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Facile synthesis of amides *via* acceptorless dehydrogenative coupling of aryl epoxides and amines†

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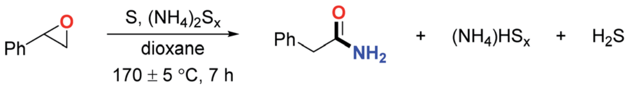
The synthesis of amides is significant in a wide variety of academic and industrial fields. We report here a new reaction, namely acceptorless dehydrogenative coupling of epoxides and amines to form amides catalyzed by ruthenium pincer complexes. Various aryl epoxides and amines smoothly convert into the desired amides in high yields with the generation of H_2 gas as the only byproduct. Control experiments indicate that amides are generated kinetically faster than side products, possibly because of the facile activation of epoxides by metal–ligand cooperation, as supported by the observation of a ruthenium-enolate species. No alcohol or free aldehyde are involved. A mechanism is proposed involving a dual role of the catalyst, which is responsible for the high yield and selectivity of the new reaction.

Introduction

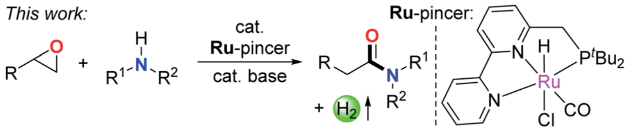
Amides are a very important class of compounds due to the wide presence of their structural units in peptides, natural products, pharmaceuticals, and polymers.[1] Hence, the efficient synthesis of amides is of great interest in organic synthesis. Traditionally, amides are synthesized *via* the condensation of carboxylic acids and their derivatives with amines using activation reagents.[2] To meet the requirement of environmentally friendly synthesis, various catalytic methods have been established in the past decades by employing various starting materials.[3,4] In this respect, epoxides are potentially attractive candidates toward the preparation of amides. As versatile and useful intermediates in organic synthesis, epoxides have been applied to the preparation of various functional molecules through straightforward and atom economical methods.[5–7] In that sense, discovery of direct, waste-free amidation of epoxides with amines can offer an attractive environmentally benign procedure for the synthesis of amides. In addition, since epoxides are generally accessed from alkenes *via* industrialized procedures and numerous other methods,[8,9] the amidation of epoxides also provides a two-step strategy for transforming alkenes into amides.[10] Nonetheless, to our knowledge, only one case of amidation of epoxides has been reported, based on the Willgerodt reaction which consumes large amounts of sulfur powder and ammonium and generates copious toxic waste (Scheme 1a).[11] The main challenges to successfully achieve the waste-free amidation of epoxides might include the following issues: (i) amines are strong nucleophiles that could lead to nucleophilic ring-opening of epoxides to generate amino alcohols as byproducts, counteracting the occurrence of the major reaction;[7] (ii) the highly reactive epoxide easily decomposes and thus results in side reactions;[5,6] (iii) and most importantly, regioselective ring-opening of epoxides is required for the amidation to take place. Therefore, developing a new strategy to overcome these challenges and efficiently realize the coupling of epoxides and amines is necessary.

Metal–ligand cooperation *via* dearomatization/aromatization is a useful tool for the activation of chemical bonds.[12] To our knowledge, the activation of epoxides in such a manner has not been realized so far. As a continuation of our research interest in pincer complex catalyzed dehydrogenative coupling reactions,[4b,f,13] we herein report the ruthenium pincer complex catalyzed acceptorless dehydrogenative coupling of epoxides and amines to form amides (Scheme 1b). The epoxides were found to efficiently convert into amide products with generally excellent yields in a single step with the generation of

(a) The only case for direct amidation of epoxide (Willgerodt reaction)



(b) Ruthenium pincer complex catalyzed coupling of epoxides and amines



Scheme 1 Synthesis of amides from epoxides.

