A Rh(II)-catalyzed multicomponent reaction by trapping an α-amino enol intermediate in a traditional two-component reaction pathway

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Multicomponent reactions (MCRs) represent an ideal organic synthesis tool for the rapid construction of complex molecules due to their step and atom economy. Compared to two-component reactions, the development of new MCRs has been greatly limited during the 170 years since the first MCR was reported. Theoretically, the trapping of an active intermediate generated from two components by a third component could change the traditional two-component reaction pathway, leading to the discovery of MCRs. We report an example of the trapping of α-amino enols generated in situ from 1-sulfonyl-1,2,3-triazoles via α-amino metal carbene species by vinylamine ions using C(2)-substituted indoles and paraformaldehyde as precursors in the presence of a rhodium(II) catalyst. The traditional enol-ketone transformation pathway was suspended by the trapping procedure and efficiently switched to an MCR pathway to produce α-amino-β-indole ketones in moderate to good yields. Unexpectedly, the resulting products and the theoretical density functional theory (DFT) calculation results indicated that the enolic carbon had a stronger nucleophilicity than the well-known traditional enamic carbon in the trapping process. The reaction mechanism was investigated using control experiments and detailed DFT calculations, and the synthetic application of the products was also illustrated. The developed strategy provides a mild and rapid access to α-amino-β-indole ketones and suggests a rationale for the discovery of MCRs by trapping an active intermediate with a third component in a traditional two-component reaction pathway.

INTRODUCTION
Multicomponent reactions (MCRs) represent one of the most efficient approaches to realize atom-economical and green synthetic processes (1–8). Given the challenges in modulating the matching reactivity of all involved components, serendipity has always played an important role in the discovery of MCRs, even though several classical MCRs, such as the Strecker (9), Biginelli (10), and Ugi (11) reactions, are well established. Compared to two-component reactions, the development of new MCRs has been greatly limited during the 170 years since the first example of MCR was reported. Rational design strategies aimed at the discovery of novel MCRs have gained importance over the past decade (12–18). For instance, Nair et al. (14) demonstrated a conceptual framework involving the capture of a zwitterionic species by an electrically complementary component to develop a series of new MCRs for the construction of heterocyclic compounds. Other efficient rational design strategies, such as a single reactant replacement in a known MCR, the modulation of reaction sequences via versatile reactive intermediates, and the divergence of a reaction pathway by changing the reaction conditions, have been summarized in detail by Ruijter et al. (17). However, because of the continuous demand of novel MCRs, new strategies are urgently needed.

It is well known that numerous traditional two-component reactions proceed via an active intermediate through a sequence of two elementary steps, a reversible and an irreversible (rate-determining) step (19), in which the latter drives the equilibrium to the product side. When the irreversible step occurs after the generation of the active intermediate (Fig. 1A, blue line), it is theoretically possible that the trapping of this active intermediate generated by two components with a third component might change the traditional reaction pathway and switch to a new energetically favored three-component pathway (Fig. 1A, red line).

Our group has continuously focused on the development of transition metal–catalyzed multicomponent transformations of diazo compounds, alcohols/amines/indoles, and electrophiles (20–28). In these transformations, diazo compounds and alcohols/amines/indoles generate in situ ylides or zwitterions that can be successfully trapped by electrophiles, such as imines and aldehydes. Whereas in the traditional reaction pathway, the active ylides or zwitterions readily undergo a proton transfer process (29–34) to form X–H (X = C, N, and O) insertion products. A theoretical DFT calculation investigation showed that it is the proton transfer step rather than the active ylide generation step that is the rate-determining step in the reaction, leading to the X–H insertion product formation (see fig. S1). Thus, we envisaged that the trapping of the active intermediate with a third component to suspend this irreversible two-component transformation step could provide a general strategy for discovering novel MCRs.

