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

Yaoyu Liang, Jie Luo, David Milstein*

Department of Molecular Chemistry and Materials Science, Weizmann Institute of Science, Rehovot, 76100, Israel

E-mail: david.milstein@weizmann.ac.il

Table of Contents

1. General considerations ................................................................. 1

2. Conditions evaluation .................................................................. 2

3. General procedures for amidation reaction and characterization data of amides .................................. 3

4. Mechanistic studies ..................................................................... 11

5. References .................................................................................. 26

6. NMR spectra of amides ................................................................. 28
1. General considerations

All the catalytic experiments were carried out under an atmosphere of purified nitrogen in a Vacuum Atmosphere glovebox equipped with a MO 40-2 inert gas purifier or using standard Schlenk techniques. Toluene, benzene, dioxane, and tetrahydrofuran (THF) were refluxed over sodium/benzophenone, distilled under argon or nitrogen atmosphere, and stored over activated 3Å molecular sieves (MS). Other solvents were used after degassing with nitrogen. Deuterated benzene was degassed with nitrogen and stored in the glovebox over 3Å MS. NMR spectra were recorded on Bruker AVANCE III (300 MHz) or AVANCE III HD (500 MHz) spectrometers and are reported in ppm (δ). 1H NMR spectra are referred to the TMS signal (δ = 0 ppm) or CHCl₃ (δ = 7.26 ppm), and 13C NMR spectra are referred to the residual solvent signal (δ = 77.16 ppm). 31P{1H} NMR chemical shifts are referenced with respect to an external solution of 85% phosphoric acid in D₂O. NMR spectroscopy abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. GC-MS analyses were carried out on HP 6890/5973 (MS detector) instruments equipped with a 30 m column (Restek 5MS, 0.32 mm internal diameter) with a 5% phenylmethylsilicone coating (0.25 mm) with He as carrier gas.

Analytical TLC was performed on Merck silica gel 60 F254 plates and visualized under 254 nm UV light. Column chromatography was performed on 200-300 mesh silica gel. Complexes Ru-1, Ru-2, Ru-3, Ru-4, Mn-1, and Co-1 were prepared according to the literature procedures. Epoxide 1a and 1f were commercially available and used after purifying by flash silica gel column chromatography, and other epoxides were prepared according to the literature procedures. All the amines were commercially available and used after degassing with nitrogen and stored in the glovebox over 3Å MS.
2. Conditions evaluation

Table S1. Conditions evaluation for amidation of epoxide 1a and amine 2a

| entry | cat.   | solvent | temp (°C) | time (h) | yield (%) | 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     |           |
| 6c    | Co-1   | toluene | 120       | 12       | nd/72     |           |
| 7     | Ru-3   | toluene | 135       | 12       | 61/4      |           |
| 8     | Ru-3   | toluene | 150       | 12       | 91/4      |           |
| 9d    | Ru-3   | toluene | 150       | 12       | nd/96     |           |
| 10e   | Ru-3   | toluene | 150       | 12       | nd/77     |           |
| 11    | Ru-3   | toluene | 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     |           |
| 16f   | Ru-3   | toluene | 150       | 12       | nd/3      |           |
| 17    | Ru-3   | toluene | 150       | 24       | 91/4      |           |
| 18    | Ru-3   | toluene | 150       | 36       | 91/4      |           |

*Conditions: 1a (0.5 mmol), 2a (0.5 mmol), cat. (1 mol%), 'BuOK (1.2 mol%), solvent (1 mL).

bNMR yield using mesitylene as the internal standard. c1 mol% NaBEt3H was added. dWith 1 mol% Zn(OTf)2. eWith 1 mol% BF3·Et2O. fWithout 'BuOK. nd = not detected.
Table S2. Conditions evaluation for amidation of epoxide 1a and amine 2j

| entry | cat. | solvent     | temp (°C) | time (h) | yield (%)<sup>b</sup> |
|-------|------|-------------|-----------|----------|------------------------|
| 1     | Ru-3 | toluene     | 150       | 12       | nd                     |
| 2     | Ru-1 | toluene     | 150       | 12       | 71 (66)                |
| 3     | Ru-2 | toluene     | 150       | 12       | nd                     |
| 4     | Ru-10| toluene     | 150       | 12       | nd                     |
| 5     | Ru-11| toluene     | 150       | 12       | <5                     |
| 6     | Ru-12| toluene     | 150       | 12       | nd                     |
| 7     | Ru-1 | mesitylene  | 150       | 12       | 67                     |
| 8<sup>c</sup> | Ru-1 | mesitylene  | 150       | 12       | 55                     |
| 9     | Ru-1 | toluene     | 135       | 12       | 42                     |
| 10    | Ru-1 | toluene     | 150       | 36       | 71                     |

<sup>a</sup>Conditions: 1a (0.5 mmol), 2j (0.5 mmol), cat. (1 mol%), 1 BuOK (1.2 mol%), solvent (1 mL).

