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Divergent Rhodium-Catalyzed Electrochemical Vinylic C–H Annulation of Acrylamides with Alkynes

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Abstract

A Rh-catalyzed electrochemical vinylic C–H annulation of acrylamides with alkynes has been developed in an undivided cell, affording cyclic products in good to excellent yield. Divergent syntheses of α -pyridones and cyclic imidates are accomplished by employing N-phenyl acrylamides and N-tosyl acrylamides as substrates, respectively. Additionally, excellent regioselectivities are achieved when using unsymmetrical alkynes. This electrochemical process is environmentally benign compared to traditional transition metal-catalyzed C–H annulations because it avoids the use of stoichiometric metal oxidants. DFT calculations elucidated the reaction mechanism and origins of substituent-controlled chemoselectivity. The sequential C–H activation and alkyne insertion under rhodium catalysis leads to the seven-membered ring vinyl-rhodium intermediate. This intermediate undergoes either the classic

neutral concerted reductive elimination to produce α -pyridones, or the ionic stepwise pathway to produce cyclic imidates.

Introduction

α -Pyridones and α -pyrones are ubiquitous structural motifs found in natural products and biologically active small molecules.¹ Transition metal-catalyzed vinylic C–H annulation of acrylic amides or acrylic acids with alkynes has recently emerged as one of the most powerful tools for their synthesis.² In 2009, Miura and co-workers described an early example of Rh-catalyzed oxidative coupling of substituted acrylic acids with terminal alkynes using Ag_2CO_3 as the oxidant, affording α -pyrones.³ Subsequently, the groups of Li and Rovis reported Rh-catalyzed vinylic C–H annulation of acrylamides with alkynes to afford α -pyridones under elevated temperature using stoichiometric transition metal oxidants (Scheme 1A, left side).⁴ Inspired by these seminal works, various transition metal-catalyzed vinylic C–H annulation reactions with alkynes have been developed to prepare α -pyridones or α -pyrones, including ones catalyzed by Rh,⁵ Ru,⁶ Co,⁷ Pd,⁸ and Fe⁹ catalysts. Despite these advances, important challenges remain, including: 1) typically high reaction temperatures (100–120 °C); 2) stoichiometric transition metal oxidants such as $\text{Cu}(\text{OAc})_2$ or AgOAc are generally required to regenerate catalysts; 3) a highly selective divergent synthesis of α -pyridones and cyclic imidates (Scheme 1A, right side) from acrylamides is still lacking.^{4a}

Electrochemical organic synthesis has received tremendous attention because electric current offers an environmentally benign alternative to conventional methods for oxidation and reduction of organic compounds, such as those involving chemical oxidants and reductants.^{10–}

¹² Transition metal-catalyzed electrochemical arene C–H annulation with alkynes has been

Scheme 1. Rh-Catalyzed Vinylic C–H Annulation of Acrylamides with Alkynes

developed using catalysts including Co,¹³ Ru,¹⁴ Rh,¹⁵ and Cu.¹⁶ In contrast, electrochemical vinylic C–H annulation with alkynes is less studied. Recently, we reported an Ir-catalyzed electrochemical vinylic C–H annulation reaction of acrylic acids with internal alkynes, affording α -pyrones in good yields, but terminal alkynes are not tolerated.¹⁷ Subsequently, Ackermann and co-workers demonstrated Ru-catalyzed electrochemical vinylic C–H annulation of acrylamides with symmetric internal alkynes at elevated temperature (140 °C).¹⁸ Herein, we report the first example of a transition metal-catalyzed electrochemical vinylic C–H annulation of acrylamides with alkynes in an undivided cell under mild reaction conditions, specifically by the action of a Rh catalyst. Importantly, divergent syntheses of α -pyridones and cyclic imidates are achieved by varying the N-substituent of the acrylamides. Furthermore, terminal alkynes are well tolerated in this Rh-catalyzed electrochemical vinylic C–H annulation (Scheme 1B). We also probed the reaction mechanism by carrying out cyclic voltammetric analysis and kinetic isotopic experiments. Density functional theory (DFT) calculations elucidated origins of substituent-controlled chemoselectivity. The sequential C–H activation

and alkyne insertion under rhodium catalysis leads to the seven-membered ring vinyl-rhodium intermediate. This intermediate undergoes either the classic neutral concerted reductive elimination to produce pyridones, or the ionic stepwise pathway to produce cyclic imidates. The electronic nature of the N-substituent has exactly the reversal effect on the rates of neutral concerted and ionic stepwise reductive elimination pathways, which switches the chemoselectivity.

