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Study of Sustainability and Scalability in the Cp*Rh(III)-Catalyzed Direct C−H Amidation with 1,4,2-Dioxazol-5-ones

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Supporting Information

ABSTRACT: The practical aspects of Cp*Rh(III)-catalyzed direct C−H amidation with 1,4,2-dioxazol-5-ones were investigated on the operational safety, use of green solvent, and scalability. Differential scanning calorimeter (DSC) measurement showed that 3-phenyl-1,4,2-dioxazol-5-one is thermally stable while benzoyl azide, a conventionally employed precursor of acyl nitrene, rapidly decomposes to isocyanate. It was confirmed that the replacement of acyl azide with 1,4,2-dioxazol-5-one brings not only high reactivity but also improvement in safety. In respect to a green process development, functional group tolerant Cp*Rh(III) catalyst exhibited high reactivity in ethyl acetate, successfully replacing 1,2-dichloroethane solvent used in the original report. Upon the validation on safety and environmental concerns, scalability was also tested. Two different types of arenes bearing pyridyl and oxime directing groups showed excellent conversions on tens of gram scale reactions, and single recrystallization gave desired products with high yields and purity.

INTRODUCTION

Direct C−H amination is one of the most important themes in C−H functionalization which has been studied intensively by many research teams, eventually replacing conventional approaches utilizing alkenyl or aryl (pseudo)halides.[1,2] Our group has also participated in the development of highly efficient and environmentally benign catalytic C−H amination reactions.[3] During the search of robust catalytic systems, we recently disclosed Cp*Rh(III)-catalyzed C−H amidation with 1,4,2-dioxazol-5-ones, which possesses attractive features such as low catalyst loading, mild conditions, broad scope of substrates with high functional group tolerance, no requirement of external oxidants, and release of carbon dioxide as a single byproduct (Scheme 1).[4]

Our mechanistic investigation on the Cp*Rh(III)-mediated C−H amidation process unveiled that competitive binding of the rhodium metal center to an amidating reagent or substrate is closely related to the reaction efficiency (Scheme 2).[3a−c,4] An amino precursor with strong coordination affinity would facilitate the formation of a metallacycle intermediate **3** bound to an amidating reagent over the resting state **2**. A group of dioxazolone derivatives were found to have 10^3 to 10^8 times higher coordination propensity than organic azides. Among those dioxazolones, 1,4,2-dioxazol-5-one exhibited especially excellent efficiency on the imido insertion process, thus leading to a robust catalytic C−H amidation system. In addition to the observed high reactivity, 1,4,2-dioxazol-5-ones were found to be more convenient for the preparation, storage, and use when compared to the corresponding acyl azides.

To obtain an additional feature of this C−H amidation protocol, we decided to scrutinize the practical aspect of the originally optimized reaction conditions. When a reaction goes to a large-scale production, many factors should be considered and adjusted mainly due to the critical issues of reproducibility, safety, environmental effect, cost, and so on.[5] Described herein is our investigations on the safety, environmental parameters including solvent, and scalability (Scheme 3).

RESULTS AND DISCUSSION

Safer Amidating Reagent—Acyl Azide versus 1,4,2-Dioxazol-5-one. Acyl azides have been known as a facile carbon donor to furnish an amide group upon the Curtius rearrangement to the corresponding isocyanates.[6] For the utilization of acyl azides as a nitrogen donor in the acyl amino group transfer, our group recently developed two complementary catalytic systems of Ir(III) and Ru(II), which have opened a new synthetic opportunity of acyl azides in organic synthesis.[3a,d,e] However, their fast rearrangement to isocyanates still leaves a concern on the selectivity and safety in the use of acyl azides.[3e] In particular, the safety issue related to an explosiveness of azide compounds always hampers large-scale applications.[7] In this context, dioxazolones have drawn attention as safe alternatives to acyl azides.[8] Research teams of Sanofi[9] and Pfizer[10] demonstrated the process applicability of dioxazolones as an intermediate for the isocyanate formation (Lossen rearrangement).[11] Given that acyl nitrene is a common intermediate obtained from both acyl azide and dioxazolone, several examples were reported for the use of dioxazolones as an acyl nitrene source including our recent development of highly reactive Cp*Rh(III)-mediated C−H amidation (Scheme 4).[4,12]