<sup>b</sup>NMR yield using mesitylene or benzyl benzoate as the internal standard, isolated yields in parentheses. <sup>c</sup>Under open system. nd = not detected.

3. General procedures for the amidation reaction and characterization data of amide products

In a N₂ glovebox, Ru-3 (2.4 mg, 0.005 mmol), 1 BuOK (0.7 mg, 0.006 mmol), and toluene (1 mL) were added into the Schlenk flask. The mixture was stirred at room temperature for 20 min. Epoxides (0.5 mmol) and amines (0.5 mmol) were added into the flask in succession. The flask was sealed and taken out of the glovebox, and the resulting mixture was heated at 150 °C. After heating for 12 h, the reaction was cooled
to room temperature. 0.5 M HCl (5 mL) was added to the flask and the mixture was extracted with CH$_2$Cl$_2$ three times. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using a short flash silica gel column to yield the corresponding amide.

![Chemical Structure](attachment:structure.png)

**2-Phenyl-N,N-dipropylacetamide (3a).** Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3a as a colorless oil (91% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.34 – 7.03 (m, 5H), 3.62 (s, 2H), 3.21 (t, $J = 7.7$ Hz, 2H), 3.10 (t, $J = 7.7$ Hz, 2H), 1.57 – 1.35 (m, 4H), 0.79 (t, $J = 7.4$ Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.69, 135.65, 128.76, 128.65, 126.71, 49.99, 47.59, 41.04, 22.26, 20.88, 11.47, 11.27. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.$^8$

![Chemical Structure](attachment:structure.png)

**N,N-Dibutyl-2-phenylacetamide (3b).** Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3b as a colorless oil (95% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33 – 7.12 (m, 5H), 3.62 (s, 2H), 3.24 (t, $J = 7.8$ Hz, 2H), 3.13 (t, $J = 7.8$ Hz, 2H), 1.51 – 1.31 (m, 4H), 1.29 – 1.11 (m, 4H), 0.84 (t, $J = 7.4$, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.58, 135.70, 128.80, 128.70, 126.74, 48.18, 45.81, 41.11, 31.22, 29.83, 20.36, 20.19, 13.99, 13.93. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.$^9$

![Chemical Structure](attachment:structure.png)
N,N-Dibenzyl-2-phenylacetamide (3c). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3c as a colorless oil (84% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31 – 7.14 (m, 11H), 7.13 – 7.07 (m, 2H), 7.01 (d, $J$ = 6.9 Hz, 2H), 4.53 (s, 2H), 4.34 (s, 2H), 3.71 (s, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.74, 137.32, 136.43, 135.05, 129.06, 128.90, 128.80, 128.66, 128.39, 127.76, 127.50, 126.99, 126.51, 50.26, 48.30, 41.06. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.

N,N-Diallyl-2-phenylacetamide (3d). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3d as a colorless oil (62% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.27 – 7.06 (m, 5H), 5.78 – 5.46 (m, 2H), 5.15 – 4.90 (m, 4H), 3.90 (d, $J$ = 5.8 Hz, 2H), 3.75 (d, $J$ = 4.6 Hz, 2H), 3.60 (s, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.80, 135.02, 132.96, 132.72, 128.62, 128.48, 126.61, 117.12, 116.62, 49.26, 47.69, 40.56. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.

N-Benzyl-N-methyl-2-phenylacetamide (3e). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3e as a colorless oil (78% yield). $^1$H NMR (300 MHz, CDCl$_3$), the major isomer: δ 7.40 – 6.91 (m, 10H), 4.54 (s, 2H), 3.72 (s, 2H), 2.83 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$), a mixture of two isomers: δ 171.66, 171.32, 137.36, 136.55, 135.19, 135.03, 129.04, 128.94, 128.82, 128.69, 128.18, 127.78, 127.49, 126.93, 126.50, 53.76, 51.10, 41.29, 40.95, 35.34, 34.16. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.
**N-Butyl-Nethyl-2-phenylacetamide (3f).** Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3f as a colorless oil (95% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.35 – 7.09 (m, 5H), 3.63 (s, 2H), 3.32 (q, \(J = 7.2\) Hz, 1H), 3.27 – 3.18 (m, 2H), 3.16 – 3.08 (m, 1H), 1.50 – 1.30 (m, 2H), 1.28 – 1.12 (m, 3H), 1.03 (q, \(J = 7.2\) Hz, 3H), 0.84 (td, \(J = 7.2, 3.4\) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 170.46, 170.40, 135.64, 129.15, 128.81, 128.75, 128.71, 128.48, 126.75, 47.86, 45.30, 42.78, 41.11, 40.99, 40.76, 31.26, 29.92, 20.36, 14.24, 13.99, 13.94, 12.94. GC-MS m/z calcd. for C\(_{14}\)H\(_{21}\)N\(_2\)O: 219.2, found: 219.1.