Results and discussion

Optimization Studies. Initially, we probed various reaction conditions using 2-methylacrylamide (**1a**) and diphenylacetylene (**2a**) as reaction partners in an undivided cell (Table 1, and see Table S1–S5 in the Supporting Information). To our delight, using (Cp*RhCl₂)₂ as the precatalyst, *n*-Bu₄NOAc as the electrolyte, and MeOH as the solvent in an undivided cell with two platinum electrodes under constant-current electrolysis at 1.5 mA for seven hours at 60 °C or room temperature, cyclic imidate **3a** can be obtained in 91% isolated yield (Table 1, entry 1). Acetonitrile as solvent affords a similar yield, while yield diminishes significantly when other solvents are used (entries 2–5). Other electrolytes such as NaOAc and NaOPiv result in slightly lower yields (entries 6 and 7). Control experiments show that no significant amount of annulation product is produced in the absence of the catalyst or electric current (entries 8 and 9). To our delight, 92% isolated yield is obtained when the reaction is carried out with IKA ElectraSyn 2.0 at room temperature (entry 10).¹⁹ Interestingly, switching to the synthesis of α -pyridones instead of cyclic imidates can be achieved by simply changing the N-substitution of acrylamides (entries 11–13). α -Pyridone **4b** can be obtained in 95%

isolated yield when N-phenyl acrylamide **1b** is used (entry 11). Other N-aryl groups afford lower yields with good selectivity of α -pyridones versus cyclic imidates (entries 12 and 13).

Table 1. Annulation Optimization with Acrylamide 1a and Diphenylacetylene

entry	1 (R)	variation from standard conditions ^a	yields(%) ^b	
			3	4
1	1a (Ts)	none	99 (91) ^c	-
2	1a	CH ₃ CN instead of MeOH	98	-
3	1a	DMF instead of MeOH	20	-
4	1a	CF ₃ CH ₂ OH instead of MeOH	17	-
5	1a	HFIP instead of MeOH	9	-
6	1a	NaOAc instead of <i>n</i> -Bu ₄ NOAc	86	-
7	1a	NaOPiv instead of <i>n</i> -Bu ₄ NOAc	82	-
8	1a	no (Cp [*] RhCl ₂) ₂	-	-
9	1a	no electric current	< 5%	-
10	1a (Ts)	IKA ElectraSyn 2.0	92 ^{c,d}	-
11	1b (Ph)	none	-	4b (95) ^c
12	1c (<i>p</i> -NO ₂ -C ₆ H ₄)	none	< 5%	4c (86) ^c
13	1d (<i>p</i> -OMe-C ₆ H ₄)	none	< 5%	4d (42) ^c

^aReaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), (Cp^{*}RhCl₂)₂ (4 mol%), *n*-Bu₄NOAc (3.0 equiv) and MeOH (3 mL), in an undivided cell with two platinum electrodes (each 1.0 x 1.0 cm²), 60 °C, 1.5 mA, 7 h. ^bThe yield was determined by ¹H NMR using 1,4-dimethoxybenzene as an internal standard. ^cIsolated yield. ^dRoom temperature.

Versatility. With the optimized reaction conditions in hand, we investigated the generality of this electrochemical C–H annulation. As shown in Table 2A, various acrylamides substituted with alkyl, ester, ether, aryl, fluoro, chloro, and bromo groups are well tolerated, affording the corresponding cyclic imidates in good to excellent yields (**3a**, **6a–6r**). A variety of alkynes react well, including diarylacetylenes (**7a–7l**) and dialkylacetylenes (**7m–7o**). With unsymmetrical alkynes, regioselectivity is governed by arene electronics. For example, moderate