To validate this conceptual hypothesis, an MCR based on the trapping of another active intermediate with a third component beyond our present ylide or zwitterion systems is needed to be demonstrated: (i) By trapping an active two-component intermediate in an irreversible traditional pathway, the resulting three-component involved intermediate formed via an energetically favored transition state could be transformed into a multicomponent product; (ii) the multicomponent product formed by a stepwise cascade process from the reaction of the traditional two-component product with a third component might be excluded to ensure that the reaction is a “true” MCR according to the modern MCR definition (Fig. 1B) (4, 13).

After the seminal work of Gevorgyan et al. (35, 36), Fokin et al. (37–39), and others (40, 41), 1-sulfonyl-1,2,3-triazoles have attracted a great deal of attention as precursors of α-amino Rh(II) carbene A, which is a practical intermediate in the synthesis of N-heterocyclic complexes. Recent additions
to the rapidly growing list of applications of 1-sulfonyl-1,2,3-triazoles under Rh(II) catalysis include transannulations and cyclopropanations (42–49), C–H insertions (50), O–H insertions/rearrangements (51–55), ring expansions (56, 57), ariations with boronic acids (58), and cycloaddition reactions (59). α-Amino enol D is a classically proposed key active intermediate via α-imino Rh(II) carbene A from the reaction of 1-sulfonyl-1,2,3-triazole with water, as reported by Miura et al. (51). The authors proposed that carbene A underwent an O–H insertion with water to furnish intermediate C, which further yielded the key intermediate α-amino enol D by imine-enamine tautomerization, and subsequently delivered an α-amino ketone product by a subsequent keto-enol tautomerization via a proton transfer process (Scheme 1). Because the formation of D from α-imino carbene A represents one of its most important transformations and provides a commonly accepted active intermediate (60, 61), the proposed α-amino enol D was consequently selected as the substrate to be trapped to validate our hypothesis.

RESULTS
Preliminary exploration of the MCR
Initially, commonly used electrophilic trapping reagents such as aldehydes or imines were used to trap α-amino enol D, as demonstrated by Nair et al. (14). However, no formation of the desired products was observed when 4-(4-bromophenyl)-1-(methylsulfonyl)-1H-1,2,3-triazole 1 was reacted with water and aldehydes or imines using rhodium(II) acetate as catalyst. Only ketone 7 (~80% yield) and trace amounts of cycloaddition product 9 were observed. These results suggested that a more active trapping component is needed to be taken into consideration to obtain a matching reactivity with α-amino enol D. It has been widely reported that indoles react with aldehydes and ketones in the presence of Lewis or Bronsted acid to generate highly reactive vinylimine ion E (Scheme 2A) (62–66), which undergoes an electrophilic reaction to yield functionalized indole derivatives. Owing to the broad application of indoles in drug discovery and our previous work on indole functionalization (21, 67–70), we thus turned our attention to the in situ–generated vinylimine ion E as a trapping component to provide the multicomponent product 4 (Scheme 2A). For this designed reaction pathway, the most important competitive pathway is a two-component [3 + 2] cycloaddition that has been illustrated by Spangler et al. (47) for the efficient synthesis of pyrrolindone architectures 5 via the combination of C(3)-substituted indole 2 and Rh(II)-associated 1-sulfonyl-1,2,3-triazoles (Scheme 2B). The authors suggested that the reaction was promoted via zwitterionic-type intermediate F from an α-imino rhodium carbene species.