2-Phenyl-1-(piperidin-1-yl)ethan-1-one (3g). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3g as a colorless oil (71% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.34 – 7.07 (m, 5H), 3.65 (s, 2H), 3.48 (t, \(J = 7.8\) Hz, 2H), 3.28 (t, \(J = 7.8\) Hz, 2H), 1.57 – 1.34 (m, 4H), 1.36 – 1.16 (m, 2H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 169.21, 135.39, 128.61, 128.54, 126.59, 47.22, 42.83, 41.11, 26.12, 25.46, 24.38. The \(^1\)H NMR and \(^{13}\)C NMR characterization data matched the literature data.\(^8\)

1-Morpholino-2-phenylethan-1-one (3h). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 5:1 v/v) to afford 3h as a colorless oil (80% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.28 – 7.21 (m, 2H), 7.16 (t, \(J = 6.1\) Hz, 3H), 3.65 (s, 2H), 3.55 (s, 4H), 3.44 – 3.29 (m, 4H). \(^{13}\)C NMR (75
MHz, CDCl$_3$  δ 169.58, 134.77, 128.76, 128.50, 126.86, 66.73, 66.40, 46.46, 42.09, 40.78. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.$^8$

1-(4-Methylpiperazin-1-yl)-2-phenylethan-1-one (3i). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 3:1 v/v) to afford 3i as a colorless oil (83% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.25 – 7.17 (m, 2H), 7.16 – 7.09 (m, 3H), 3.62 (s, 2H), 3.55 (t, $J = 5.1$ Hz, 2H), 3.34 (t, $J = 5.1$ Hz, 2H), 2.23 (t, $J = 5.1$ Hz, 2H), 2.13 (s, 3H), 2.09 (t, $J = 5.1$ Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.11, 134.81, 129.59, 129.15, 128.82, 128.71, 127.47, 126.56, 44.00, 40.81, 35.59. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.$^{12}$

$N$-Phenethyl-2-phenylacetamide (3j). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3j as a colorless oil (66% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.36 – 7.13 (m, 8H), 7.05 – 6.97 (m, 2H), 5.38 (s, 1H), 3.53 (s, 2H), 3.46 (dd, $J = 12.9, 6.8$ Hz, 2H), 2.72 (t, $J = 6.8$ Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.05, 134.87, 129.59, 129.15, 128.82, 128.71, 127.47, 126.56, 44.00, 40.81, 35.59. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.$^{13}$

$N$-Hexyl-2-phenylacetamide (3k). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3k as a
colorless oil (44% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.26 – 7.21 (m, 2H), 7.17 (t, $J$ = 6.7 Hz, 3H), 6.01 (s, 1H), 3.43 (s, 2H), 3.08 (dd, $J$ = 13.3, 6.7 Hz, 2H), 1.36 – 1.28 (m, 2H), 1.19 – 1.08 (m, 6H), 0.77 (t, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.03, 135.24, 129.25, 128.76, 127.05, 43.61, 39.65, 31.35, 29.33, 26.42, 22.45, 13.92. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.

$\text{N-Benzyl-2-phenylacetamide (3l).}$ Purified by recrystallization to afford 3l as a white solid (51% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.42 – 7.26 (m, 8H), 7.20 (d, $J$ = 7.6 Hz, 2H), 5.89 (s, 1H), 4.42 (d, $J$ = 5.7 Hz, 2H), 3.64 (s, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.02, 138.22, 134.88, 129.54, 129.13, 128.74, 127.57, 127.51, 127.48, 43.86, 43.65. The $^1$H NMR and $^{13}$C NMR characterization data matched the literature data.

$\text{2-(2-Methoxyphenyl)-N,N-dipropylacetamide (3m).}$ Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3m as a colorless oil (89% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30 – 7.20 (m, 2H), 6.93 (t, $J$ = 7.5 Hz, 1H), 6.88 (d, $J$ = 8.1 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 2H), 3.36 – 3.27 (m, 2H), 3.26 – 3.13 (m, 2H), 1.66 – 1.48 (m, 4H), 0.90 (t, $J$ = 7.4 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.28, 156.84, 130.23, 128.02, 124.51, 120.78, 110.33, 55.41, 49.96, 47.72, 34.60, 22.30, 20.99, 11.52, 11.34. GC-MS $m/z$ calcd. for C$_{13}$H$_{23}$NO$_2$ [M]$^+$: 249.2, found: 249.2.
\textbf{N,N-Dipropyl-2-(m-toly)acetamide (3n).} Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3n as a colorless oil (92\% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.22 – 7.13 (m, 1H), 7.07 (s, 1H), 7.03 (d, $J = 7.5$ Hz, 2H), 3.65 (s, 2H), 3.32 – 3.24 (m, 2H), 3.21 – 3.11 (m, 2H), 2.31 (s, 3H), 1.62 – 1.40 (m, 4H), 0.86 (td, $J = 7.4$, 3.1 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.73, 138.19, 135.46, 129.44, 128.46, 127.39, 125.72, 49.92, 47.51, 40.95, 22.19, 21.40, 20.82, 11.41, 11.21. GC-MS m/z calcd. for C$_{15}$H$_{23}$NO [M]$^+$: 233.2, found: 233.2.