Recently, the research team of Sanofi briefly described the excellent thermal stability of dioxazolones over azides during the process development of Lossen rearrangement on a kilogram scale.[9] To gain detailed information, we conducted differential scanning calorimeter (DSC) measurements of benzoyl azide (**7**) and 3-phenyl-1,4,2-dioxazol-5-one (**8**). In

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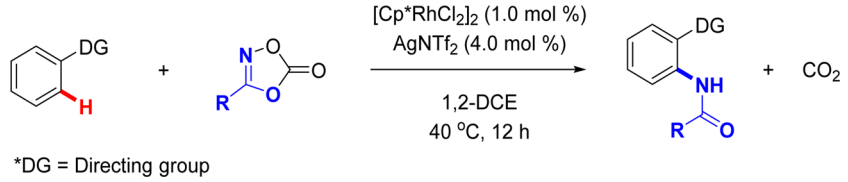
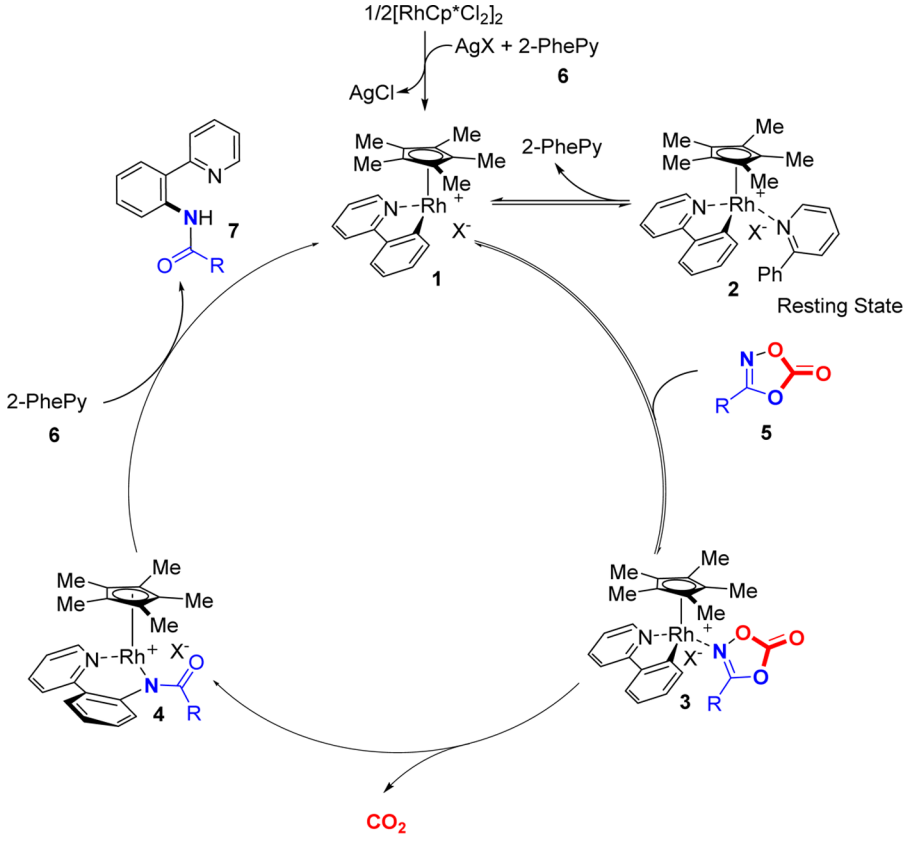
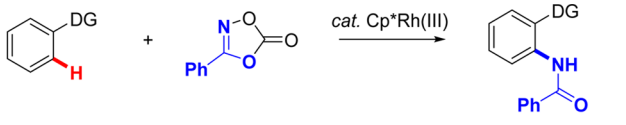
Scheme 1. Robust Cp*Rh(III)-Catalyzed C−H Amidation with 1,4,2-Dioxazol-5-one