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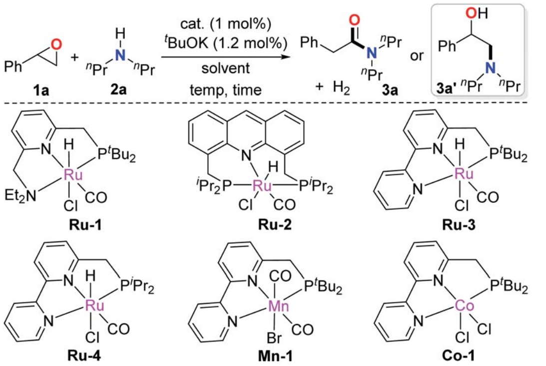
H_2 gas as the only byproduct. Side reactions were efficiently suppressed by utilizing the bipyridine- and pyridine-based PNN ruthenium complexes as catalysts. The high regioselectivity of the ring-opening of epoxides was guaranteed by the unique activation pattern by the metal complex, which results in a Ru-enolate intermediate. This amidation reaction of epoxides offers a facile and atom economical two-step strategy for transforming alkenes into amides.

Results and discussion

Amidation of epoxides

We initiated the investigation using the pyridine-based ruthenium complex **Ru-1** as the catalyst with a catalytic amount of ^{t}BuOK. The combination of **Ru-1** and base results in a dearomatized complex (**Ru-7**, *vide infra*), which was reported as the catalytically active species in the acceptorless dehydrogenative coupling of alcohols with amines to yield amides.[4b] 2-phenyloxirane (**1a**) and secondary amine **2a** were chosen as the model substrates, the latter was chosen in order to avoid potential side reactions due to possible dehydrogenation under the reaction conditions (Table 1).[4h] Upon heating at 120 °C in toluene for 12 h, low conversion of the epoxide was observed, with no desired amide formed (entry 1). Only 3% of the amino alcohol byproduct **3a′** was detected. **3a′** is likely generated by direct nucleophilic ring-opening of the epoxide with amine **2a**. Next, we screened other pincer complexes. The acridine-based **Ru-2** did not give the desired product either but produced more byproduct **3a′** than **Ru-1** (entry 2). Interestingly, a higher conversion of **1a** was observed, and 42% of amide product **3a** was formed using **Ru-3** as the catalyst (entry 3). The result prompted us to adjust the steric hindrance of the complex to improve the reaction yield further; however using the smaller ^{i}Pr$_2$P substituted ligand instead of ^{t}Bu$_2$P was less effective (entry 4). Other metal complexes based on the bipyridine PNN structure were also tested. For example, using Mn and Co complexes as catalysts, only byproduct **3a′** was formed (entries 5 and 6). An improved yield of **3a** using **Ru-3** was obtained upon increasing the reaction temperature to 135 °C (entry 7). Gratifyingly, further temperature increase to 150 °C resulted in 91% yield of product and the amount of byproduct **3a′** kept low (entry 8). As reported,[5c] Lewis acids can assist the isomerization of epoxide to aldehydes, which might lead to further amidation of the aldehyde in the current case. Therefore, the Lewis acids $Zn(OTf)_2$ and $BF_3 \cdot Et_2O$ were added as cocatalysts to the reaction to accelerate the isomerization step. However, only byproduct **3a′** was formed (entries 9 and 10). Next, the effect of solvent was explored as well. Solvents with different boiling points and polarities including xylene, chlorobenzene, benzene, dioxane, and DMF did not give higher yields of **3a** (entries 11–15). It should be mentioned that the amide was not produced without a catalytic amount of base, (entry 16). Prolonging the reaction time to 24 h or 36 h did not improve the yield (entries 17 and 18).

