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Rhodium-catalyzed regioselective C–H activation/Lossen rearrangement/annulation for the green synthesis of trisubstituted 2-pyridones†

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Multisubstituted 2-pyridones are prevalent in pharmaceuticals and bioactive molecules. We herein report an efficient and regioselective approach for the synthesis of trisubstituted 2-pyridone derivatives by a rhodium-catalyzed C–H activation/Lossen rearrangement/cyclization cascade reaction between acrylamides and propargyl alcohols. The desirable features of this protocol include a reusable catalytic system, high regioselectivity, uncommon Lossen rearrangement, good functional group tolerance, operation at room temperature, simple purification by filtration in most cases, and scale-up synthesis with as low as 1 mol% catalyst loading. Additionally, deuterium labeling and KIE assays were performed to investigate the reaction mechanism. The vital effect of the hydroxyl group on propargyl alcohols in determining the regioselectivity was demonstrated by control experiments and DFT calculations. In addition, Mulliken atomic charge analysis of the key intermediates was also carried out to probe the origin of the observed preference for the Lossen rearrangement.

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Introduction

2-Pyridone is a prevalent scaffold in organic compounds and bioactive molecules.[1] As a class of six-membered aza-heterocycles, the 2-pyridone ring possesses a nitrogen heteroatom and a carbonyl group which can act as a hydrogen bond donor/acceptor in medicinal chemistry. In this regard, 2-pyridone usually serves as a bioisostere for pyridine, amide, and N/O-containing heterocycles. Owing to their unique structures, 2-pyridones have been utilized as effective ligands for C–H functionalization as well as kinase hinge binding motifs.[2,3] In addition, the use of a 2-pyridone moiety as bioisosteres commonly has evident influences on the solubility, lipophilicity, and metabolic stability of bioactive compounds. As shown in Fig. 1, 2-pyridone derivatives exhibit a variety of pharmacological activities, such as antifungal, antiepileptic, anticancer, antifibrotic, cardiotonic, and anti-HIV activities.[3b,4] Considering the prevalence and importance of the 2-pyridone scaffold, it is appealing to develop efficient methods for the synthesis of 2-pyridones.

Over the past decades, as a direct and step-economical strategy to construct heterocycles, C–H activation reactions by tran-

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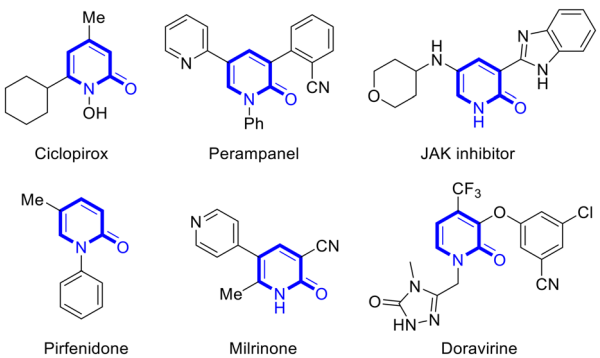
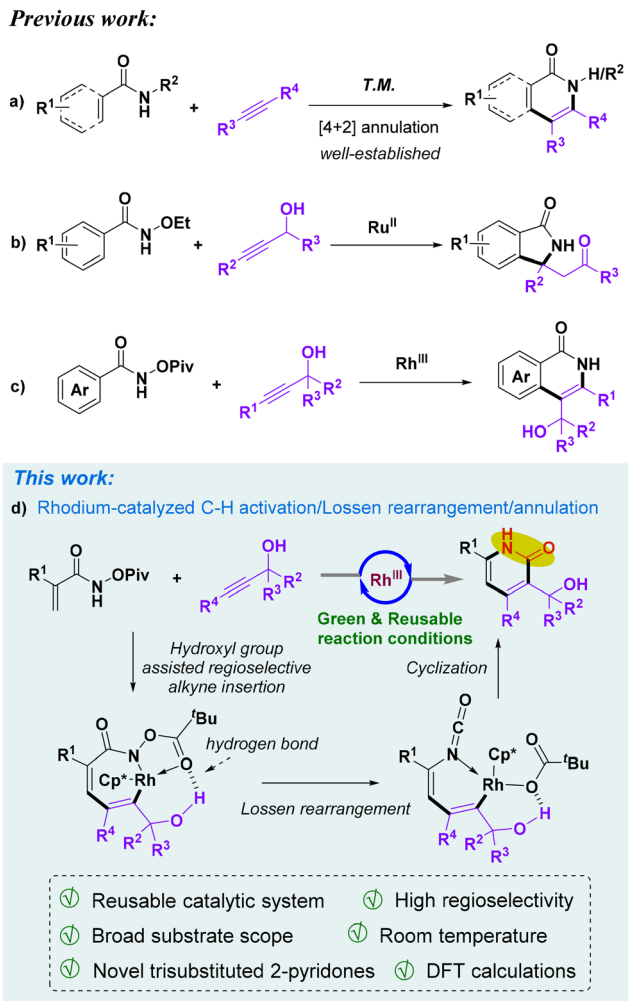