Scheme 2. Mechanistic Proposal of Rh(III)-Catalyzed C−H Amidation with 1,4,2-Dioxazol-5-one



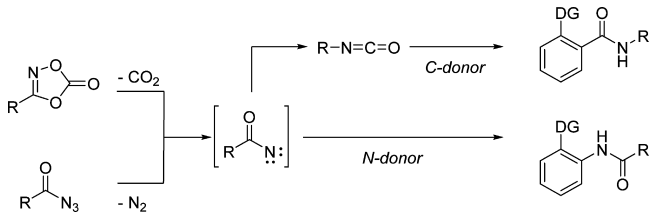
Scheme 3. Practical Aspects of Cp*Rh(III)-Catalyzed C−H Amidation with 1,4,2-Dioxazol-5-ones



Sustainable and Scalable Direct C–H Amidation

• Solvent : Ethyl Acetate • Safety : Confirmed • Scale Test : > 40 g

Scheme 4. *N*-Acyl Nitrene Formation from Acyl Azides or 1,4,2-Dioxazol-5-ones



the temperature range of −20−100 °C, crystallization temperature (T_c) and melting temperature (T_m) were observed during the first and second cycle of benzoyl azide treatment (Figure 1a). There was an abrupt decrease in intensity of both T_c and T_m peaks on the second cycle. This result can be attributed to the thermal degradation of benzoyl azide to isocyanate upon heating so that the amount of benzoyl azide is decreased accordingly. In the third cycle, no peaks of benzoyl azide were observed, again confirming the complete decomposition. In a stark contrast, when 3-phenyl-1,4,2-dioxazol-5-one was subjected to the same conditions, both T_c and T_m curves did not show any noticeable degradation over three cycles (Figure 1b). The melting enthalpy of dioxazolone **8** remained almost similar after stabilization (93.2 J/g on second cycle and 91.3 J/g on third cycle, Table 1), which indicates the good thermal stability compared to benzoyl azide. In our previous protocol of the Rh-catalyzed amidation by using 3-phenyl-1,4,2-dioxazol-5-one,[4] CO_2 was found to be released only by the action of Rh(III) catalyst so that the uncontrolled self-decomposition is not expected to occur under the optimized experimental conditions. However, we would like to emphasize that several classes of 1,4,2-dioxazol-5-ones, for example 3-fluororoalkyl ones, are known to detonate under relatively mild conditions, thus still

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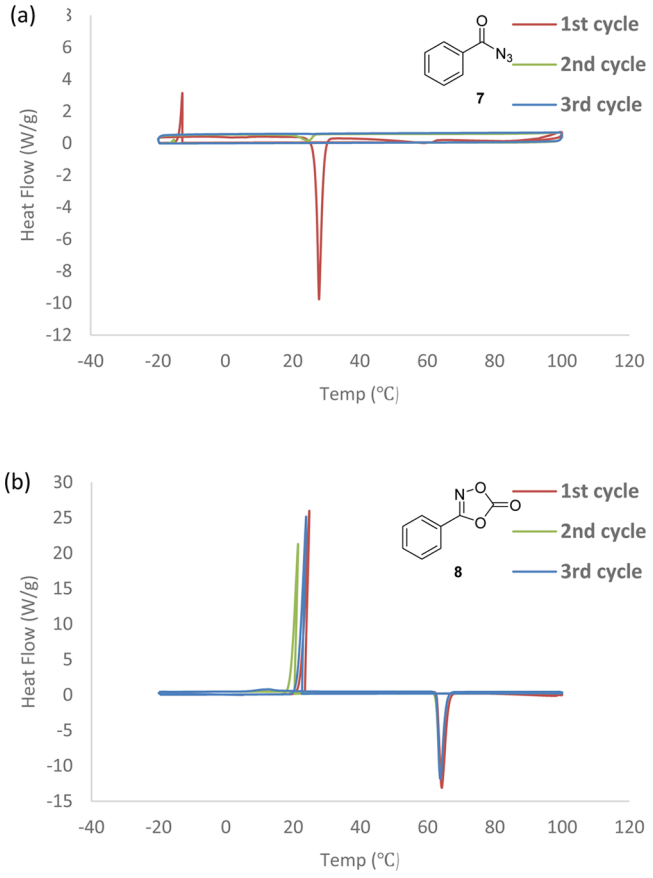