The reaction was then conducted with 4-(4-bromophenyl)-1-(methylsulfonyl)-1H-1,2,3-triazole 1a (1.0 eq), an excess of 1,3-dimethyl indole 2 (which could possibly generate the zwitterionic intermediate F, as suggested by Davies), and electrophile 3 (4.0 eq), such as an imine, isatin, aromatic aldehyde, ethyl glyoxylate, formaldehyde solution, and paraformaldehyde, in the presence of 2.0 mole percent as an imine, isatin, aromatic aldehyde, ethyl glyoxylate, formaldehyde solution, and paraformaldehyde, in the presence of N(CH3)2, indole was used instead of 1,3-dimethyl indole, and the major product was compound 5, as illustrated by Davies et al. In view of the charge effect of the electron-donating substituents on the nucleophilicity of the C(3) on the indole ring, 1,2-dimethyl indole 2 was then used instead of 1,3-dimethyl indole to investigate the possible reaction outcome (Table 1). Some multicomponent products were detected by high-performance liquid chromatography–mass spectrometry (HPLC-MS) and 1H nuclear magnetic resonance (NMR) spectroscopic analyses when ethyl glyoxylate was used as trapping reagent, but it was not possible to obtain pure products because of their low yield. Gratifyingly, an aqueous solution of formaldehyde afforded a trapping product with the desired molecular weight of 439 in 20% isolated yield. Encouraged by these positive results, paraformaldehyde was used without additional water to explore the MCR and a better yield of 29% was obtained. Both formaldehyde aqueous solution and paraformaldehyde provided major by-product 5 in a ~28% isolated yield. When using 1,3-dimethyl indole, other common electrophiles, such as imines, isatins, or aromatic aldehydes, also provided no desired three-component product but two-component by-product 5.

Optimization of the MCR conditions
To evaluate the efficiency of this new transformation, we examined the reaction conditions using paraformaldehyde, and the optimal

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**Fig. 1.** Designed strategy for the discovery of MCRs. The rational design of a general strategy based on the trapping of the active intermediates in traditional two-component reactions for the discovery of MCRs. (A) Gibbs free energy profiles for two-component reactions and MCR. (B) Strategy for discovering MCR.

**Scheme 1.** Proposed literature mechanism. Proposed mechanism of the formation of ketones from triazoles via α-amino enol D according to Miura et al. (51).
conditions are illustrated in Table 2. As shown, Rh₂(OAc)₄ was more effective than Rh₂(Oct)₄, Rh₂(Piv)₄, Rh₂(TPA)₄, and Rh₂(S-NTTL)₄ in providing the desired product 6a in 29% yield in toluene at 100°C (entries 1 to 5). Chlorobenzene was a better solvent than toluene, ethyl acetate (EA), cyclohexane, tetrahydrofuran (THF), dimethylbenzene, CHCl₃, and 1,2-dichloroethane (DCE), leading to a higher 36% yield (entries 6 to 12). No desired product was obtained from cyclohexane (entry 9), possibly because of the fact that a nonpolar hydrocarbon solvent might be unfavorable for the generation of the vinylimine ion intermediate. It was found that the reaction temperature had a profound

**Scheme 2. Designed MCR pathway.** Designed and observed transformation processes of trapping of the α-amino enol D with indole vinylimine ion E (A and C) versus competitive Davies’ cycloaddition pathway (B).

**Table 1. Preliminary study of the MCR.** The preliminary study of the MCR by trapping α-amino enol D with various electrophiles. Unless otherwise stated, all reactions were carried out in PhMe in a 0.1 mmol scale and 1a:2a:3 = 1:0.5:0.4 and 2 mol % of Rh₂(OAc)₄ catalyst were added. Yields of isolated products were obtained after purification by column chromatography. N.P., no desired product.
influence on the yield, and an optimal reaction temperature of 140°C was identified and effectively improved the yield to 70% (entries 12 to 17). A very little amount of another by-product, ketone 7a, which was generated from α-amino enol D by keto-enol tautomerization, was observed when the reaction temperature was increased to 140°C. Other metal catalysts still produced a much poor yield at the optimal reaction temperature of 140°C in chlorobenzene (entries 18 to 20). At the reaction temperature of 140°C, chlorobenzene was also demonstrated as the better solvent than other solvents when using Rh₂(OAc)₄ as catalyst (see table S1). Under the optimized conditions, the yield of by-product 5 was obviously suppressed to ~10%. The MCRs of 1-sulfonyl-1,2,3-triazoles as precursors of Rh(II) azavinyl carbenes are really restricted, although the involved two-component reactions are very fruitful (19). Here, we envisioned that a Rh(II)-catalyzed MCR with 1-sulfonyl-1,2,3-triazoles as precursors of azavinyl carbenes could be successfully developed.