Fig. 1 Selected bioactive molecules containing the 2-pyridone motif.

sition-metal catalysis have received much attention.[5] In this respect, transition-metal catalyzed C–H activation/annulation of benzamides or acrylamides with alkynes has become an efficient method for the preparation of isoquinolones or pyridones (Scheme 1a).[6–8] In recent years, propargyl alcohols have been frequently utilized in reactions because of their versatile reactivities.[9] Additionally, regioselectivity and chemoselectivity are usually controlled by both the hydroxyl group on propargyl alcohols and the directing groups (DGs) in these C–H activation reactions. For example, a ruthenium-catalyzed C–H activation/[4 + 1] annulation of benzamides and propargyl alcohols was pioneered by Liu and coworkers, in which only one carbon of propargyl alcohols was involved in the cyclization (Scheme 1b).[9b] Very recently, by employing the pivaloyl group to replace the ethyl group of directing groups, we reported a green and efficient rhodium-catalyzed C–H activation/annulation of *N*-(pivaloyloxy)benzamides and propargyl alcohols for the synthesis of isoquinolones (Scheme 1c).[10]

Given the prevalence and importance of 2-pyridones, we wish to develop an efficient and novel method to prepare novel multi-substituted 2-pyridone derivatives. Owing to the presence of a hydroxyl group on propargyl alcohols, unique chemoselectivity and regioselectivity are usually achieved. Nevertheless, propargyl alcohols are frequently coupled with aromatic substrates in C–H activation reactions. The C–H activation/annulation of alkenyl substrates and propargyl alcohols for the synthesis of multi-substituted 2-pyridones remains elusive. Inspired by previous works, we speculated whether propargyl alcohols can facilitate some novel transformations when reacted with alkenyl substrates. Thus, we herein report a green and efficient rhodium-catalyzed C–H activation/Lossen rearrangement of acrylamides and propargyl alcohols for the synthesis of novel 2-pyridone derivatives at ambient temperature (Scheme 1d).

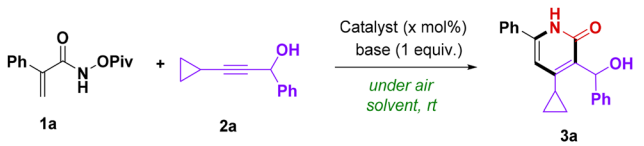


Scheme 1 C–H activation reactions of benzamides or acrylamides with alkynes.

Results and discussion

Optimization studies towards the synthesis of 4-cyclopropyl-3-(hydroxy(phenyl)methyl)-6-phenylpyridin-2(1*H*)-one **3a** are shown in Table 1. In order to develop a green chemical reaction, we first focused on the use of ethyl acetate as the solvent. Then, various transition-metal catalysts were screened in the presence of KOAc at room temperature. No reaction of 2-phenyl-*N*-(pivaloyloxy)acrylamide **1a** with 3-cyclopropyl-1-phenylprop-2-yn-1-ol **2a** was promoted by 4 mol% of $MnBr(CO)_5$, $[Cp^*IrCl_2]_2$, $Cp^*Co(CO)I_2$, and $[RuCl_2(p\text{-cym})]_2$, while the desired product **3a** was obtained in 64% isolated yield when $[Cp^*RhCl_2]_2$ was used (Table 1, entries 1–5). To our delight,