Figure 1. DSC measurement of (a) benzoyl azide **7** and (b) 3-phenyl-1,4,2-dioxazol-5-one **8**.

Table 1. Melting and Crystallization Enthalpies of 3-Phenyl-1,4,2-dioxazol-5-one[a]

ΔH (J/g)	1st cycle	2nd cycle	3rd cycle
crystallization	80.1	67.2	78.9
melting	112	93.2	91.3

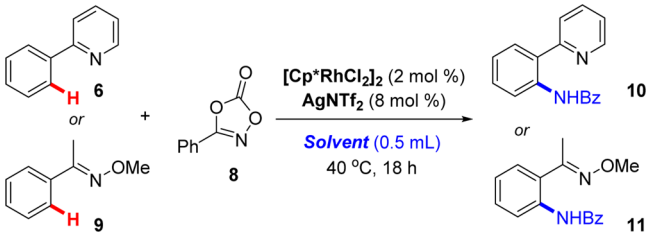
[a]Each value was obtained from the integral of crystallization and melting peak on DSC measurement. See the Supporting Information for details.

special caution should be applied on the dioxazolone handling.[12a]

Solvent Study. In our previously reported procedures on the direct C−H amidation, most reactions employed 1,2-dichloroethane as a solvent,[3,4] which has also been found to be highly efficient in numerous examples of other types of C−H functionalizations as well (Scheme 1). Upon the awareness of its undesirable side effects to environment, 1,2-dichloroethane is mostly banned in industrial applications.[13] Therefore, we envisaged that the replacement of 1,2-dichloroethane by greener solvents would increase the value of our amidation protocols.

In this context, a list of organic solvents were examined in the Cp*Rh(III)-mediated C−H amidation with 3-phenyl-1,4,2-dioxazol-5-one (**8**, Table 2). Two different substrates bearing pyridine and ketoxime directing groups were applied to validate the generality of this amidation reaction. With a 2.0 mol % catalyst loading, protic solvents such as alcohols and acids showed good efficiency with 2-phenylpyridine (**6**), but low conversion was observed with ketoxime-containing arene (**9**,

Table 2. Solvent Study in the C−H Amidation of Two Substrates with 3-Phenyl-1,4,2-dioxazol-5-one[a]



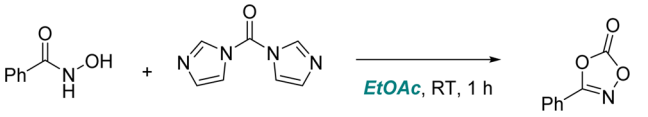
		yield (%)[b]	
entry	solvent	**10**	**11**
1	1,2-DCE	99	89
2	methanol	89	01
3	*t*-butanol	92	73
4	acetic acid	89	58
5	acetonitrile	20	<1
6	acetone	83	89
7	dimethylformamide	65	<1
8	**ethyl acetate**	**99**	**99**
9	tetrahydrofuran	91	75
10	1,2-dimethoxyethane	95	89
11	toluene	91	01

[a]Substrate (0.20 mmol) and **8** (0.22 mmol). [b]NMR yields (internal standard: 1,1,2,2-tetrachloroethane).