\begin{center}
\includegraphics{3n.png}
\end{center}

\textbf{N,N-Dipropyl-2-(p-toly)acetamide (3o).} Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3o as a colorless oil (90\% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.16 – 7.06 (m, 4H), 3.64 (s, 2H), 3.29 – 3.23 (m, 2H), 3.18 – 3.10 (m, 2H), 2.29 (s, 3H), 1.61 – 1.41 (m, 4H), 0.85 (td, $J = 7.4$ Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.74, 136.06, 132.42, 129.21, 128.48, 49.83, 47.44, 40.52, 22.15, 20.98, 20.77, 11.35, 11.16. GC-MS m/z calcd. for C$_{15}$H$_{23}$NO [M]$^+$: 233.2, found: 233.2.

\begin{center}
\includegraphics{3o.png}
\end{center}

\textbf{2-(4-(\textit{tert}-Butyl)phenyl)-N,N-dipropylacetamide (3p).} Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3p as a colorless oil (83\% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32 (d, $J = 8.2$ Hz, 2H), 7.17 (d, $J = 8.2$ Hz, 2H), 3.66 (s, 2H), 3.34 – 3.25 (m, 2H), 3.23 – 3.13 (m, 2H), 1.62 – 1.44 (m, 4H), 1.30 (s, 9H), 0.87 (t, $J = 6.7$ Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.97, 149.56, 132.58, 128.50, 125.62, 50.09, 47.75,
40.44, 34.53, 31.47, 22.35, 20.99, 11.55, 11.33. GC-MS m/z calcd. for C_{18}H_{23}NO [M]^+: 275.2, found: 275.1.

\[ \text{GC-MS m/z calcd. for C}_{18}\text{H}_{23}\text{NO [M]^+: 275.2, found: 275.1.} \]

2-(4-Fluorophenyl)-N,N-dipropylacetamide (3q). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3q as a colorless oil (80% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.20 (dd, \(J = 8.3, 5.5\) Hz, 2H), 7.01 – 6.93 (m, 2H), 3.65 (s, 2H), 3.31 – 3.24 (m, 2H), 3.22 – 3.12 (m, 2H), 1.62 – 1.45 (m, 4H), 0.87 (td, \(J = 7.3, 5.3\) Hz, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.54, 161.84 (d, \(J = 244.7\) Hz), 131.35 (d, \(J = 3.2\) Hz), 130.42 (d, \(J = 7.9\) Hz), 115.48 (d, \(J = 21.3\) Hz), 50.03, 47.73, 39.96, 22.35, 20.93, 11.49, 11.33. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -116.47. GC-MS m/z calcd. for C_{14}H_{20}FNO [M]^+: 237.2, found: 237.1.

\[ \text{2-(4-Fluorophenyl)-N,N-dipropylacetamide (3q). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3q as a colorless oil (80% yield).} \]

N,N-Dipropyl-2-(4-(trifluoromethyl)phenyl)acetamide (3r). Purified by a short flash silica gel column chromatography (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3r as a colorless oil (85% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.56 (d, \(J = 8.1\) Hz, 2H), 7.36 (d, \(J = 8.1\) Hz, 2H), 3.74 (s, 2H), 3.33 – 3.25 (m, 2H), 3.23 – 3.13 (m, 2H), 1.64 – 1.47 (m, 4H), 0.92 – 0.84 (m, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.81, 139.77, 129.81 (q, \(J = 32.5\) Hz), 129.41, 125.57 (q, \(J = 3.8\) Hz), 124.33 (q, \(J = 271.8\) Hz), 50.10, 47.86, 40.47, 22.42, 20.96, 11.49, 11.33. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -63.47. GC-MS m/z calcd. for C_{15}H_{22}F_{3}NO [M]^+: 287.2, found: 287.1.

\[ \text{N,N-Dipropyl-2-(4-(trifluoromethyl)phenyl)acetamide (3r). Purified by a short flash silica gel column chromatography (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3r as a colorless oil (85% yield).} \]
N,N-Dibutyl-2-phenylpropanamide (3s). Purified by column chromatography using a short flash silica gel column (eluent: hexane/EtOAc = hexane to 10:1 v/v) to afford 3s as a colorless oil (65% yield). 1H NMR (300 MHz, CDCl3) δ 7.27 – 7.09 (m, 5H), 3.75 (q, J = 6.8 Hz, 1H), 3.47 – 3.33 (m, 1H), 3.25 – 3.11 (m, 1H), 3.10 – 2.98 (m, 1H), 2.96 – 2.81 (m, 1H), 1.49 – 1.29 (m, 6H), 1.26 – 1.07 (m, 5H), 0.86 – 0.74 (m, 6H). 13C NMR (75 MHz, CDCl3) δ 173.12, 142.54, 128.80, 127.31, 126.70, 47.43, 45.93, 43.25, 31.20, 29.70, 21.06, 20.29, 20.14, 13.92, 13.87. The 1H NMR and 13C NMR characterization data matched the literature data.14