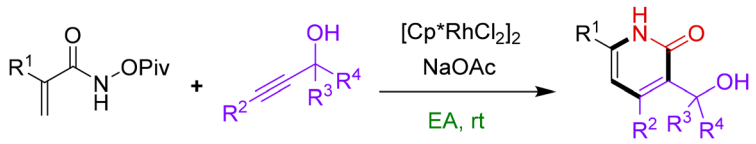
Table 1 Optimization of reaction conditions[a]

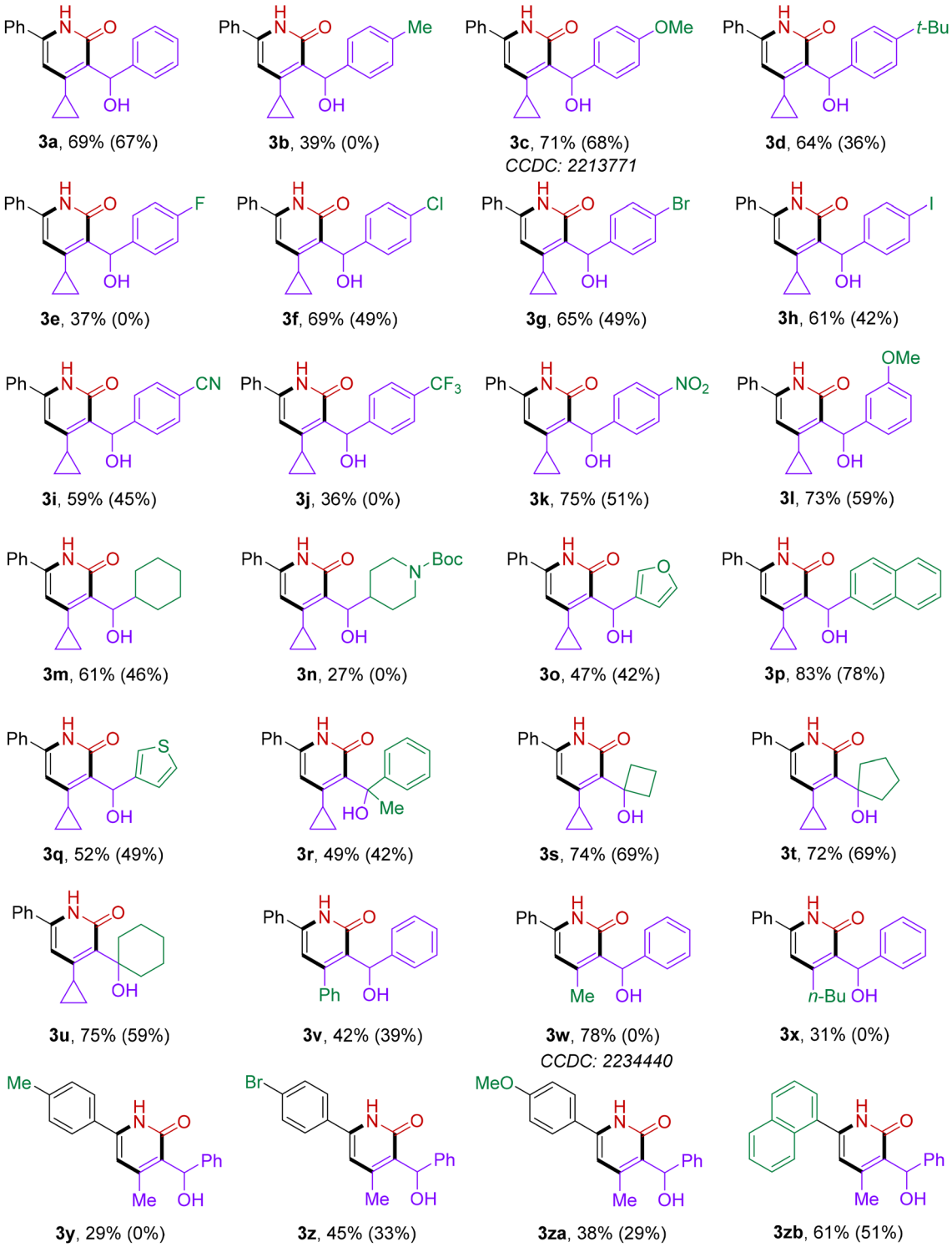


1a 2a 3a

Entry	Catalyst	Additive	Solvent	Yield[b,c] (%)
1	$MnBr(CO)_5$	KOAc	EA	0
2	$[Cp^*IrCl_2]_2$	KOAc	EA	0
3	$Cp^*Co(CO)I_2$	KOAc	EA	0
4	$[Ru(p\text{-cym})Cl_2]_2$	KOAc	EA	0
5	$[Cp^*RhCl_2]_2$	KOAc	EA	64 (59)
6	$[Cp^*RhCl_2]_2$	KOAc	EtOH	22 (16)
7	$[Cp^*RhCl_2]_2$	KOAc	TFE	40
8	$[Cp^*RhCl_2]_2$	KOAc	DCM	44
9	$[Cp^*RhCl_2]_2$	KOAc	Acetone	44 (36)
10	$[Cp^*RhCl_2]_2$	NaOAc	EA	69 (67)
11	$[Cp^*RhCl_2]_2$	Na_2CO_3	EA	58 (47)
12	$[Cp^*RhCl_2]_2$	$NaHCO_3$	EA	69 (58)
13	$[Cp^*RhCl_2]_2$	CsOAc	EA	44 (37)
14[d]	$[Cp^*RhCl_2]_2$	KOAc	EA	57 (35)
15[d]	$[Cp^*RhCl_2]_2$	NaOAc	EA	59 (51)
16[e]	$[Cp^*RhCl_2]_2$	NaOAc	EA	73 (70)

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (4 mol%), additive (0.2 mmol), under air, solvent (1.0 mL), room temperature, 12 h. [b] Total isolated yield. [c] Isolated yield by filtration is shown in parenthesis. [d] $[Cp^*RhCl_2]_2$ (2.5 mol%). [e] Reaction time was 6.0 h.