entries 2−4). Acetonitrile was ineffective for both substrates presumably due to the strong affinity of solvent to the metal center, thus blocking imido complex formation (entry 5). A series of polar aprotic solvents gave good conversion overall (entries 6−10). Delightfully, excellent reactivity was observed in ethyl acetate, a desirable green solvent for the process chemistry. The use of ethyl acetate as a reaction solvent is not a general option because of reactive ester functionality. We believe that excellent functional group tolerance and mild reaction conditions of the present Cp*Rh(III) catalytic system make it possible to accommodate ethyl acetate as a reaction medium.[4]

We also examined a similar solvent screening in the preparation of 1,4,2-dioxazol-5-ones to accommodate the guidelines.[13] The replacement of solvent to ethyl acetate from dichloromethane turned out to be successfully adaptable in a reaction between carbonyldiimidazole and benzohydroxamic acid (Scheme 5); thus the complete elimination of chlorinated solvents could be realized both in the preparation of amidating reagents and in the key C−H amidation reaction.

Scheme 5. Synthesis of 3-Phenyl-1,4,2-dioxazol-5-one



100 mmol 100 mmol **11.8 g (72%)**

Scale-up Study. We previously demonstrated the scalability in a gram-scale C−H amidation (5 mmol) of 2-phenylpyridine with 3-phenyl-1,4,2-dioxazol-5-one with a 0.50 mol % catalyst loading using 1,2-dichloroethane as a solvent.[4] Since we found that the greener solvent ethyl acetate could replace 1,2-dichloroethane in a submmol reaction, its applicability even on

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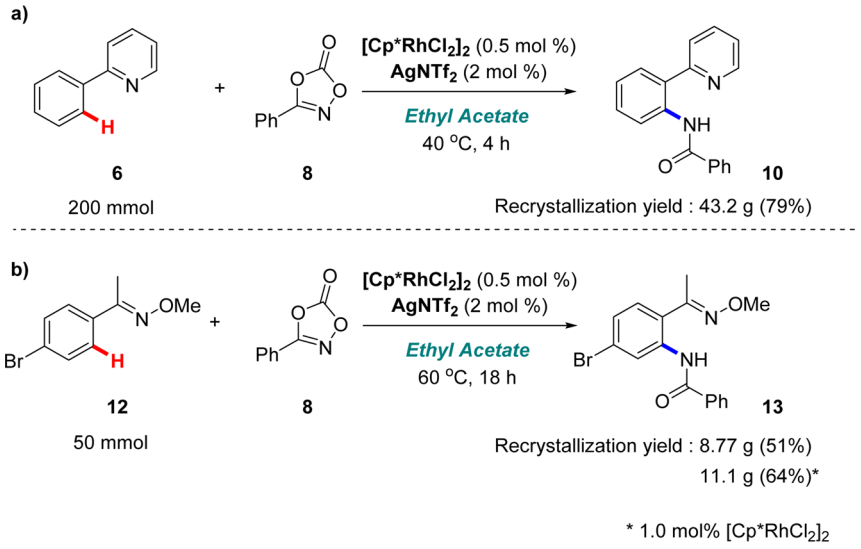
Scheme 6. Large Scale C−H Amidations Using Cp*Rh(III) Catalyst with 1,4,2-Dioxazol-5-one