Table 1 Optimization of reaction conditions[a]

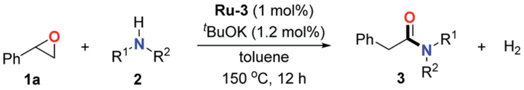


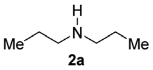
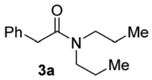
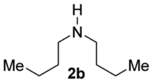
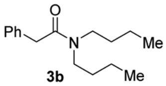
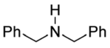
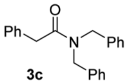
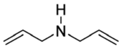
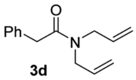
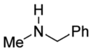
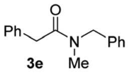
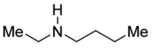
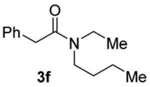
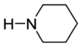
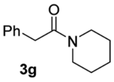
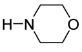
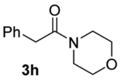
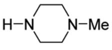
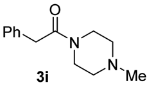
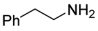
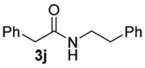
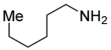
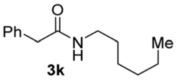
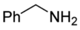
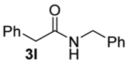
Entry	Cat	Solvent	Temp (°C)	Time (h)	Yield (%)[b] 3a/3a′
1	**Ru-1**	Toluene	120	12	nd/3
2	**Ru-2**	Toluene	120	12	nd/6
3	**Ru-3**	Toluene	120	12	42/3
4	**Ru-4**	Toluene	120	12	30/5
5	**Mn-1**	Toluene	120	12	nd/86
6[c]	**Co-1**	Toluene	120	12	nd/72
7	**Ru-3**	Toluene	135	12	61/4
8	**Ru-3**	Toluene	150	12	91/4
9[d]	**Ru-3**	Toluene	150	12	nd/96
10[e]	**Ru-3**	Toluene	150	12	nd/77
11	**Ru-3**	Xylene	150	12	81/4
12	**Ru-3**	PhCl	150	12	12/15
13	**Ru-3**	Benzene	150	12	52/11
14	**Ru-3**	Dioxane	150	12	83/8
15	**Ru-3**	DMF	150	12	nd/12
16[f]	**Ru-3**	Toluene	150	12	nd/3
17	**Ru-3**	Toluene	150	24	91/4
18	**Ru-3**	Toluene	150	36	91/4

[a] Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), cat. (1 mol%), ^{t}BuOK (1.2 mol%), solvent (1 mL). [b] NMR yield using mesitylene as the internal standard. [c] 1 mol% of $NaBEt_3H$ was added. [d] With 1 mol% $Zn(OTf)_2$. [e] With 1 mol% $BF_3 \cdot Et_2O$. [f] Without ^{t}BuOK.

With the optimal conditions in hand, the scope of amine substrates was firstly evaluated (Table 2). Secondary amines with different chain lengths gave the desired amides with excellent isolated yields (**3a–3b**, 91–95%). Steric hindrance of the employed amines has an impact on the reaction yield. For example, in the case of the dibenzyl substituted amine **2c** (entry 3), amide **3c** was generated in less than 50% yield under the optimal conditions. Nevertheless, using an open system with the release of the generated H_2, 84% of isolated yield was obtained after extending the reaction time to 48 h (entry 3). In addition, the amidation reaction can proceed with an amine bearing C═C bonds, generating the targeted amide product (**3d**) in 62% yield. Notably, the C═C double bond on the amide product provides good opportunities for its further functionalization. Asides from symmetric secondary amines, other secondary amines such as *N*-methylbenzylamine (**2e**) and ethylbutylamine (**2f**) also worked well to give the corresponding products under the optimal conditions (**3e–3f**). In addition, cyclic secondary amines **2g–2i** were also evaluated, the reaction yields being just slightly affected (71–83%).