Determination of the MCR products
All the products were respectively characterized by ¹H NMR, ¹³C NMR, and high-resolution mass spectrometry (HRMS) (see the Supplementary Materials). Surprisingly, the structure of the multicomponent product corresponded to α-amino-β-indole ketone 6 rather than the designed product 4, as determined using single-crystal x-ray analysis by analogy with 6i (see figure in Table 3 and fig. S2). This suggests a selectivity of the nucleophilicity between α-C and β-C in enol D during the trapping process.

Substrate scope of the MCR
The scope of this effective process was then surveyed with respect to the triazole and indole coupling partners. As shown in Table 3, a broad range of triazoles 1 provided the corresponding products in moderate to good yields (entries 1 to 9). 1-Mesyl–substituted triazoles bearing a bromide or other electron-rich groups at the C-4′ of the phenyl ring produced good yields of the corresponding products (entries 1 to 3). 1-Mesyl–substituted triazole 1d featuring a heterocyclic group also produced a good yield of the desired product (entry 4). By-product 7c was also observed and isolated in 10% yield when an OEt (R₂) substituent was present at the C-4′ on the phenyl ring (entry 3), whereas electron-deficient groups (for example, –CF₃ and –COOMe) provided trace amounts of the desired product (entry 5). Bulky triazoles 1 were found to be tolerated despite the steric effect and can equally furnish the

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corresponding products (entries 6 to 10). This transformation was also applicable to a range of C(2)-substituted indoles (Table 3, entries 11 to 15). An evaluation of the substituents on the indolic nitrogen revealed that N-H and N-Bn indoles were both compatible with the reaction conditions to provide the products in 55 and 62% yield, respectively (entries 11 and 12). It is unclear why a methoxy group at the C(5) of the indole core produced a low yield of 10% (entry 16).

**Synthetic application of the MCR**

The synthetic application of multicomponent product 12 was illustrated by the simple reduction of ketone 6c to alcohol 11, followed by a ring closure with triphosgene to afford 3-(methylsulfonyl)oxazolidin-2-one derivative 12, which frequently serves as a pivotal pharmaceutical moiety (Scheme 3) (71–73). The relative configuration of 12 was determined to be (1S,2R) on the basis of the corresponding two-dimensional (2D) 1H−1H nuclear Overhauser effect spectroscopy (NOESY) spectrum (see fig. S3).

**Experimental mechanistic investigation**

This effective chemical transformation strongly motivated us to explore its reaction mechanism. The observation of the formation of by-product 7 indicated that intermediate enol D generated from water and carbene A might be involved in this MCR. The reaction was thus performed with the original three components and heavy oxygen water (H$_2$O$_{18}$) to provide the isotope-labeled product 6i′ (Scheme 4A). The molecular ion peak of 6i′ was observed at 432.2 and 434.2 (calculated [M + H]$^+$ for 6h′ is 433.2 and 435.2) (see fig. S4). However, when 4 Å molecular sieves were added to the reaction solution, the desired product did not form (Scheme 4B). The results of these control experiments confirmed that water participated in the multicomponent process, and the reaction could be run in air. A sample of the reaction mixture solution was analyzed by HPLC-MS to monitor the progress of the reaction, and the results showed that a molecular ion peak was observed at 174.9, which might be attributed to vinylimine ion E generated from indole and HCHO (see fig. S5; calculated [M + H]$^+$ for E was 174.9).

Considering that triazoles can be decomposed by heating, the reaction was conducted at 140°C in chlorobenzene without Rh$_2$(OAc)$_4$, and no desired product was observed (Scheme 4C), which indicated that the reaction was catalyzed by Rh$_2$(OAc)$_4$. A further control experiment was conducted by reacting triazole 1i with paraformaldehyde under the identified conditions to exclude another possible pathway, according to which the HCHO molecules would first react with C(2)-substituted indole 2 to generate an intermediate, which subsequently reacted with α-amino enol D.