a large scale was next examined. Pleasingly, the same level of reactivity was observed in a large scale reaction (Scheme 6). At first, the synthesis of 1,4,2-dioxazol-5-one was carried out at a 100 mmol scale (Scheme 5). The addition of 1,1-carbonyldiimidazole (CDI) to a suspension of benzohydroxamic acid in ethyl acetate gave a complete conversion within 1 h. Extraction of the crude reaction mixture with aqueous 1 N HCl solution (250 mL, 2.5 equiv) removed imidazole almost completely. The crude mixture after the removal of ethyl acetate was dissolved in toluene, and then filtration of undissolved impurities followed by evaporation of toluene gave the desired product in 72% yield (11.8 g). The Rh(III)-catalyzed C−H amidation was subsequently conducted (Scheme 6). To the solution of 3-phenyl-1,4,2-dioxazole-5-one **8** (210 mmol, 1.05 equiv), $[Cp^*RhCl_2]_2$ (0.500 mol %, 1.00 mmol), and $AgNTf_2$ (2.00 mol %, 4.00 mmol) in ethyl acetate (120 mL) at 40 °C, 2-phenylpyridine **6** (200 mmol, 1.00 equiv) was added over 3.5 h using a syringe pump, maintaining the reaction temperature under 45 °C.[14] Since the C−H amidation was found to be highly exothermic (−290 kJ/mol),[15] a careful control of reaction rate was required to prevent uncontrollable heat and CO_2 emission. When 2-phenylpyridine was added at once, a surge of heat and CO_2 emission was observed. The resulting temperature elevation caused further rate amplification; thus a loss of control was witnessed.[16] The amidation was completed in 4 h checked by ^{1}H NMR monitoring. Insoluble silver salt was removed by filtration. The crude mixture obtained after evaporation of ethyl acetate was recrystallized in 2-butanol (200 mL) at room temperature to give 43.2 g product **10** (79% yield), and its purity was determined to be >99% by HPLC analysis.

The same procedure was also applied to a substrate **12** bearing a ketoxime directing group (50.0 mmol scale, Scheme 6b). Although the reaction required slightly higher temperature (60 °C), the desired amidation product **13** was obtained in good yields (51% with 0.500 mol % catalyst and 64% with 1.00 mol % catalyst) by following the same purification procedure as that of **10**.

CONCLUSIONS

In conclusion, we examined the practical aspects in the Cp*Rh(III)-catalyzed C−H amidation with 1,4,2-dioxazolone. Several key guidelines for the potential process chemistry were successfully checked: good thermal stability of the present amidating reagent, the use of nonchlorinated solvents (ethyl acetate herein), nontoxic byproducts (CO_2 only), mild conditions (40−60 °C), no need of special equipment to maintain inert atmosphere, convenience in handling reagents, and easy purification procedure of products. Under these satisfactory prerequisites, the direct C−H amidation was readily conducted up to tens of gram scale without difficulty to afford the desired amidated products in high yields. Since the reaction is also featured by broad substrate scope and excellent functional group tolerance, we anticipate the use of this highly sustainable and efficient C−N bond formation method in process chemistry in the near future.

EXPERIMENTAL SECTION

General Methods. All commercial reagents and solvents (HPLC or reagent grade) were used as received. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates. Visualization on TLC was achieved by UV light (254 nm). ^{1}H NMR was recorded on Agilent Technologies DD2 (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the residual solvent peak ($CHCl_3$) or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, m = multiplet. Coupling constants, *J*, were reported in hertz (Hz). ^{13}C NMR was obtained on Agilent Technologies DD2 (150 MHz) and was fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the residual solvent ($CHCl_3$) peak. Infrared (IR) spectra were acquired on Bruker Alpha ATR FT-IR spectrometer. Frequencies are given in wave numbers (cm^{-1}), and only selected peaks were reported. High-resolution mass spectrum was obtained from the KAIST Research Analysis Center by using ESI method. DSC scans were recorded on TA Instruments DSC Q20. Purity of compounds were examined using Shimadzu Prominence HPLC system composed of LC-

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20A pump, SPD-M20A photodiode array detector, and Shim-pack prep-ODS(H) column (4.6 mm × 250 mm) with acetonitrile as an eluent at the flow rate of 1.0 mL/min. Reaction enthalpy was measured on Omnical SuperCRC calorimeter.[17] Reaction temperature and pressure were recorded using Vernier LabQuest system.