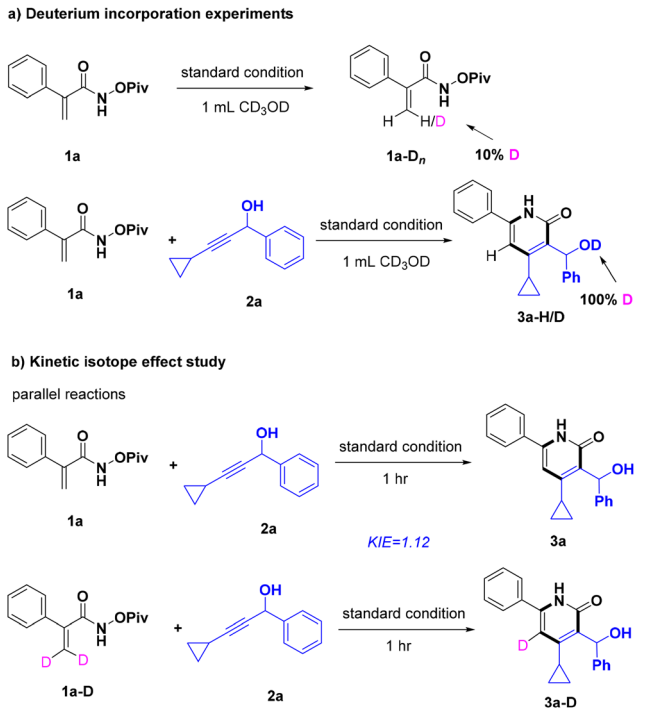




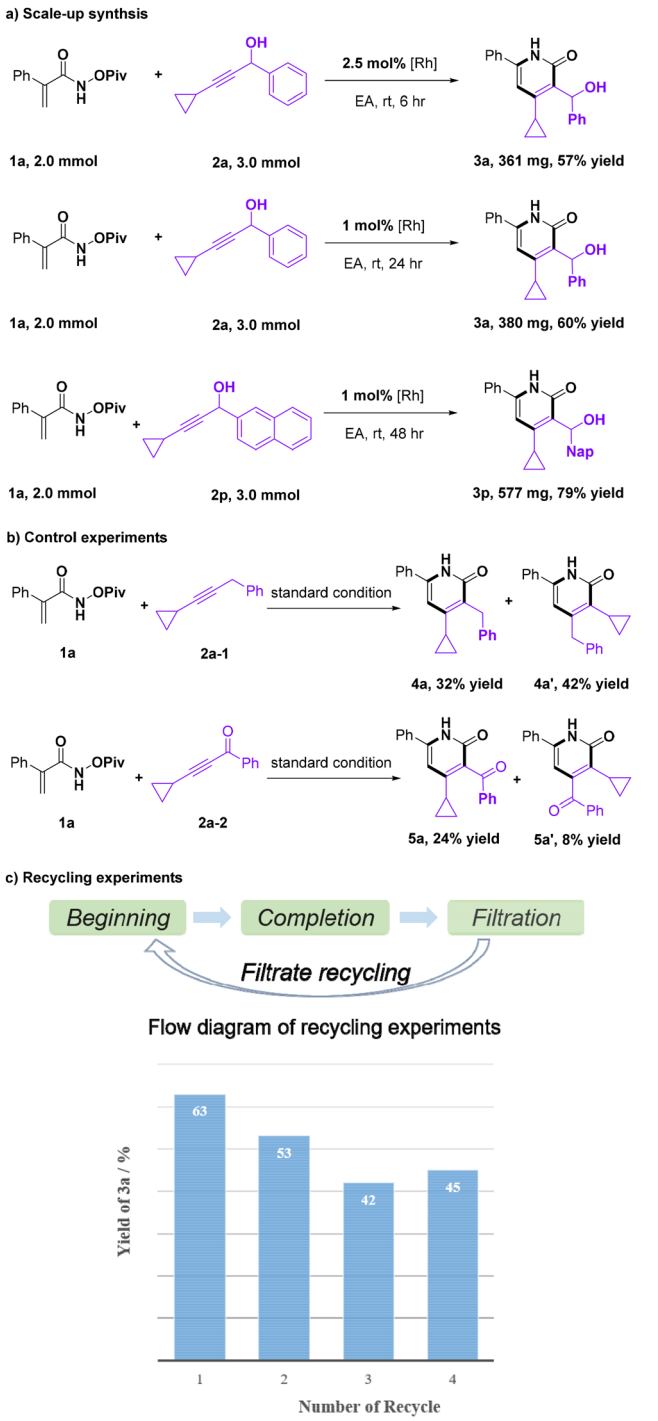
Scheme 2 Substrate scope. Reaction conditions: **1** (0.25 mmol), **2** (0.375 mmol), catalyst (4 mmol%), NaOAc (1.0 equiv.), under air, ethyl acetate (1.0 mL), rt, 6–12 h. Isolated yields by simple filtration are shown in parentheses.

most parts of the product could be isolated by simple filtration, which avoided the use of large amounts of organic solvents for purification. Different solvents were also investigated. Unfortunately, none was superior to our initial choice, EA (entries 6–9). Additive screening revealed that NaOAc and $NaHCO_3$ were the best bases in terms of total isolated yields (entries 10–13). However, the product was obtained in 67% filtration yield in the presence of NaOAc while 58% filtration yield was obtained when $NaHCO_3$ was added. The yield was decreased when KOAc and 2.5 mol% $[Cp^*RhCl_2]_2$ were used, when compared to entry 5 (entry 14). Similarly, when the base was changed to NaOAc, the total yield also declined to 59% by using 2.5 mol% $[Cp^*RhCl_2]_2$ (entry 15). The above-mentioned reactions were conducted for 12 hours. Subsequently, the reaction time was decreased to 6 hours. Surprisingly, the yield of **3a** improved slightly compared with that obtained in 12 hours (entry 16).

The optimal reaction conditions were then applied to various substrates, as summarized in Scheme 2. Acrylamides reacted well with different propargyl alcohols. When the cyclopropyl group was placed at R^2, both electron-donating (Me and OMe) and electron-withdrawing (F, Cl, Br, I, CN, NO_2 and CF_3) substituents were compatible, with the isolated yields ranging from 39% to 75% (**3b–3k**). The structure of **3c** was confirmed by X-ray crystallographic analysis (CCDC number 2213771 for **3c**, see the ESI† for more details). In addition, alkynols containing cyclohexyl, *N*-Boc protected piperidyl, and a series of heteroaromatic rings such as thienyl, naphthyl and furyl rings also provided the corresponding products smoothly (**3m–3q**). It is also noteworthy that the corresponding products showed excellent results when using tertiary alcohols, especially toward those naphthenic groups whose yields even surpassed that of the template reaction (**3r–3u**). This suggested that the reaction could overcome the issue of steric effect. We next investigated phenyl, methyl and *n*-butyl at R^2 and the reactions also took place smoothly with yields of 42%, 78% and 31%, respectively (**3v–3x**). Besides, the structure of **3w** was also con-