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**Table 3. Substrate scope study.** The substrate scope of the MCR by using various trizole and indole components. Unless otherwise stated, all reactions were carried out in PhCl in a 0.2-mmol scale at 140°C and 1:2:3 = 1.0:5.0:4.0 and 2 mol % of Rh$_2$(OAc)$_4$ were added.

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*Isolated yields after purification by column chromatography. °NP: A trace amount of product was monitored by LC-MS.
Mechanistic insight based on a theoretical calculation investigation

To further understand the two competitively crucial transformation pathways of α-amino enol D into ketone 7 by keto-enol tautomerization versus trapping by vinylimine intermediate E into product 6, we performed detailed DFT calculations for the transformation of the two key intermediates, for example, α-amino enol D and vinylimine ion E. The typically calculated free energy profiles for the formation and the elementary transformations of α-amino enol D are shown in Fig. 2. First, we were interested in how to generate α-amino enol D. It is well known that Rh(II)-associated carbenes readily react with water/alcohol to form the corresponding active oxonium ylides, which can yield O–H bond insertion products through a proton transfer process (74–76). Xia et al. (77) also demonstrated this process by theoretical calculations. Our group further demonstrated that these oxonium ylides could be trapped by electrophiles during the experiments before the proton transfer took place (78, 79). Furthermore, both free energy profiles for active ylide intermediate B (52) and water O–H bond insertion intermediate C were optimized for the transformation of α-imino Rh(II) carbene A, as proposed by Miura et al. (51). It was found that the formation of ylide B from reactant A and one water molecule had no barrier. The transformation of ylide B to enol D was extremely exothermic by 29.9 kcal/mol via a specific five-membered ring transition state TS1, suggesting that intermediate D is easily formed via ylide B. Ylide B can also easily transform to intermediate C via a water-associated proton shift according to the calculations by Liang et al. (80). In our calculated energy profiles, the activation energy barrier for the transformation of ylide B into intermediate C was 36.3 kcal/mol via a concerted transition state TS2* and 27.5 kcal/mol via a water-associated TS2, which indicates that this transformation pathway is unfavorable. Then, the proposed key process,
namely, the imine-enamine tautomerization from intermediate C to enol D, was investigated. Considering that proton shuttles might greatly facilitate the imine tautomerization process to enamine, water molecules were included in the transformation. The calculated activation energy barrier for the proton transfer in the imine-enamine tautomerization process from intermediate C to enol D was high, up to 39.1 kcal/mol via TS6 assisted by one water molecule and up to 35.1 kcal/mol via TS7 assisted by two water molecules (Fig. 3), which implies that the conversion from intermediate C to D is impossible.

Subsequently, the key transition states of the transformation of enol D into ketone 7 and product 6 were located in the energy profiles (Fig. 2), respectively. The calculated activation energy barrier for the proton transfer in the imine-enamine tautomerization process from intermediate C to enol D was as high as 45.6 kcal/mol, which rules out the possibility of a reverse transformation from ketone 7 to enol D. The theoretically calculated results are in good agreement with the observations in our control experiments that multicomponent product 6 could not be obtained by reacting the isolated ketone 7 with indole 2 and paraformaldehyde under the same reaction conditions.

The key transition state TS4 for the nucleophilic addition of enol D to vinylimine intermediate E in chlorobenzene at 140°C was also obtained. As shown in Fig. 2, the evaluated barrier for the forward reaction

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\Delta G_{\text{sol}} \text{ kcal/mol}
\]

Fig. 2. DFT investigation of the MCR. Calculated free energy profiles at 140°C in chlorobenzene for the generation and transformation of enol D into ketones and into the multicomponent product with vinylimine intermediate E. All the energy values are expressed in kilocalorie per mole.