General Procedure for the Solvent Study (Table 2). To an oven-dried screw capped vial with a spinvane triangular-shaped Teflon stirbar were added 2-phenylpyridine or 1-phenylethan-1-one *O*-methyl oxime (0.20 mmol), 3-phenyl-1,4,2-dioxazol-5-one (36 mg, 0.22 mmol), $[Cp^*RhCl_2]_2$ (2.4 mg, 2.0 mol %), $AgNTf_2$ (6.2 mg, 8.0 mol %), and solvent (0.5 mL) under atmospheric conditions. The reaction mixture was stirred in a heating block at 40 °C for 18 h. The reaction was cooled to room temperature, filtered through a pad of Celite, and then washed with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure, and yield was measured by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane (34 mg, 0.20 mmol) as an internal standard.

Measurement of Reaction Enthalpy. A vial (21 × 70 mm) equipped with a magnetic stir bar and a Teflon septa cap was charged with $[Cp^*RhCl_2]_2$ (15.5 mg, 0.0250 mmol), $AgNTf_2$ (38.8 mg, 0.100 mmol), 3-phenyl-1,4,2-dioxazol-5-one (856 mg, 5.25 mmol), and ethyl acetate (3 mL) [sample vial]. The other vial was prepared identically except the addition of $[Cp^*RhCl_2]_2$ and $AgNTf_2$ [reference vial]. Both vials were placed in a calorimeter which was preheated at 40 °C. Two gastight syringes with 2-phenylpyridine (776 mg, 5.00 mmol) were placed in syringe ports. Once thermal equilibrium was achieved, 2-phenylpyridine in each port was rapidly injected at the same time. All injection ports were plugged with cotton wool for insulation. Strong heat emission was detected from the sample vial. The reaction was allowed to run until no heat transfer was observed. The vials were removed, and ^1H NMR analyses showed full conversion (>98%) of the sample vial and no conversion or degradation of the reference vial. The integration of the observed heat flow vs time curves using Win-CRC software gave a value of −1450 J for 5 mmol scale, which is equal to −290 kJ/mol.

Synthesis of 3-Phenyl-1,4,2-dioxazol-5-one (8) (100 mmol Scale). An oven-dried 300 mL round-bottom flask was equipped with a magnetic stir bar. Benzohydroxamic acid (13.7 g, 100 mmol), ethyl acetate (200 mL), and 1,1′-carbonyldiimidazole (16.3 g, 101 mmol) were added sequentially under atmospheric conditions. After vigorous stirring for 1 h, the reaction mixture was quenched with 1 N HCl (250 mL, 2.5 equiv) and extracted with ethyl acetate (200 mL). The separated organic layer was dried over $MgSO_4$ (12 g), and the solvent was removed under reduced pressure. The crude product was redissolved in toluene (200 mL) and filtered through a pad of Celite. The solvent was evaporated under reduced pressure to afford the desired product as a white solid (11.8 g, 72%).

Synthesis of 1-(4-Bromophenyl)ethan-1-one *O*-methyl Oxime (12) (100 mmol Scale). A round-bottom flask (500 mL) equipped with magnetic stir bar and reflux condenser was charged with a solution of 4′-bromoacetophenone (19.9 g, 100 mmol) in methanol (100 mL) and H_2O (250 mL). NaOAc (32.8 g, 400 mmol) and methoxyamine hydrochloride (39.1 g, 468 mmol) were added in one-portion under atmospheric condition. The resulting mixture was stirred in a preheated oil bath at 80 °C for 12 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (200 mL × 2). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL) and dried over $MgSO_4$ (12 g). The solvent was removed under reduced pressure to afford the desired product as a light yellow oil (22.6 g, 99% yield).