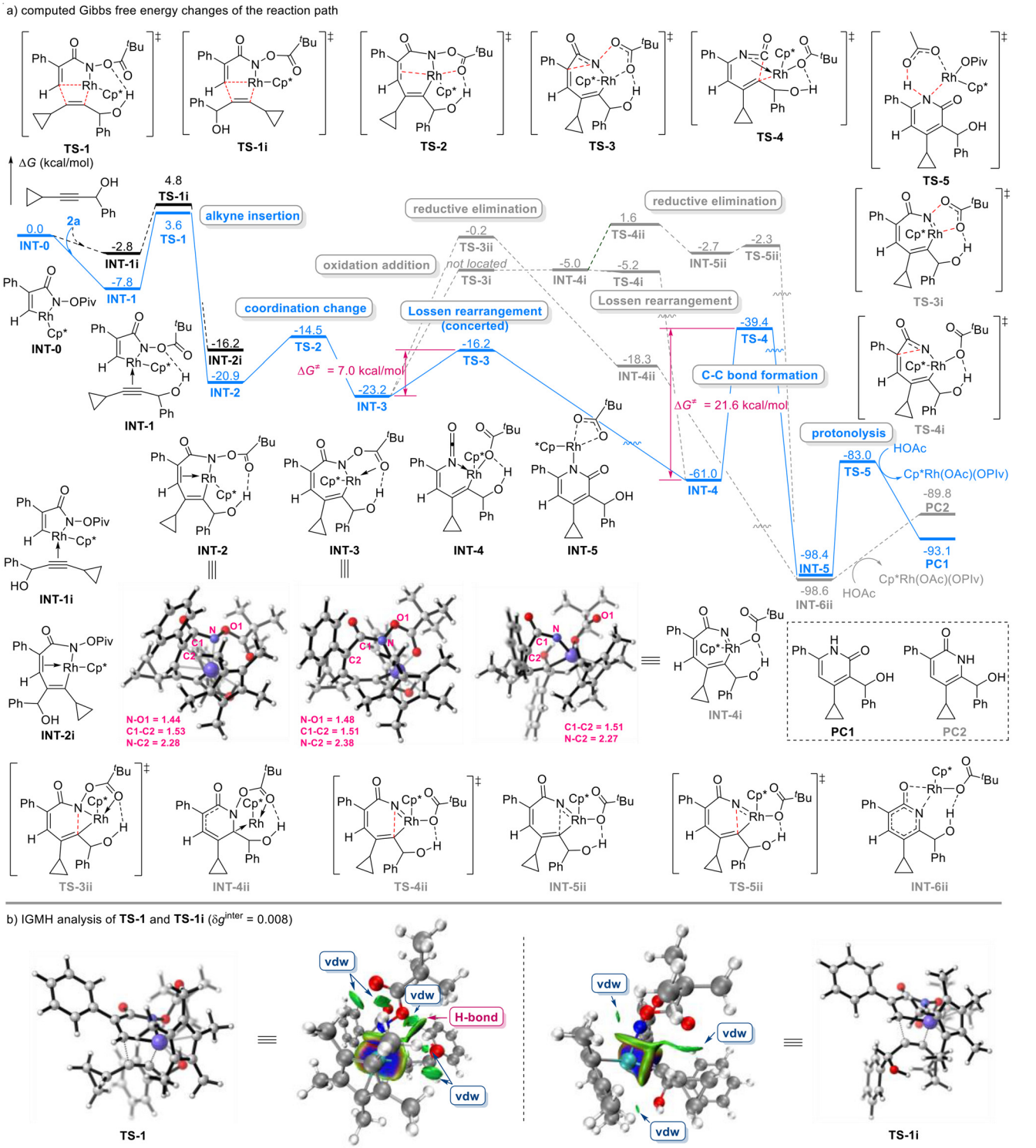
Scheme 3 Deuteration and KIE experiments.