Fig. 3. DFT investigation of the imine-enamine tautomerization. Calculated free energy profiles for the imine-enamine tautomerization from intermediate C to enol D. The blue line denotes the pathway via the transition state TS6 through one water molecule, whereas the red curve denotes the pathway via TS7 through two water molecules, respectively.
was 8.7 kcal/mol, appearing more favorable compared to the 35.3 kcal/mol of TS3 in the keto-enol tautomerization, which illustrates the dominant transformation of enol D with vinylimine intermediate E to generate product 6. The calculated barrier for this step is also consistent with the experimental observation that the multicomponent transformation was rapidly completed in half an hour. The DFT calculations on the reaction mechanism suggest that the active α-amino enol D was trapped by the in situ-generated vinylimine ion E to promote the MCR by an intermolecular reassembly.

To explain the selectivity of the nucleophilicity between α-C and β-C in enol D, the activation energy barrier of the forward reaction at the α-C site of the enol attacked by vinylimine intermediate E via TS5 was also evaluated (Fig. 2), and a value of 13.0 kcal/mol was obtained. The barrier of TS5 was higher than that of TS4 by 4.3 kcal/mol, suggesting a lower probability for this precursor to react with intermediate E at the α-C to α-D of enol D to yield product 4. Moreover, the free energy of product 4 was higher than that of enol D by 12.1 kcal/mol, indicating that the forward reaction from enol D to product 4 is unfavorable from the thermodynamic point of view.

It is interesting and noteworthy that the water molecules play a crucially important role in the formation of vinylimine ion E to promote the multicomponent process on the basis of the DFT calculations (see fig. S6). The theoretical results support the assumption that a hydrated proton, but not a free proton, promoted the generation of vinylimine ion E, which is consistent with our control experimental results that a Brønsted acid, such as phosphoric acid, could not accelerate or improve the multicomponent transformation. Possibly because of the difference between the electronic features of paraformaldehyde and alkyl or aryl aldehyde (Scheme 2), no intermediate product 10 could be located in the DFT energy profile (fig. S6), which is also in accordance with the observation that no indole product 10 was obtained experimentally.

**DISCUSSION**

The determination of the product structure indicates that a selective nucleophilic attack occurred at the enolic carbon (β-C) rather than at the enamic carbon (α-C) of the key amino enol intermediate D (Scheme 2C versus Scheme 2A). Interestingly, to some extent, the structure of α-amino enol intermediate D is similar to that of N-heterocyclic carbene (NHC) intermediates (81–86), such as the Breslow intermediate in the Stetter reaction (Scheme 5) (87, 88). Breslow intermediates are classical examples of umpolung chemistry in which the α-C (enamine reactivity) rather than the β-C (enol reactivity) dominates the nucleophilic attack (89–91). Although both α-C and β-C in α-amino enol D can theoretically perform a nucleophilic addition to vinylimine intermediate E, the enolic carbon (β-C) here unexpectedly exhibited a higher reactivity than that of the enamic carbon, leading to the formation of α-amino-β-indole ketones.

The substrate scope survey demonstrates the efficiency of this MCR in affording α-amino-β-indole ketones, which exhibit important bioactivity profiles in drug discovery (92, 93) and can be used as synthetic intermediates for the production of α-amino alcohols (94–97) or natural products (98, 99). To the best of our knowledge, this represents the first example of an effective multicomponent sequence that rapidly affords α-amino-β-indole ketones.

For the classical two-component transformation of α-imino Rh(II) carbene A (which can be generated in situ from the reaction of 1-sulfonyl-1,2,3-triazole with water) into the corresponding ketone, a
mechanism was proposed (SI) via key intermediate α-amino enol D by imine-enamine tautomerization from water O–H bond insertion intermediate C, subsequently followed by keto-enol tautomerization via a proton transfer process. Our investigations based on detailed DFT calculations and control experiments have excluded possible transformations of both imine-enamine tautomerization from C to D and keto-enol tautomerization from ketones (products) to α-amino enol D. An extremely favored energy profile suggests that α-imino Rh(II) carbene A can possibly yield key intermediate α-amino enol D via metal-associated ylide B.