Synthesis of *N*-[2-(Pyridin-2-yl)phenyl]benzamide (10) (200 mmol Scale). To an oven-dried 250 mL three-neck round-bottom flask equipped with a magnetic stir bar were added 3-phenyl-1,4,2-dioxazol-5-one (34.2 g, 210 mmol), $[Cp^*RhCl_2]_2$ (620 mg, 1.00 mmol), and $AgNTf_2$ (1.55 g, 4.00 mmol) under atmospheric condition. After the addition of ethyl acetate (120 mL), the flask was placed on the preheated oil bath of 40 °C. Sensors were installed to monitor the pressure and temperature of reaction mixture and temperature of heating bath. 2-Phenylpyridine (31.0 g, 200 mmol) was added using a syringe pump over 3.5 h while maintaining the reaction temperature under 45 °C (see the Supporting Information for a temperature log). With a placement of needle of 22 gauge as a CO_2 outlet, no sign of pressure accumulation was detected. The completion of amidation was confirmed at 4 h by ^1H NMR. White precipitation was formed during cooling down to room temperature; ethyl acetate (400 mL) was added to dissolve the precipitate. The reaction mixture was filtered through a Celite pad to remove undissolved silver salts and washed with ethyl acetate (30 mL). The solvent was removed under reduced pressure, and resulting solid was recrystallized in 2-butanol (200 mL) at ambient temperature for 12 h. The resulting precipitate was filtered and washed with 2-butanol (120 mL) to afford the desired product as a white solid (43.2 g, 79% yield, > 99% purity by HPLC analysis at 254 and 280 nm).

Synthesis of *N*-{5-Bromo-2-[1-(methoxyimino)ethyl]-phenyl}benzamide (13) (50 mmol Scale). To an oven-dried 250 mL round-bottom flask equipped with a magnetic stir bar were added 3-phenyl-1,4,2-dioxazol-5-one (8.56 g, 52.5 mmol), $[Cp^*RhCl_2]_2$ (155 mg, 0.250 mmol), and $AgNTf_2$ (388 mg, 1.00 mmol) under atmospheric condition. After the addition of ethyl acetate (30 mL) and 1-(4-bromophenyl)ethan-1-one *O*-methyl oxime (11.4 g, 50.0 mmol), the flask was capped with septum and equipped with empty balloon to mediate the pressure of liberated CO_2. The resulting mixture was stirred in a preheated oil bath at 60 °C for 18 h. The reaction was cooled to room temperature, and precipitation was formed. After dissolving the precipitate with the additional ethyl acetate (100 mL), the resulting solution was filtered through a Celite pad and washed with ethyl acetate (50 mL). The solvent was removed under reduced pressure, and the resulting solid was dissolved in 2-butanol (50 mL) for recrystallization at ambient temperature for 12 h. The resulting precipitate was filtered and washed with 2-butanol (25 mL) to afford the desired product as a pale yellow solid (8.77 g, 51% yield, > 99% purity by HPLC analysis at 254 and 280 nm). The same procedure with $[Cp^*RhCl_2]_2$ (310 mg, 0.500 mmol) and $AgNTf_2$ (776 mg, 2.00 mmol) gave the product of 11.1 g (64% yield, > 99% purity by HPLC analysis at 254 and 280 nm). Mp 125−127 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 11.79 (s, 1H), 9.04 (s, 1H), 7.96 (d, J = 7.7 Hz, 2H), 7.58−7.52 (m, 1H), 7.51−7.45 (m, 2H), 7.35 (d, J = 1.5 Hz, 1H), 7.30−7.22 (m, 1H), 4.01 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 157.1, 138.5, 135.6, 132.1, 129.8, 128.7 (2C), 127.6, 126.3 (2C), 124.2, 124.0, 121.7, 62.5, 13.9; IR (cm^{-1}) 3104, 3066, 3031, 2958, 1675, 1598, 1566, 1522, 1398, 1282, 1046, 698; HRMS (ESI) m/z calcd. for $C_{16}H_{15}BrN_2O$ $[M + Na]^+$: 369.0215, found: 369.0229.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of DSC data, heat transfer measurement, reaction temperature log, NMR spectra, and HPLC chromatograms. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00164.

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Notes

The authors declare no competing financial interest.

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(14) Temperature logs are available in the Supporting Information.

(15) The heat of reaction was obtained from integration of heat flow vs time data using a calorimeter. See the Supporting Information for details.

(16) In case of a large scale (200 mmol), heat alleviation was not efficient with a system of flask and oil bath. The reaction temperature was raised to reflux (82 °C) in 15 min. See the Supporting Information for details.

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