Scheme 4 Scale-up preparation, control experiments, and recycling experiments.

firmed by X-ray crystallographic analysis (CCDC number 2234440 for **3w**, see the ESI† for more details). Subsequently, the introduction of other groups at R^1 was examined. Obviously, several substituents with different electron perturbations were tolerated and the yields were moderate (**3y–3zb**). In addition, it was difficult to obtain a few products (**3b**, **3j**, **3n**, **3w**, **3x**, and **3y**) just by simple filtration probably due to their good solubility in ethyl acetate.

To probe the reaction mechanism, deuterium labeling and KIE assays were carried out (Scheme 3). In the presence of **1a**,



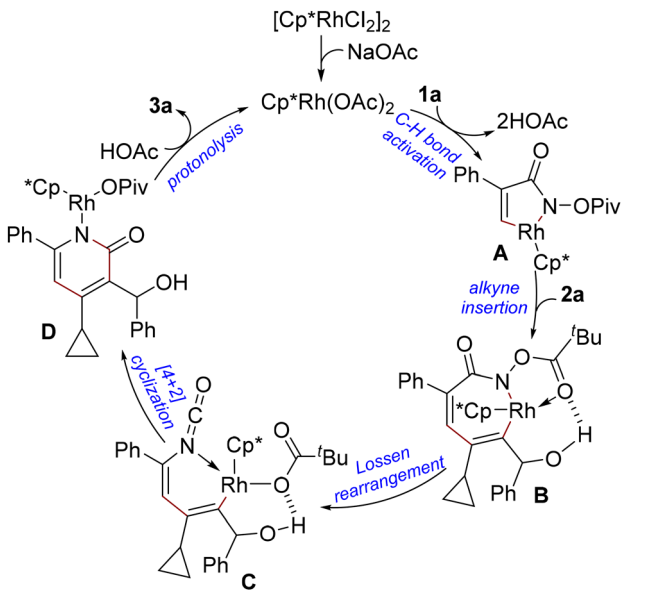
Scheme 5 DFT calculations.

NaOAc, $[Cp^*RhCl_2]_2$, and 1.0 mL methanol-d^4, about 10% deuterium incorporation occurred at the olefinic bond of acrylamide **1a**. The result indicated that the cleavage of the C(sp^2)–H bond could be reversible. Approximately 100% deuteration occurred at the hydroxyl group of **3a** when **2a** was added, and no obvious deuteration was observed at other positions. In addition, two parallel reactions were performed to give a KIE value of 1.12 (Scheme 3b), suggesting that the step of C–H activation was not the rate-determining step.

Besides, to explore the synthetic utility of the methodology, several scale-up experiments were performed with lower catalyst loading. As shown in Scheme 4a, product **3a** was obtained in an ideal isolated yield (57%) with 2.5 mol% rhodium catalyst. Then, when 1.0 mol% rhodium catalyst was used, the corresponding product **3a** was afforded in 60% yield, respectively. Inspired by these results, we further explored another substrate **2p**, and the reaction afforded product **3p** in 79% yield. To explore the effect of the hydroxyl group on propargyl alcohols in determining the regioselectivity, two control experiments were conducted (Scheme 4b). The hydroxyl group of **2a** was removed to prepare **2a-1** and **2a-2**. The annulation of **1a** and **2a-1** gave two rearrangement products **4a** and **4a′** at the same time with comparable yields. Similarly, the reaction between **1a** and 3-cyclopropyl-1-phenylprop-2-yn-1-one **2a-2** also afforded two regioisomers **5a** and **5a′** in low yields. The structures of these compounds were determined by using NOESY spectra. A relatively higher regioselectivity could be detected for **2a-2** in comparison with **2a-1**; we proposed that the observed regioselectivity might be due to the electron-withdrawing character of the carbonyl moiety. These results indicated that the hydroxyl group plays a vital role in controlling the regioselectivity. Significantly, the recycling experiments of the catalytic system were carried out four times with desirable isolated yields under the standard conditions (Scheme 4c).