Table 2. Substrate Scope for Cyclic Imidate Synthesis

A. Scope for the synthesis of iminoesters with Ika ElectraSyn 2.0

B. Gram-scale experiment and synthetic application

^aIsolated yields are reported. Reaction conditions: **1a** or **5** (0.3 mmol), **2** (0.2 mmol), $(\text{Cp}^*\text{RhCl}_2)_2$ (4 mol%), $n\text{-Bu}_4\text{NOAc}$ (3.0 equiv), and MeOH (6 mL) in an undivided cell with two platinum electrodes (each 3.0 x 0.8 cm²), room temperature, 1.5 mA, 7–12 h. ^b**5** (0.15 mmol), **2** (0.3 mmol). ^cThe reaction was carried out at 60 °C.

regioselectivity is achieved with *n*-butyl phenyl acetylene (**7p**). In contrast, excellent regioselectivities are obtained when electron-deficient arylacetylenes are employed (**7q** and **7r**). In addition, excellent regioselectivities and yields are accomplished using terminal alkynes, with the alkyl or aryl groups oriented proximal to the oxygen heteroatom in the product (**7s**–**7x**). (As a reminder, terminal alkynes are not tolerated in the aforementioned Ir-catalyzed electrochemical C–H annulation.¹⁷) Furthermore, the structures of **3a**, **6c**, **6o**, **7r**, and **7s** were unambiguously verified by X-ray analysis. Finally, we demonstrated the preparative utility of this Rh-catalyzed electrochemical C–H annulation reaction by running a reaction containing 6.0 mmol of substrate **1a** and 4.0 mmol of substrate **2a** to afford cyclic imide **3a** in 84% yield, which can be further converted into α -pyrone **3aa** (Table 2B).

Table 3. Substrate Scope for α -Pyridone Synthesis^a

^aReaction conditions: **1b** or **8** (0.3 mmol), **2** (0.2 mmol), $(\text{Cp}^*\text{RhCl}_2)_2$ (4 mol%), *n*-Bu₄NOAc (3.0 equiv) and MeOH (3 mL), in an undivided cell with two platinum electrodes (each 1.0 x 1.0 cm²), 60 °C, 1.5 mA, 7–12 h

We also examined the reactivity of a series of substituted acrylamides and alkynes for the synthesis of α -pyridones (Table 3). Acrylamides bearing a variety of functional groups such as

alkyl, ester, ether, and aryl are well tolerated under the standard reaction conditions, affording α -pyridones in moderate to good yields (**4b**, **9a–9l**).

Mechanistic Investigation. A series of experiments were carried out to elucidate the mechanism of this electrochemical C–H annulation reaction. First, acrylamide **1a** was subjected to the electrochemical C–H annulation reaction conditions in CH₃OD in the absence of an alkyne. Significant H/D exchange was observed, indicating that the putative C–H activation step is reversible (Scheme 2A). A kinetic isotope effect (KIE) value was determined by comparing parallel experiments using acrylamide **5e** and corresponding deuterated substrate **5e-d4** (Scheme 2B). A KIE value of 1.4 was observed (see Supporting Information for details). In addition, we executed the stoichiometric reaction of acrylamides, diphenylacetylene **2a**, and (Cp*RhCl₂)₂ in the absence of electric current. To our delight, the rhodium sandwich complexes **10** and **11** were obtained in good yield, with the corresponding cyclic imidate as a neutral η^4 ligand. Their structures were unambiguously confirmed by X-ray analysis (Scheme 3A). Upon anodic oxidation, the product **3a** is released from **10**, and is a coordinatively saturated, 18-electron complex (Scheme 3B). Additionally, **3a** is obtained in good yield when a catalytic amount of **10** is employed, which suggests that **10** is a competent intermediate and catalyst in this electrochemical C–H annulation (Scheme 3C).

Complex **10** in 0.1 M solution of *n*-Bu₄NPF₆ in MeCN exhibits the first oxidation peak at 0.70 V versus SCE (curve d, Figure 1), which is significantly lower than the oxidation potentials for the oxidation of other components in the reaction system (Figure 1). This supports the hypothesis that the role of anodic oxidation is to oxidize a diene-Rh(I) complex to an active Rh(III) species with concomitant release of the product.