4. Mechanistic studies

4.1 Formation of 3a’ and 4

To get insight into the reaction mechanism, some control experiments were carried out as shown below:

(a) Upon treatment of epoxide 1a with amine 2a in the absence of Ru-3, 51% of amino alcohol 3a’ was obtained after 20 h at 150 °C. However, 3a’ did not transform into the amide under the standard conditions. The result indicated that 3a’ was not an intermediate in formation of amide 3a.

(b) Epoxide 1a slowly converted into ester 4 catalyzed by Ru-3 and tBuOK in the absence of amine. 14% yield was obtained when the reaction proceeded for 20 h at
150 °C. Ester 4 hardly converted to amide 3a under the standard conditions. These results demonstrated that the ester 4 was not an intermediate either.

The correlation between reaction time and yields of 3a, 3a', and 4 was drawn in Figure S1 to investigate why amide 3a was generated as the major product instead of 3a' or 4. As shown in the figure, the formation of 3a was rapid under the standard conditions, and the reaction was finished in about 8 to 10 h (blue curve). In contrast, the formation of 3a' in the absence of catalyst and the formation of 4 in the absence of amine were both slower than the formation of amide 3a at the same temperature. Only a trace amount of 3a' and 4 were observed after 10 h (red and black curves). Thus, almost all of the epoxides would quickly convert into amides.

![Figure S1. Correlation between yields and reaction time](image)

**Procedure for conducting the experiment of the blue curve:** In a N₂ glovebox, Ru-3 (2.4 mg, 0.005 mmol), 1BuOK (0.7 mg, 0.006 mmol), and toluene (1 mL) were added into the Schlenk flask. The mixture was stirred at room temperature for 20 min. Epoxide 1a (60.1 mg, 0.5 mmol) and amine 2a (50.6 mg, 0.5 mmol) were added into the flask in succession. The flask was sealed and taken out of the glovebox, and the resultant mixture was heated at 150 °C. After heating for the given time, the reaction was cooled to room temperature and the solvent was evaporated in vacuo. The residue
was transferred to an NMR tube to determine the yield of 3a using mesitylene as an internal standard.

**Procedure for conducting the experiment of the red curve:** In a N₂ glovebox, toluene (1 mL), epoxide 1a (60.1 mg, 0.5 mmol), and amine 2a (50.6 mg, 0.5 mmol) were added to the Schlenk flask. The flask was sealed and taken out of the glovebox, and the resultant mixture was heated at 150 °C. After heating for the given time, the reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was transferred to an NMR tube to determine the yield of 3a′ using mesitylene as an internal standard.

**Procedure for conducting the experiment of the black curve:** In a N₂ glovebox, Ru-3 (2.4 mg, 0.005 mmol), tBuOK (0.7 mg, 0.006 mmol), and toluene (1 mL) were added to the Schlenk flask. The mixture was stirred at room temperature for 20 min. Epoxide 1a (60.1 mg, 0.5 mmol) was added into the flask. The flask was sealed and taken out of the glovebox, and the resultant mixture was heated at 150 °C. After heating for the given time, the reaction was cooled to room temperature and removed the solvent. The residue was transferred to an NMR tube to determine the yield of 4 using mesitylene as an internal standard.

4.2 The possibility of alcohol as an intermediate in the generation of amides

The dehydrogenative coupling of alcohols and amines could potentially generate amides under the catalysis of ruthenium pincer complexes. Epoxides can possibly be hydrogenated to primary alcohols by hydrogen generated in the developed reaction. To investigate if the alcohol can be generated as an intermediate, two control experiments were conducted as shown below:
(a) The developed amidation reaction can generate 1.0 equivalent of H2. Therefore ~0.4 bar (using a 90 mL Fischer-Porter tube, the gas is more than 1 equivalent to 1a) of hydrogen gas was added to the epoxide 1a under the standard conditions. It was found that only 15% of primary alcohol 5 along with 6% of ester 4 were produced. This result suggested that the hydrogen gas generated from the amidation reaction was inefficient for converting the epoxide into primary alcohol.

(b) Next, the amidation reaction was carried out in an open system with nitrogen flow, since the open system could remove the generated hydrogen gas. It was found that 95% of amide was obtained. The result demonstrated that the developed amidation reaction can proceed without the participation of hydrogen gas.

The above experiments revealed that the primary alcohol 5 was not an intermediate in the generation of amide 3a.