Having established the Rh(III)-catalyzed sequential C–H activation/Lossen rearrangement/[4 + 2] annulation cascade of acrylamides with propargyl alcohols, we were next interested to clarify the deep origin of the unconventional regio-/chemoselectivity by detailed DFT calculations. As shown in Scheme 5a, the five-membered rhodacycle **INT-0** was rationally selected as the starting point, which coordinated with propargyl alcohol **2a** followed by a regioselective migratory alkyne insertion. The calculated results revealed that an additional hydrogen bond affinity between the hydroxyl group and the DG was involved in **TS-1** ($\Delta G^{\ddagger}$ = 3.6 kcal mol^{-1}) to give **INT-2** with a free energy of −25.2 kcal mol^{-1}, while a relatively higher energy barrier was involved in the converse regioselectivity *via* **TS-1i** ($\Delta G^{\ddagger}$ = 4.8 kcal mol^{-1}). Further IGMH analysis showed obvious hydrogen bond and van der Waals force interactions in **TS-1**, while only van der Waals force interaction was observed in **TS-1i** (Scheme 5b). Subsequent coordination change *via* **TS-2** ($\Delta G^{\ddagger}$ = −14.5 kcal mol^{-1}) afforded **INT-3**, from which different reaction paths were calculated. The concerted Lossen rearrangement/N–O bond cleavage from **INT-3** occurred *via* **TS-3** with an energy barrier of 7.0 kcal mol^{-1} (from **INT-3** to **TS-3**) to furnish the isocyanate intermediate **INT-4** with an obvious exothermic process. Alternatively, the classic C–N bond reductive elimination *via* **TS-3ii** ($\Delta G^{\ddagger}$ = −0.2 kcal mol^{-1}) involved a higher energy barrier of 23.0 kcal mol^{-1} (from **INT-3** to **TS-3ii**), which was in line with the experimental result that no 3-phenylpyridin-2(1*H*)-one framework was formed. Moreover, the Rh(III)–Rh(V)–Rh(III) reaction pathway involving an oxidative addition process from **INT-3** was also ruled out owing to the relatively higher free energies of **TS-4i/TS-4ii**. Taken together, the DFT calculations illustrated a hydrogen bond assisted regioselective alkyne insertion/Lossen rearrangement/intramolecular [4 + 2] cyclization reaction pathway for the developed protocol. In addition, further Mulliken atomic charge analysis of the key intermediates was also carried out to probe the origin of the observed preference for Lossen rearrangement rather than other reaction manifolds (see the ESI† for details). The results suggested that the C2 atom in **INT-3** occupied a relatively more positive charge in comparison with the similar benzamide substrate (0.0346 *vs.* 0.0216). Thus, it can be inferred that there was an inclination to undergo a nucleophilic attack from the N atom, ultimately leading to the Lossen rearrangement process.

On the basis of the above mechanistic studies and literature precedents, we proposed a plausible catalytic cycle for the developed transformation (Scheme 6). Initially, the active $Cp^*Rh(OAc)_2$ species was generated by anion ligand exchange in the presence of NaOAc, which coordinated with the acrylamide substrate and participated in the alkenylic C–H bond activation to afford intermediate **A**. Subsequent regioselective alkyne insertion led to the formation of intermediate **B**, in which the hydrogen bond affinity played a crucial role in determining the regioselectivity. Furthermore, the Lossen rearrangement process occurred smoothly to give the isocyanate intermediate **C**, which underwent an intramolecular [4 + 2] cyclization to deliver the 2-pyridone skeleton **D**. Finally, the protonolysis of **D** with the assistance of HOAc released the



Scheme 6 Proposed catalytic cycle.

desired product **3a** along with the regeneration of the Rh(III) catalyst.

Conclusions

In summary, a green and efficient rhodium(III)-catalyzed C–H activation/Lossen rearrangement of acrylamides and propargyl alcohols for the synthesis of novel 2-pyridone derivatives at ambient temperature was developed. This protocol features a reusable catalytic system, high regioselectivity, uncommon Lossen rearrangement, good functional group tolerance, metal oxidant-free process, operation at room temperature, simple purification by filtration in most cases, scale-up synthesis, and air compatibility. Additionally, deuterium labeling and KIE assays were performed to investigate the reaction mechanism. The vital effect of the hydroxyl group on propargyl alcohols in determining the regioselectivity was also demonstrated by control experiments and DFT calculations. In addition, Mulliken atomic charge analysis of the key intermediates was also carried out to probe the origin of the observed preference for Lossen rearrangement.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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