Table 2 Amidation of epoxides with different amines[a]



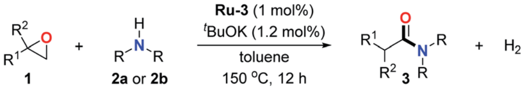
Entry	Amine	Product	Isolated yield (%)
1	 **2a**	 **3a**	91
2	 **2b**	 **3b**	95
3[b]	 **2c**	 **3c**	84
4	 **2d**	 **3d**	62
5	 **2e**	 **3e**	78
6	 **2f**	 **3f**	95
7	 **2g**	 **3g**	71
8	 **2h**	 **3h**	80
9	 **2i**	 **3i**	83
10[c]	 **2j**	 **3j**	66
11[c]	 **2k**	 **3k**	44
12[c]	 **2l**	 **3l**	51

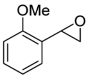
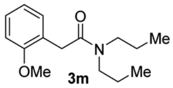
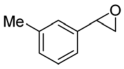
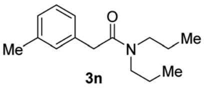
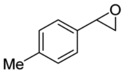
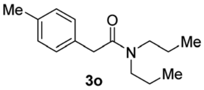
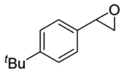
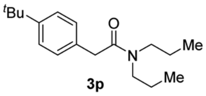
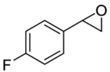
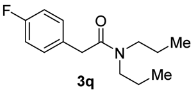
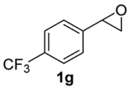
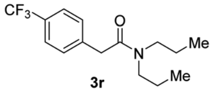
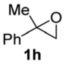
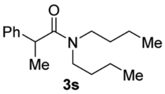
[a] Conditions: **1a** (0.5 mmol), **2** (0.5 mmol), **Ru-3** (1 mol%), ᵗBuOK (1.2 mol%), toluene (1 mL), 150 °C, 12 h. [b] Reaction time is 48 h with mesitylene as solvent in an open system. [c] **Ru-1** (1 mol%) was used as catalyst instead of **Ru-3**.

To further extend the scope of amines, we turned our attention to examining primary amines. However, when 2-phenylethylamine **2j** was used, diphenethylamine was formed as the major product. Mechanistically speaking, this result could be attributed to the easy dehydration of the hemiaminal intermediate that led to the formation of imine, which subsequently underwent hydrogenation to produce the secondary amine under the current system. To access the desired amide product from primary amines, further optimization was carried out (see Table S2†). Interestingly, using **Ru-1** as a catalyst, the reaction of epoxide **1a** and amine **2j** resulted in formation of amide **3j** in 66% isolated yield under the optimal conditions, but the formation of the secondary amine and amino alcohol was inevitable in this case. The conditions were also suitable for other primary amines. Hexylamine **2k** gave the amide product, although in only 44% isolated yield, presumably because of its relatively low boiling point. Benzylamine **2l** transformed into the corresponding amide with medium isolated yield (51%). These results indicate the compatibility of this method for both secondary and primary amines.

Next, the scope of epoxides was explored under the standard conditions (Table 3). The steric hindrance of the aryl-substituted epoxide had no impact on the reaction yield. For example, *ortho*-substituted epoxide **1b** smoothly produced the desired amide **3m** in 89% yield. As expected, *meta*-methyl substituted epoxide **1c** gave an excellent result (**3n**, 92%). When a variety of epoxides bearing functional groups, *i.e.*, Me-, ᵗBu-, F-, and CF_3 at the *para*-position of the phenyl ring were utilized,

Table 3 Amidation of different epoxides[a]



Entry	Epoxide	Product	Isolated yield (%)
1	 **1b**	 **3m**	89
2	 **1c**	 **3n**	92
3	 **1d**	 **3o**	90
4	 **1e**	 **3p**	83
5	 **1f**	 **3q**	80
6	 **1g**	 **3r**	85
7[b]	 **1h**	 **3s**	65

[a] Conditions: **1a** (0.5 mmol), **2a** or **2b** (0.5 mmol), **Ru-3** (1 mol%), ᵗBuOK (1.2 mol%), toluene (1 mL), 150 °C, 12 h. [b] Use of open system operation with mesitylene as solvent.

the reactions gave the corresponding products with high yields (**3o–3r**, 80–90%). The electron density of the epoxides slightly affected the yield of the reaction. Electron-rich epoxides (**1b–1d**) gave higher yields compared to the electron-deficient epoxides (**1f–1g**). To our surprise, 1,1-disubstituted epoxide **1h** also generated the desired amide with good yield (**3s**, 65%) when mesitylene was used as solvent in an open system. It is worth mentioning that amides bearing a tertiary carbon stereogenic center on the α-position are important in many areas.[1] Unfortunately, use of aliphatic epoxides resulted in low conversion and only provided a trace amount of product under the reaction conditions.

