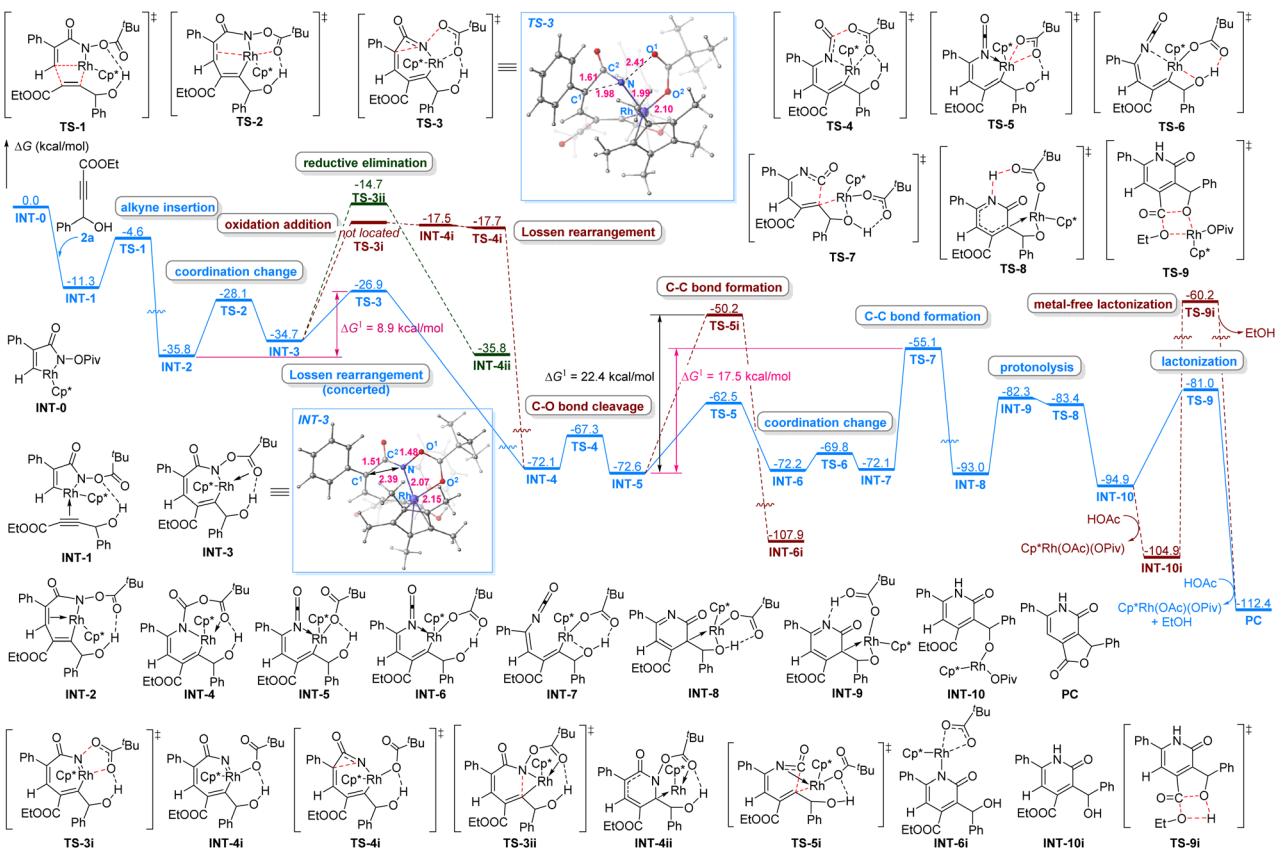
Several experiments were conducted to probe the reaction mechanism. In the presence of **1a**, Na_2CO_3, $[Cp^*RhCl_2]_2$, and 1.0 ml methanol-d^4, the experiment of H/D exchange occurring at the olefinic bond of acrylamide was performed (Scheme 3a). And no obvious deuterium incorporation was observed at this position (8% D). In addition, there was also almost no D at the olefinic bond of **3a** after adding **2a**. The result demonstrated that the cleavage of the C–H bond could be irreversible. Additionally, two parallel reactions were performed giving a KIE value of 0.98 (Scheme 3b), which suggested that the C–H activation step was less likely to be involved in the rate-determining step.