4.3 The possibility of generating free aldehyde as an intermediate

The Meinwald rearrangement of epoxides is a well-known procedure for converting epoxides into aldehydes, which is another possible intermediate for the generation of an amide under the current catalytic system. Control experiments were carried out to check this possibility.
Under the standard reaction conditions, epoxide 1a could not convert to phenylacetaldehyde, as shown in the first experiment. When phenylacetaldehyde was employed as an alternative substrate under the standard conditions, enamine 6 was generated as the major product (see the crude $^1$H NMR below).

Figure S2. Crude $^1$H NMR spectrum of enamine formation in CDCl$_3$

Note: mesitylene was used as the internal standard. * unidentified impurity

The above results indicate that the amidation reaction does not generate the free aldehyde as the intermediate.
4.4 The reaction intermediates and epoxide activation pathway

To determine the catalytically active species, Ru-3 was combined with tBuOK (1.2 equiv to Ru-3) in a THF solution at room temperature. After 1 h, the dark green solution was filtered through a small piece of cotton. The solution was concentrated to get the dearomatized complex Ru-5. Using Ru-5 as the catalyst for the reaction of epoxide 1a with amine 2a resulted in 92% yield of the amide 3a. This result indicates that Ru-5 is the actual catalyst for this amidation reaction.

Next, Ru-5 was combined with epoxide 1a in toluene-\textit{d}_8 in a 1:3 ratio at room temperature to explore the activation process. NMR spectra revealed the formation of new complexes, which were identified by $^{31}$P NMR and $^1$H NMR as two isomers (Z and E) of Ru-6 in a 1:2 ratio with an enolate coordinated to the aromatic ruthenium complex.

**Procedure for generating Ru-6:** In a N$_2$ glovebox, Ru-5 (8.9 mg, 0.02 mmol) was added to an NMR tube and dissolved by toluene-\textit{d}_8. 1a (7.2 mg, 0.06 mmol) was added to the solution. The NMR tube was sealed and then rotated at room temperature for about 10 min to produce Ru-6.
NMR data for the major configuration of Ru-6:

$^1$H NMR (500 MHz, toluene-$d_8$) δ 8.78 (br, 1H, Py$H$), 7.74 (d, $J = 5.1$ Hz, 1H, OCH$CH$Ph), 7.48 (d, $J = 7.4$ Hz, 2H, Ph$H$), 7.44 – 7.35 (m, 1H, Py$H$), 7.30 (d, $J = 7.0$ Hz, 1H, Py$H$), 7.21 (d, $J = 7.0$ Hz, 1H, Py$H$), 7.10 – 7.02 (m, 2H, Py$H$, overlapping with excess styrene oxide), 6.83 (t, $J = 7.2$ Hz, 1H, Ph$H$), 6.76 (d, $J = 7.4$ Hz, 2H, Ph$H$), 6.36 (br, 1H, Py$H$), 4.79 (d, $J = 5.1$ Hz, 1H, OCH$CH$Ph), 3.29 (dd, $J = 15.9$, 9.2 Hz, 1H, PyCHH$P$), 3.00 (dd, $J = 15.9$, 9.2 Hz, 1H, PyCHH$P$), 1.32 (d, $J = 12.8$ Hz, 9H, PC(CH$_3$)$_3$), 1.16 (d, $J = 12.8$ Hz, 9H, PC(CH$_3$)$_3$), -15.35 (d, $J = 24.2$ Hz, 1H, Ru$-H$).

$^{13}$C NMR (126 MHz, toluene-$d_8$) δ 208.12 (d, $J = 14.7$ Hz, RuCO), 165.07 (s, OCH$CH$Ph), 161.91 (s, Py$C$), 156.44 (s, Py$C$), 152.45 (s, Py$C$), 143.65 (s, Py$C$), 138.57 (s, Ph$C$), 136.83 (s, Py$C$), 135.99 (s, Py$C$), 129.18 (s, Ph$C$), 128.53 (s, Py$C$), 127.37 (s, Py$C$), 125.48 (s, Ph$C$), 122.41 (s, Py$C$), 121.89 (d, $J = 9.0$ Hz, Py$C$), 119.85 (s, Ph$C$), 99.28 (s, OCH$CH$Ph), 37.50 (d, $J = 13.9$ Hz, PC(CH$_3$)), 37.25 (d, $J = 11.5$ Hz, PyCH$_2$P), 37.12 (d, $J = 11.5$ Hz, PyCH$_2$P), 35.24 (d, $J = 23.2$ Hz, PC(CH$_3$)), 29.67 (d, $J = 4.2$ Hz, PC(CH$_3$)$_3$), 29.35 (d, $J = 3.3$ Hz, PC(CH$_3$)$_3$).