Mechanistic investigation

To gain insight into the mechanism of the amidation reaction, control experiments were conducted. As demonstrated in Table 1, epoxide **1a** can undergo nucleophilic ring-opening with amine **2a** to produce the amino alcohol byproduct **3a′**. According to previous works, **3a′** can be formed spontaneously without catalyst.[7a,c] Therefore, when epoxide **1a** was treated with amine **2a** at 150 °C with toluene as solvent, 51% yield of **3a′** was obtained after heating for 20 h (Fig. 1a, top). **3a′** was proved unable to transform into the corresponding amide under the standard reaction conditions, indicating that **3a′** is not an intermediate toward formation of amide **3a**. Meanwhile, ester **4** was observed under the catalysis of **Ru-3** and ^{t}BuOK using the epoxide in the absence of amine (Fig. 1a, bottom, 14% yield after 20 h). As reported, esters can convert into amides with **Ru-3** and ^{t}BuOK as catalysts under refluxing conditions, according to our previous results.[4f] However, only a trace amount of **3a** was observed when ester **4** was subjected to the current conditions in a closed system (Fig. 1a, bottom). The results suggest that ester **4** is not an intermediate toward amide formation in this reaction either.

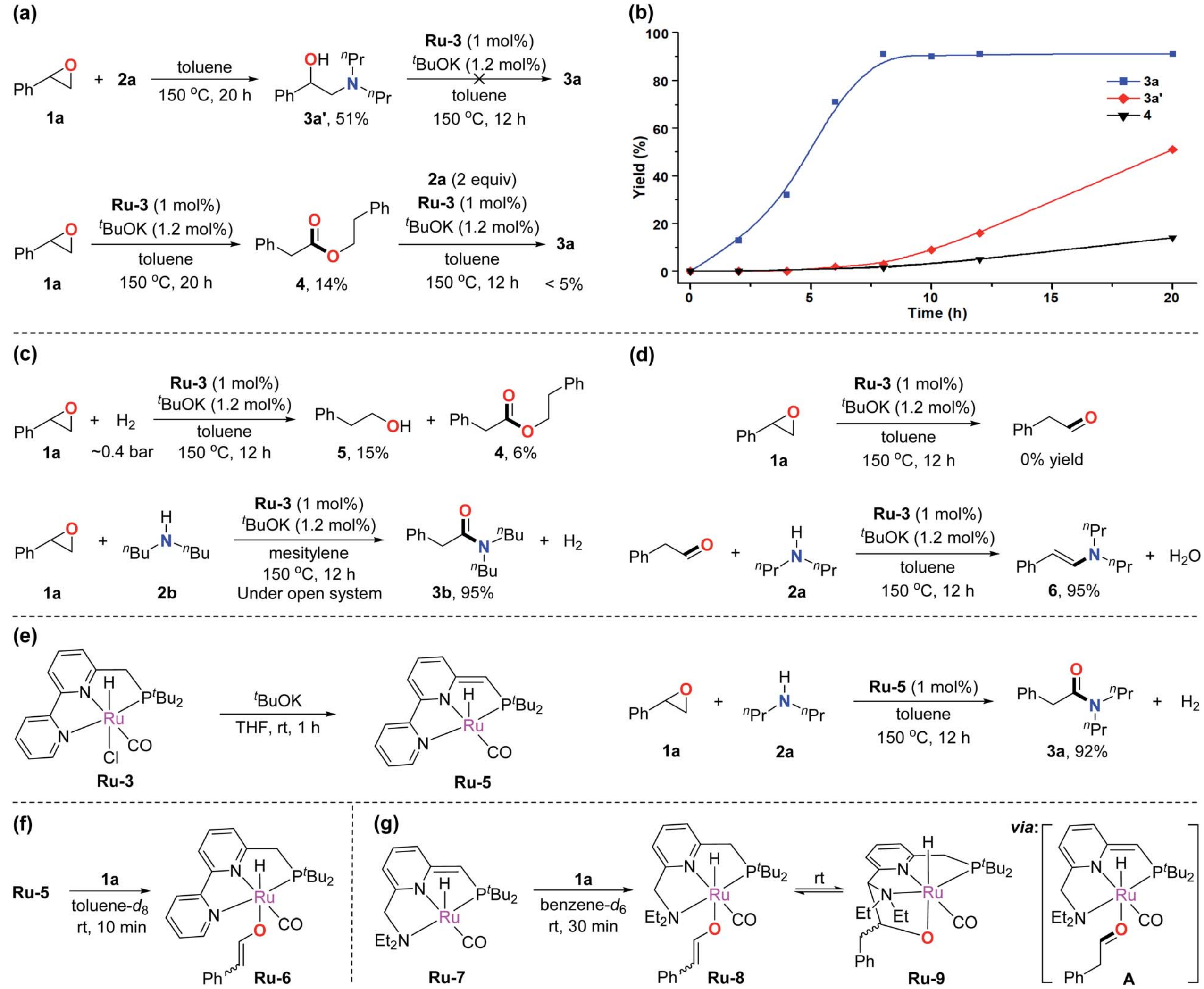


Fig. 1 Mechanistic aspects of the reaction. (a) Investigation of the generation of byproducts **3a′** and **4**, and the possibility of converting into **3a**. (b) The correlation between reaction time and yields of **3a** (standard conditions), **3a′** (without catalyst), and **4** (without amine). (c) Control experiments for excluding the participation of H_2. (d) Control experiments for excluding the generation of free aldehyde. (e) The active catalytic species of amidation reaction. (f) Formation of Ru-enolate intermediates **Ru-6** in the reaction. (g) Formation of **Ru-8** and its reversible conversion into **Ru-9**.

These observations led us to investigate why **3** could be generated as the major products rather than amino alcohols or esters under the developed reaction. The rate of formation of **3a**, **3a′**, and **4** was compared, and the results are exhibited in Fig. 1b. It was found that the formation of amide **3a** was relatively rapid under the standard conditions, and the reaction was finished in about 8 to 10 h (blue curve). In contrast, the formation of amino alcohol **3a′** in the absence of catalyst, and the formation of ester **4** in the absence of amine were both slower than the formation of amide **3a** at the same temperature (red and black curves). Thus, almost all of the epoxides would quickly convert into amides in the actual catalysis.