A. H/D exchange experiment

B. Kinetic isotopic effect experiments

Scheme 2. H/D Exchange Experiment and Kinetic Isotopic Effect Experiments

A. Stoichiometric reactions in the absence of electric current

B. Anodic oxidation of complex 10

C. Catalytic reaction with complex 10

Scheme 3. Stoichiometric Reaction

Figure 1. Cyclic Voltametric study. Cyclic voltammograms recorded on a Pt electrode (area = 0.03 cm²) with a scan rate of 100 mV s⁻¹: (a) MeCN containing 0.1 M *n*-Bu₄NPF₆; (b) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM **3a**; (c) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM **1a**; (d) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM **10**; (e) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM complex (Cp^{*}RhCl₂)₂; (f) MeCN containing 0.1 M *n*-Bu₄NPF₆, after addition of 4 mM **2a**.

Computational Results. We next explored the reaction mechanism and the origins of substrate-controlled chemoselectivity through density functional theory (DFT) calculations²⁰. From the active catalyst Cp^{*}Rh(OAc)₂, sequential vinyl C–H activation of N-tosyl acrylamide **1a** and diphenylacetylene insertion generate the seven-membered ring vinyl–rhodium intermediate **int1** (Figure S1 and Figure 2).²¹ **Int1** can undergo competing reductive eliminations to form either the α -pyridone product or cyclic imidate (Figure 2). The classic neutral concerted reductive elimination (red pathway) occurs through the three-membered ring transition state **TS2**, generating the α -pyridone product-coordinated complex **int3**. This neutral concerted reductive elimination requires an insurmountable barrier of 31.6 kcal/mol, which is unfeasible under the experimental conditions. Alternatively, we found that the ionic stepwise pathway (black pathway) can be operative and produce the cyclic imidate product. This ionic stepwise pathway, discovered by Hong and coworkers²² in a similar Ru-catalyzed transformation, initiates through a heterolytic cleavage of the Rh–N bond via **TS5** with the assistance of methanol to generate the zwitterionic intermediate **int6**. From **Int6**, methanol dissociates to generate **int7**, subsequent facile C–O bond formation through **TS8** produces **int9**. The zwitterionic species **int7** also has the possibility for Rh–O bond formation via **TS10**.

(labeled in purple), but requiring a higher barrier as compared to the C–O bond formation.

Comparing the free energy barriers of the two competing pathways, the ionic stepwise reductive elimination is more favorable by 7.7 kcal/mol (**TS2** vs. **TS5**), which is consistent with the experimental chemoselectivity favoring cyclic imidate when N-tosyl acrylamide is employed.

Figure 2. DFT-computed free energy changes in competing for reductive elimination pathways from seven-membered ring vinyl-rhodium intermediate when N-tosyl acrylamide **1a** was employed as the substrate.

The DFT-computed free energy changes of the same competing reductive elimination pathways for the N-phenyl acrylamide **1b** substrate are shown in Figure 5. From N-phenyl acrylamide **1b**, the sequential vinyl C–H activation and diphenylacetylene insertion generate the seven-membered ring vinyl–rhodium intermediate **int12** (Figure S2). This intermediate can undergo the classic neutral concerted reductive elimination pathway via **TS13** (red pathway), with a barrier of 21.9 kcal/mol. The alternative ionic stepwise pathway through **TS16** is significantly less favorable due to the unstable zwitterionic species **int18**. Comparing to the tosyl substituent, the phenyl substituent significantly lowers the barrier of the neutral concerted pathway while

Figure 3. DFT-computed free energy changes in competing for reductive elimination pathways from seven-membered ring vinyl–rhodium intermediate int10 when N-phenyl acrylamide **1b** was employed as the substrate.

increasing the barrier of the ionic stepwise pathway, which results in the chemoselectivity reversal. The acceleration of the neutral concerted reductive elimination by the phenyl substituent is consistent with Hartwig’s previous mechanistic studies;²³ the electron-donating substituent on the reactive ligand undergoing reductive elimination would decrease the ionic character of the metal–ligand bond, leading to a weaker metal–ligand bond and lower reductive elimination barrier. For the ionic stepwise pathway, the stability of the zwitterionic intermediate—more specifically the stability of the anionic terminal—depends highly on the N-substituent. The electron-donating phenyl substituent destabilizes this zwitterionic intermediate, leading to a 27.3 kcal/mol endergonic Rh–N bond cleavage from **int12** to **int18** (Figure 3), while the same process is only 3.0 kcal/mol endergonic with the electron-

withdrawing tosyl substituent (**int1** to **int7**, Figure 2). Therefore, the electronic nature of Ts and Ph N-substituents has opposing effects on the rates of neutral concerted and ionic stepwise reductive elimination pathways, which accounts for the chemoselectivity switch. These insights provide a mechanistic basis for rational reaction design in related transformations.