$^{31}$P NMR (202 MHz, toluene-$d_8$) δ 105.23 (s).
Figure S3. $^{31}$P NMR spectrum of Ru-6 in toluene-$d_8$

Figure S4. $^1$H NMR spectrum of Ru-6 in toluene-$d_8$
Figure S5. $^{13}$C-DEPTQ NMR spectrum of Ru-6 in toluene-$d_8$

Figure S6. HSQC spectrum of Ru-6 in toluene-$d_8$
Figure S7. HSQC spectrum (zoom in) of Ru-6 in toluene-$d_8$.

Figure S8. H-H COSY spectrum of Ru-6 in toluene-$d_8$. 
The combination of Ru-1 and ‘BuOK in THF solution also generated the well-known dearomatized complex Ru-7. A new complex Ru-8 was formed when Ru-7 was reacted with epoxide 1a in deuterated benzene at room temperature. The Ru-enolate intermediate Ru-8 demonstrated the activation pathway of the epoxide.

**Procedure for generating Ru-8:** In a N₂ glovebox, Ru-1 (9.8 mg, 0.02 mmol) and ‘BuOK (2.2 mg, 0.02 mmol) were added into a vial. THF (2 mL) was added and stirred at room temperature for 1 h. The solvent was removed, and the residue was redissolved in pentane. The mixture was filtered through a piece of cotton. The solution was concentrated to afford the dearomatized complex Ru-7. Next, benzene-d₆ and 1a were added to the vial containing Ru-7, and the solution was
stirred at room temperature for about 30 min to produce Ru-8. The solution was transferred to the NMR tube for analysis.

NMR data for the major configuration of Ru-8:

$^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 8.07 (d, $J$ = 6.0 Hz, 1H, OCH$\text{CH}$Ph), 7.83 (d, $J$ = 7.4 Hz, 2H, Ph$\text{H}$), 7.23 – 7.10 (m, 2H, Ph$\text{H}$, overlapping with residual benzene), 6.95 – 6.90 (m, 2H, Ph$\text{H}$ and Py$\text{H}$), 6.51 (d, $J$ = 7.9 Hz, 1H, Py$\text{H}$), 6.44 (d, $J$ = 7.1 Hz, 1H, Py$\text{H}$), 5.34 (d, $J$ = 6.0 Hz, 1H, OCH$\text{C}$Ph), 4.97 (d, $J$ = 14.6 Hz, 1H, Py$\text{CH}$HN), 3.41 – 3.34 (m, 1H, NCH$\text{HH}$CH$_3$), 3.17 – 3.10 (m, 1H, NCH$\text{HH}$CH$_3$), 3.01 (d, $J$ = 14.6 Hz, 1H, PyCH$\text{HP}$), 2.90 (dd, $J$ = 16.4, 10.2 Hz, 1H, Py$\text{CH}$HP), 2.72 (dd, $J$ = 16.4, 8.4 Hz, 1H, PyCH$\text{HP}$), 2.53 – 2.43 (m, 1H, NCH$\text{HH}$CH$_3$), 2.27 (dd, $J$ = 11.5, 5.7 Hz, 1H, NCH$\text{HH}$CH$_3$), 1.18 (d, $J$ = 7.2 Hz, 9H, PC(CH$_3$)$_3$), 1.16 (d, $J$ = 7.2 Hz, 9H, PC(CH$_3$)$_3$), 0.91 (t, $J$ = 6.6 Hz, 3H, NCH$_2$CH$_3$), 0.75 (t, $J$ = 6.6 Hz, 3H, NCH$_2$CH$_3$), -15.75 (d, $J$ = 26.9 Hz, 1H, Ru$\text{H}$).

$^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$ 208.74 (d, $J$ = 16.6 Hz, Ru$\text{CO}$), 166.25 (s, OCH$\text{CH}$Ph), 161.70 (d, $J$ = 4.1 Hz, Py$\text{C}$), 161.59 (s, Py$\text{C}$), 144.00 (s, Ph$\text{C}$), 136.59 (s, Py$\text{C}$), 127.96 (s, Ph$\text{C}$), 125.53 (s, Ph$\text{C}$), 120.38 (s, Ph$\text{C}$), 119.81 (d, $J$ = 9.2 Hz, Py$\text{C}$), 118.68 (s, Py$\text{C}$), 99.94 (s, OCH$\text{CH}$Ph), 64.43 (s, Py$\text{CH}$$_2$N), 53.89 (s, NCH$_2$CH$_3$), 50.30 (s, NCH$_2$CH$_3$), 37.59 (d, $J$ = 12.4 Hz, PC(CH$_3$)$_3$), 37.40 (d, $J$ = 19.5 Hz, Py$\text{CH}$$_2$P), 34.53 (d, $J$ = 22.9 Hz, PC(CH$_3$)$_3$), 30.36 (d, $J$ = 3.0 Hz, PC(CH$_3$)$_3$), 29.33 (d, $J$ = 4.3 Hz, PC(CH$_3$)$_3$), 10.68 (s, NCH$_2$CH$_3$), 8.77 (s, NCH$_2$CH$_3$).