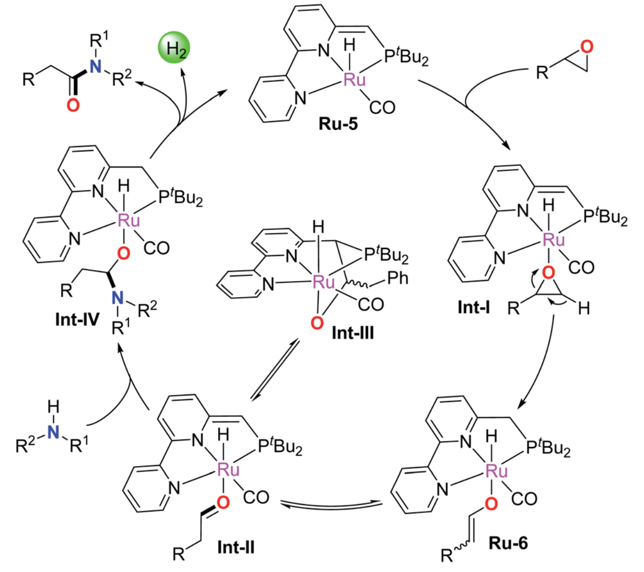
In a closed system, epoxides can potentially undergo hydrogenation by the generated H_2 in the current reaction to produce primary alcohols,[6g,h] which could further couple with amines to generate amides catalyzed by the employed ruthenium pincer complexes.[4b,14] To explore this possibility, epoxide **1a** was treated with ~0.4 bar of H_2 (in a 90 mL Fischer–Porter tube, relevant to the amount of generated H_2 in the amidation reaction) at 150 °C, forming only 15% of primary alcohol **5** along with 6% of ester **4** under similar conditions (Fig. 1c, top). This result suggests that the hydrogen gas generated by the amidation reaction was inefficient in converting the epoxide into primary alcohol. Moreover, the amidation reaction was carried out in an open system to further exclude the effect of the generated hydrogen gas. Considering the boiling points of the employed components, mesitylene and dibutylamine were selected as the solvent and amine, respectively. It was found that the amide product was formed in the same yield as that in the closed system (Fig. 1c, bottom). This result proves that H_2 is not involved in the catalytic cycle. Thus, an alcohol does not serve as an intermediate in this transformation.

The Meinwald rearrangement of epoxides is a well-known procedure for converting epoxides into aldehydes,[6e,15] hence the possibility of an aldehyde intermediate in amide formation under the current catalytic system should be considered. The ruthenium pincer complex **Ru-3** may also act as a Lewis acid catalyst to facilitate the rearrangement of epoxide **1a** to phenylacetaldehyde. However, no aldehyde product was observed when **1a** was subjected to the standard conditions in the absence of amine (Fig. 1d, top). Besides, when phenylacetaldehyde was employed as an alternative substrate under the standard conditions, enamine **6** was generated as the major product (Fig. 1d, bottom). These results suggest that no free aldehyde is produced in this reaction.

Next, we turned our attention to investigating the actual ruthenium catalytic species in the developed reaction. According to our previous studies,[16] **Ru-3** undergoes dearomatization upon treatment with base to produce the dearomatized complex **Ru-5** as the catalytically active species (Fig. 1e, left). Indeed, utilizing the independently prepared **Ru-5** as the catalyst in the amidation reaction, the desired amide **3a** was obtained in 92% yield under similar conditions (Fig. 1e, right). Interestingly, mixing of **Ru-5** and epoxide **1a** in a 1 : 3 ratio at room temperature led to the formation of new complexes, which were identified by ^{31}P NMR and ^{1}H NMR as two isomers of **Ru-6** in a 1 : 2 ratio with an enolate (Z and E isomers) coordinated to the aromatic ruthenium complex (Fig. 1f). The ^{31}P NMR spectrum exhibits two new peaks at 105.2 and 104.7 ppm in a 2 : 1 ratio; the chemical shifts of the signals indicate the formation of aromatized complexes. In the ^{1}H NMR spectrum, two characteristic doublets corresponding to the alkene were observed at 7.74 and 4.79 ppm. H–H COSY spectrum confirms their correlations ($J = 5.1$ Hz) (see ESI page S17† for more characterization data). The formation of **Ru-6** presumably stems from ring-opening of the epoxide followed by proton transfer to the side arm of **Ru-5**. We believe that generation of the relatively stable vinylbenzene enolate intermediate is an important driving force for the activation of the epoxide. Such evidence can also explain why the aliphatic epoxides were less effective in the amidation reaction.