On the basis of the abovementioned results, a plausible reaction pathway was proposed, as shown in Scheme 6. Initially, a ring-chain tautomerization of D.-enol and keto-enol tautomerization from ketones (products) to α-amino enol D. An extremely favored energy profile suggests that α-imino Rh(II) carbene A can possibly yield key intermediate α-amino enol D via metal-associated ylide B. This active ylide B subsequently undergoes a 1,4-proton transfer to afford key intermediate α-imino enol D, regenerating the rhodium(II) catalyst. Simultaneously, the other key intermediate, vinylimine intermediate E, is generated in situ from indole and paraformaldehyde via a water-associated transition state. Finally, vinylimine intermediate E is attacked by α-amino enol D to generate the multicomponent product with release of water.

In summary, an MCR based on the trapping of an active α-imino enol intermediate in a traditional two-component reaction pathway was successfully illustrated. This transformation was realized by trapping active α-imino enol intermediates obtained using 1-sulfonyl-1,2,3-triazoles as precursors by vinylimine ions generated in situ from indoles and paraformaldehyde to suspend the traditional enol-ketone tautomerization in favor of a new multicomponent pathway in the presence of rhodium(II) acetate as catalyst. Compared to classical NHC intermediates, the enolic carbon had a stronger nucleophilicity than that of the enamic carbon in the trapping process. Both series of control experiments and detailed DFT theoretical calculations aided to demonstrate the MCR mechanism. The developed MCR provides a mild, efficient, and convenient access to α-amino-β-indole ketones, and further synthetic application of the resulting products was illustrated.

Although the presently developed MCR has a substrate scope limitation, its extension to other electrophiles other than paraformaldehyde as trapping reagents, such as benzaldehyde, could provide a mean to achieve an asymmetric version of this MCR. Further efforts on extending this process to different reactants and trapping other active intermediates for the discovery of new MCRs are currently being pursued in our laboratory.

MATERIALS AND METHODS

Experimental design

All 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on Bruker spectrometers using CDCl3 as solvent. Tetramethylsilane served as internal standard (δ = 0) for 1H NMR, whereas CDCl3 was used as internal standard (δ = 77.0) for 13C NMR. Chemical shifts were reported in parts per million with the following multiplicity: singlet, doublet, triplet, quartet, multiplet, and broad. HRMS was performed on IonSpec Fourier transform–ion cyclotron resonance or Waters Micromass Q-TOF micro synapt high definition mass spectrometry. Melting points were uncorrected. Single-crystal x-ray diffraction data (6i) were recorded on a Bruker-AXS SMART APEX II single-crystal x-ray diffractometer.
0.02 eq) were added to an oven-dried test tube. The test tube was placed under an air atmosphere. Chlorobenzene (2.0 ml) was added, and the reaction was heated at 140°C under vigorous stirring for 15 to 30 min. After completion of the reaction (monitored by TLC or LC-MS), the mixture was cooled to room temperature and all the volatiles were removed in vacuum. The resulting crude residue was purified by flash chromatography (EA/PE, 1:15 to 1:8) to provide the title compound.

General procedure for the control experiment
Indole (0.5 mmol, 5.0 eq), triazole 1 (0.1 mmol, 1.0 eq), paraformaldehyde (0.4 mmol, 4.0 eq), H$_2$O$_{18}$ (1.0 mmol, 10.0 eq), and Rh$_2$(OAc)$_4$ (0.9 mg; 0.02 mmol, 0.02 eq) were added to an oven-dried test tube. The test tube was placed under an air atmosphere. Chlorobenzene (1.0 ml) was added, and the reaction was heated at 140°C under vigorous stirring for 15 to 30 min. After completion of the reaction (monitored by TLC or LC-MS), the mixture was cooled to room temperature and all the volatiles were removed in vacuum. The crude residue was purified by flash chromatography (EA/PE, 1:15 to 1:8) to provide oxazolidin-2-one 6i.