$^{31}$P NMR (202 MHz, C$_6$D$_6$) $\delta$ 110.19 (d, $J$ = 6.4 Hz).

It should be mentioned that 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. For example, the chemical shift of H$^1$ on compound a below is 7.05 ppm, and H$^2$ on compound b is 8.10 ppm, according to the
Figure S10. $^{31}$P NMR spectrum of Ru-8 in C$_6$D$_6$

Figure S11. $^1$H NMR spectrum of Ru-8 in C$_6$D$_6$
Figure S12. $^{13}$C-DEPTQ NMR spectrum of Ru-8 in C$_6$D$_6$

Figure S13. HSQC spectrum of Ru-8 in C$_6$D$_6$
Ru-8 was unstable at room temperature, and part of it slowly converted to another new complex reaching a chemical equilibrium. On the basis of the chemical shifts of the $^{31}$P NMR and $^1$H NMR, 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.
Figure S15. $^{31}$P NMR spectrum of the chemical equilibrium in C$_6$D$_6$

Figure S16. $^1$H NMR spectrum of the chemical equilibrium in C$_6$D$_6$

5. References

(1) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* 2005, **127**, 10840-10841.
(2) C. Gunanathan, D. Milstein, Angew. Chem. Int. Ed. 2008, 47, 8661-8664.
(3) E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon, D. Milstein, J. Am. Chem. Soc. 2010, 132, 16756-16758.
(4) U. K. Das, Y. Ben-David, Y. Diskin-Posner, D. Milstein, Angew. Chem. Int. Ed. 2018, 57, 2179-2182.
(5) L. Zhang, Z. Zuo, X. Leng, Z. Huang, Angew. Chem. Int. Ed. 2014, 53, 2696-2700.
(6) W. Liu, W. Li, A. Spannenberg, K. Junge, M. Beller, Nat. Catal. 2019, 2, 523-528.
(7) C. E. Paul, D. Tischler, A. Riedel, T. Heine, N. Itoh, F. Hollmann, ACS Catal. 2015, 5, 2961-2965.
(8) M. C. D’Amaral, N. Jamkhou, M. J. Adler, Green Chem. 2021, 23, 288-295.
(9) B. Xiong, L. Zhu, X. Feng, J. Lei, T. Chen, Y. Zhou, L.-B. Han, C.-T. Au, S.-F. Yin, Eur. J. Org. Chem. 2014, 20, 4244-4247.
(10) Z.-W. Chen, H.-F. Jiang, X.-Y. Pan, Z.-J. He, Tetrahedron 2011, 67, 5920-5927.
(11) L. Cu, J. Lim, J. L. Cheong, S. S. Lee, Chem. Commun. 2014, 50, 7017-7019.
(12) R. M. Lanigan, P. Starkov, T. D. Sheppard, J. Org. Chem. 2013, 78, 4512-4523.
(13) A. Álvarez-Pérez, M. A. Esteruelas, S. Izquierdo, J. A. Varela, Org. Lett. 2019, 21, 5346-5350.
(14) Y. Yuan, F.-P. Wu, C. Schünemann, J. Holz, P. C. Kamer, X.-F. Wu, Angew. Chem. Int. Ed. 2020, 59, 22441-22445.
(15) M. Kondo, T. Kochi, F. Kakiuchi, J. Am. Chem. Soc. 2011, 133, 32-34.
(16) X. Zhang, J. Ye, L. Yu, X. Shi, M. Zhang, Q. Xu, M. Lautens, Adv. Synth. Catal. 2015, 357, 955-960.
6. NMR spectra of amides

Figure S17. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3a

Figure S18. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3a
Figure S19. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3b

Figure S20. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3b
Figure S21. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3e

Figure S22. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3e
Figure S23. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3d

Figure S24. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3d
Figure S25. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3e

Figure S26. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3e
Figure S27. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3f

Figure S28. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3f
Figure S29. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3g

Figure S30. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3g
Figure S31. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3h

Figure S32. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3h
Figure S33. \(^1^H \text{NMR} (300 \text{ MHz, CDCl}_3)\) spectrum of compound 3i

Figure S34. \(^{13}^C \text{NMR} (75 \text{ MHz, CDCl}_3)\) spectrum of compound 3i
Figure S35. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3j

Figure S36. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3j
Figure S37. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 3k

Figure S38. $^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 3k
Figure S39. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3I

Figure S40. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3I
Figure S41. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3m

Figure S42. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3m
Figure S43. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3n

Figure S44. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3n
Figure S45. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3o

Figure S46. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3o
Figure S47. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3p

Figure S48. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3p
Figure S49. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3q

Figure S50. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3q
Figure S51. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3r

Figure S52. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3r
Figure S53. $^1$H NMR (300 MHz, CDCl$_3$) spectrum of compound 3s

Figure S54. $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of compound 3s