To further obtain the mechanistic features of the unprecedented Rh(III)-catalyzed sequential C–H activation/Lossen rearrangement/[4 + 2] annulation/lactonization cascade, we next performed DFT calculations on the key reaction steps: alkyne insertion, Lossen rearrangement, [4 + 2] annulation and lactonization. As shown in Scheme 4, the five-membered rhodacycle **INT-0** derived from C–H activation was rationally



Scheme 3 Deuteration and KIE experiments.

selected as the starting point, which coordinated with propargyl alcohol **2a** and produced the intermediate **INT-1** ($\Delta G^{\ddagger}$ = −11.3 kcal mol^{-1}) involving hydrogen-bonding between the hydroxyl group of **2a** and the pivalate group. Then the C–C unsaturated bond of **2a** was inserted into the Rh–C bond *via* **TS-1** ($\Delta G^{\ddagger}$ = −4.6 kcal mol^{-1}) to deliver **INT-2** with a free energy of −35.8 kcal mol^{-1}. The subsequent facile coordination change *via* **TS-2** ($\Delta G^{\ddagger}$ = −28.1 kcal mol^{-1}) produced the unstable intermediate **INT-3** which afforded different reaction paths. The concerted Lossen rearrangement/N–O bond cleavage from **INT-3** occurred *via* **TS-3** ($\Delta G^{\ddagger}$ = −26.9 kcal mol^{-1}) which demanded an energy barrier of 8.9 kcal mol^{-1} (from **INT-2** to **TS-3**) to give the intermediate **INT-4** along with a considerable quantity of heat. The relatively elongated N–O^1 bond (1.48 Å *vs.* 1.42 Å in **INT-0**) in the geometry of **INT-3** and the significantly elongated N–O^1 bond (2.41 Å) and shortened C^1–N bond (1.98 Å) in the transition state **TS-3** suggest that the Lossen rearrangement was assisted by the pivalate group and the rhodium center. Alternatively, classic C–N bond reductive elimination *via* **TS-3ii** ($\Delta G^{\ddagger}$ = −14.7 kcal mol^{-1}) involved a higher energy barrier of 21.1 kcal mol^{-1} (from **INT-2** to **TS-3ii**). Moreover, the Rh(III)–Rh(V)–Rh(III) reaction path involving an oxidative addition process from **INT-3** was also ruled out owing to the relatively high free energies of **INT-4i**/**TS-4i**. After low-barrier isomerization *via* **TS-4**, **INT-4** was transformed into the isocyanate intermediate **INT-5** from which the direct C–C bond formation/annulation occurred *via* **TS-5i** ($\Delta G^{\ddagger}$ = −50.2 kcal mol^{-1}) and required a barrier of 22.4 kcal mol^{-1} (from **INT-5** to **TS-5i**). However, the coordination change *via*



Scheme 4 DFT calculations of the reaction pathways.

TS-5/**TS-6** led to a more favorable C–C bond formation reaction *via* **TS-7** ($\Delta G^{\ddagger}$ = −55.1 kcal mol^{-1}) which only needs an activation energy of 17.5 kcal mol^{-1}. Afterwards, the protonolysis reaction *via* **INT-9**/**TS-8** was followed by lactonization *via* **TS-9** ($\Delta G^{\ddagger}$ = −81.0 kcal mol^{-1}). Alternatively, the metal-free lactonization without the rhodium complex goes through **TS-9i** ($\Delta G^{\ddagger}$ = −60.2 kcal mol^{-1}) which is of a much higher barrier and can be ruled out.

In order to shed light on the driving force of the Lossen rearrangement, we examined closely the geometry change along the intrinsic reaction coordinate (IRC) corresponding to **TS-3** (see the ESI for details†). The results revealed that at the beginning the N–O^1 bond distance increases which seems to drive the C^1 atom attack on the N atom. The reaction goes through **TS-3** and then the N–O^1 bond breaks which is followed by C^1–N bond formation and C^1–C^2 bond cleavage. This gives a chance for the O^1 atom to attack the positively charged C^2 atom. With the assistance of the pivalate group and the rhodium center, the Lossen rearrangement involves multiple σ-bond metathesis processes.

Conclusions

In summary, we have developed a rare four-step tandem reaction between acrylamides and 4-hydroxy-2-alkynoates to prepare novel furo[3,4-*c*]pyridine-1,4-diones. This unique tandem reaction consists of C–H activation, Lossen rearrangement, [4 + 2] annulation, and lactonization. The protocol features good functional group tolerance, obtainment of pure products by simple filtration, room temperature, and air compatibility. In addition, DFT calculations were conducted to shed some light on the reaction mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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