Scheme 4. Plausible Catalytic Cycle

Based on our mechanistic studies, we propose a plausible catalytic cycle as shown in Scheme 4. Initially, C–H activation takes place to afford a cyclometallated Rh(III) intermediate **B**, following ligand exchange to deliver complex **C**. Next, migratory alkyne insertion results in the seven-membered rhodium complex **D**,²⁴ which undergoes ionic stepwise or neutral concerted reductive elimination to give Rh(I) complex **10** or **E**. Intermediate **10** or **E** is a coordinately saturated, 18-electron complex. Upon anodic oxidation, the product is released from **10** or **E**, and complex **A** is regenerated.

Conclusions

In summary, we have demonstrated the first example of Rh(III)-catalyzed electrochemical vinylic C–H annulation of acrylamides with alkynes in an undivided cell under mild reaction

conditions. Owing to the robustness of this electrochemical C–H annulation, the reaction can be operated with IKA ElectraSyn 2.0 at room temperature, affording cyclic imidates with good to excellent yields. Additionally, divergent syntheses of α -pyridones and cyclic imidates are realized by simply switching the N-substitution of acrylamides. Furthermore, excellent regioselectivities are achieved with unsymmetrical alkynes, including terminal alkynes. Mechanistic and DFT studies combined to provide a rationale for the chemoselectivity switch and a basis for future reaction design in related transformations.

EXPERIMENTAL PROCEDURES

General Procedure for the Electrolysis. The electrocatalysis was carried out in an IKA ElectraSyn 2.0 equipped with two platinum electrodes (each $0.8 \times 3.0 \text{ cm}^2$). Acrylic amide (0.3 mmol, 1.5 equiv), alkyne (0.2 mmol, 1.0 equiv), *n*-Bu₄NOAc (0.6 mmol, 3.0 equiv) and (Cp*RhCl₂)₂ (4.0 mol %, 99 wt.%) were dissolved in MeOH (6.0 mL). Electrocatalysis was performed at room temperature with a constant current of 1.5 mA maintained for 7–12 h (2.0–3.4 F mol⁻¹). After the reaction, the mixture was concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the annulation product.

More experimental procedures and photographic guide for electrochemical C–H annulation are provided in the Supplemental Information.

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Tian-Sheng Mei (mei7900@sioc.ac.cn).

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AUTHOR CONTRIBUTIONS

Y.-K.X. and Q.-L.Y. discovered the reaction. X.-R.C. and S.-Q.Z. performed the DFT calculation. H.-M.G., X.H., and T.-S.M. directed the project. Y.-K.X., X.H. and T.-S.M. wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Figures

Figure 1

Cyclic Voltametric study. Cyclic voltammograms recorded on a Pt electrode (area = 0.03 cm²) with a scan rate of 100 mV s⁻¹: (a) MeCN containing 0.1 M n-Bu₄NPF₆; (b) MeCN containing 0.1 M n-Bu₄NPF₆, after addition of 4 mM 3a; (c) MeCN containing 0.1 M n-Bu₄NPF₆, after addition of 4 mM 1a; (d) MeCN containing 0.1 M n-Bu₄NPF₆, after addition of 4 mM 10; (e) MeCN containing 0.1 M n-Bu₄NPF₆, after addition of 4 mM complex $(\text{Cp}^*\text{RhCl}_2)_2$; (f) MeCN containing 0.1 M n-Bu₄NPF₆, after addition of 4 mM 2a.

Figure 2

DFT-computed free energy changes in competing for reductive elimination pathways from seven-membered ring vinyl-rhodium intermediate when N-tosyl acrylamide 1a was employed as the substrate.

Figure 3

DFT-computed free energy changes in competing for reductive elimination pathways from seven-membered ring vinyl–rhodium intermediate int10 when N-phenyl acrylamide 1b was employed as the substrate.

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