To further determine the formation of Ru-enolate intermediate, we turned our attention to the dearomatized **Ru-7**, obtained from **Ru-1** by treatment of base.[13a] As mentioned above, **Ru-1** catalyzed the current amidation reaction when primary amines were utilized. Mixing of **Ru-7** and epoxide **1a** in a 1 : 1 ratio, a Ru-enolate species **Ru-8** was also observed in a 1 : 3 ratio of its isomers (Fig. 1g). In the ^{1}H NMR spectrum, two doublets corresponding to the enolate were observed at 8.07 and 5.34 ppm. The proton chemical shift of the methyne group (CH) connected to the ORu appears at the low field (8.07 ppm), in the range characteristic of corresponding enol ethers. The correlation of these two signals was observed in the H–H COSY spectrum. The DEPTQ spectrum further confirms their adjacent carbons belong to sp^2 CH units (see ESI† for more characterization). All these evidences are similar to the observation in **Ru-6**, thus confirming the formation of Ru-enolate intermediate. In addition, **Ru-8** slowly converted into another new complex reaching a chemical equilibrium. The ^{1}H NMR of the solution showed four different Ru-H signals due to the existence of isomers in both complexes (see Fig. S16†). We propose that the enolate on **Ru-8** isomerizes to an aldehyde intermediate **A**, *via* a keto–enol equilibrium, which rapidly converted to **Ru-9** *via* electrophilic attack of the aldehyde on the side arm of intermediate **A**. Aldehyde attack on the side arm of **Ru-7** analogous to the generation of **Ru-9** was previously reported.[17] The chemical shifts of phosphine and Ru-H in the NMR spectra match the previously reported works, which further confirm our assumption.

Based on the above results and previous studies,[4b,f,13,16] a plausible reaction pathway is depicted in Scheme 2. The epoxide is firstly activated by catalyst **Ru-5** to form the active adduct intermediate **Int-I**, which subsequently undergoes ring-opening and β-H extraction of the epoxide by metal–ligand cooperation to afford the enolate intermediate **Ru-6** with high regioselectivity. **Ru-6** reversibly converts into the Ru-aldehyde adduct **Int-II**, which transforms into the off-cycle intermediate **Int-III** in the absence of amines. Notably, free aldehyde was not generated at this stage, avoiding the formation of the enamine byproduct. In addition, the epoxide activation process *via* metal–ligand cooperation is distinct from the Lewis acid activated Meinwald rearrangement. Next, the nucleophilic amine attacks the bound aldehyde in **Int-II** to yield the hemiaminal intermediate **Int-IV**, which further undergoes β-H elimination



Scheme 2 Proposed mechanism.

to release the amide product and a molecule of H_2, regenerating the active catalyst **Ru-5** to enter the second catalytic cycle. Clearly, the mechanism demonstrates that **Ru-5** plays a dual role in the current reaction. On the one hand, it facilitates epoxide activation to produce the Ru-enolate complex, which rapidly and reversibly transforms into the aldehyde intermediate **Int-II**; on the other hand, **Ru-5** catalyzes the well-known dehydrogenative process *via* metal–ligand cooperation, namely amidation of intermediate aldehydes with amines.

Conclusion

In conclusion, we have developed a novel strategy for the synthesis of amides based on ruthenium pincer complex catalyzed acceptorless dehydrogenative coupling of terminal aryl epoxides and amines. The reaction yields are generally high. Various functional groups are tolerated under the reaction conditions. Control experiments demonstrate that the epoxide is activated by the ruthenium pincer complex through metal–ligand cooperation, leading to an observed Ru-enolate intermediate formed by reaction of the dearomatized ruthenium complex with the epoxide. Noteworthy, no alcohol or free aldehyde are involved in this reaction. The ruthenium pincer complex plays a dual role in the whole transformation. Notably, the reaction provides an environmentally friendly and convenient two-step procedure for transforming alkenes into amides. Further studies about the transformation of epoxides are underway in our laboratory.

Author contributions

D. M. and Y. L. conceived the project and designed the experiments. Y. L. performed the experiments and analyzed the data. J. L. synthesized part of catalysts and provided helpful discussions on the project. Y. L., J. L., and D. M. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental details, compound characterization data, NMR spectra.

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