Triazole 11 (0.1 mmol, 1.0 eq), paraformaldehyde (0.4 mmol, 4.0 eq), 4 Å molecular sieves (30 mg), and Rh$_2$(OAc)$_4$ (0.9 mg; 0.02 mmol, 0.02 eq) were added to an oven-dried test tube. The test tube was placed under an air atmosphere. Chlorobenzene (1.0 ml) was added, and the reaction was heated at 140°C under vigorous stirring for 15 to 30 min. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and all the volatiles were removed in vacuum. The reaction was monitored by LC-MS, but we failed to obtain the two-component product 8 of the reaction of II with paraformaldehyde.

General procedure for the synthesis of oxazolidin-2-one 12 (105)
A 2.5 M LiAlH$_4$ solution (0.4 mmol) in THF was added to a stirred solution of 6c (82 mg, 0.2 mmol) in THF (2.0 ml) at 0°C. The mixture was stirred at 0°C for 1 hour. After completion of the reaction (monitored by TLC or LC-MS), the mixture was quenched with 1 M aq. HCl and extracted with EA (×2). The combined organic layers were washed with saturated aq. NaHCO$_3$ and brine and then dried over MgSO$_4$. After evaporation under reduced pressure, the residue was purified by silica gel flash column chromatography (PE/EA, 10:1 to 3:1) to provide α-amino alcohol 11 (71 mg, yield 85%) as a yellow solid. Pyridine (0.1 ml) and triphosgene (19 mg, 0.06 mmol) in CH$_2$Cl$_2$ (0.5 ml) were added to a stirred solution of 11 (20 mg, 0.05 mmol) in CH$_2$Cl$_2$ (1.0 ml) at −98°C. The mixture was stirred at −78°C for 20 min and then gradually warmed to room temperature for more than 1 hour. The mixture was quenched with 1 M aq. HCl and extracted with EA (×2). The combined organic layers were washed with saturated aq. NaHCO$_3$ and brine and then dried over MgSO$_4$. After evaporation under reduced pressure, the residue was purified by silica gel flash column chromatography (PE/EA, 10:1 to 3:1) to provide oxazolidin-2-one 12 (10 mg, yield 52%) as a white solid.

Computational methods
All the DFT calculations were carried out by using the Gaussian09 software package (106). The structures of intermediates and transition states were optimized using the M06 (107) functional combined with the 6-31G* (108) basis set for nonmetal elements as well as the LanL2dz (109) basis set for metal elements, which is denoted as the M06/LanL2dz +6-31G* method. The single-point energy calculations and frequency analyses were further performed on the basis of the optimized structures, with the larger basis sets of 6-311G** (108) basis set used for nonmetal elements and the Stuttgart/Dresden (SDD) (110) basis set used for metal elements, denoted as the M06/SDD+6-311G** method. The solution effect of chlorobenzene was estimated using the Solvation Model based on Density (SMD) model (111) in Gaussian09 on the basis of the optimized structures in gas phase. All the energies presented in the content refer to the Gibbs free energies $\Delta G_{\text{sol}}$ calculated at the temperature of 140°C, including the corrections of solvation energies in chlorobenzene.

SUPPLEMENTARY MATERIALS
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/3/e1602467/DC1

fig. S1. Rate-determining step of the proton transfer process compared with the active intermediate generation step in the reaction coordinate of the X-H (X = O, N) insertion product formation.
fig. S2. Single-crystal x-ray structure determination of compound 6i (CCDC no. 1407544).
fig. S3. Two-dimensional 1H-1H NOESY spectrum of compound 12.
fig. S4. LC-MS spectra of the reaction solution containing indole, triazole, paraformaldehyde, H$_2$O$_{18}$, and Rh$_2$(OAc)$_4$.
fig. S5. LC-MS spectra of the reaction solution containing indole, triazole, paraformaldehyde, and Rh$_2$(OAc)$_4$.
fig. S6. Calculated free energy profiles of the formation of vinylimine ion E at 140°C in chlorobenzene.
table S1. Reaction condition screening.
data file S2. X-ray crystal data.
data file S3. NMR spectra of compounds.
data file S4. DFT calculation data.

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