Tetrahedron 76 (2020) 131481

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of Oxindole Derivatives *via* Intramolecular C–H Insertion of Diazoamides Using Ru(II)-Pheox Catalyst

Nga Phan Thi Thanh, Huong Dang Thi Thu, Masaya Tone, Hayato Inoue, Seiji Iwasa*

Department of Applied Chemistry and Life Science, Toyohashi University of Technology, 1–1 Hibarigaoka, Tempaku-cho, Toyohashi, Aichi, 441–8580, Japan

ARTICLE INFO

Article history:
Received 27 March 2020
Received in revised form
30 July 2020
Accepted 4 August 2020
Available online 21 August 2020

Keywords:
C-H insertion
Ru(II)-Pheox
Oxindole
Diazoamide

ABSTRACT

This work presented the efficient intramolecular aromatic C–H insertion of diazoacetamide. The **1a**–**1o** diazo compounds (except for **1k**) were converted into their corresponding oxindoles *via* an intramolecular C–H insertion reaction in the presence of a Ru catalyst. The Ru-Pheox catalyst was shown to be highly efficient in this transformation in terms of the regioselectivity, producing the desired products in excellent yield (99%). The efficiency of the Ru catalyst reached 580 (TON) and 156 min^{-1} (TOF).

© 2020 Elsevier Ltd. All rights reserved.

1. Introduction

The oxindole framework is prevalent as an important scaffold in numerous natural products and pharmaceutically active compounds due to its diverse biological activities, such as antifungal, antibacterial and antiviral, antimicrobial, and antioxidant activities [1].

Over the past few decades, the emerging therapeutic potential of the oxindole structural motif has encouraged the medicinal chemists to synthesize novel oxindole derivatives. Therefore, many reports on the approach toward the oxindole substructure include the derivatization of isatin and indoles [2], Heck reactions of aniline derivatives [3], and the Friedel–Crafts procedure using palladium (Pd)-catalyzed C–H functionalization [4].

However, these methods usually require harsh reaction conditions (strongly acidic conditions and high temperatures) and a multi-step synthesis of the corresponding starting materials as a functionalized precursor. Therefore, existing methods are limited in their scope and generality.

The oxindole framework can be constructed *via* intramolecular C–H insertion reactions of α-diazo compounds [5] using transition metals, such as Rh [6], Ru [7], Ag [8], and Pd [9], as catalysts. In this regard, Parul Garg et al. made a significant contribution in 2017, demonstrating a copper-catalyzed (5 mol%) ligand-free divergent route for synthesizing oxindoles and isatins via intramolecular cyclization of α-diazoanilide with a yield up to 93% (Scheme 1a) [10]. Recently, Solé and coworkers studied the Pd-catalyzed intramolecular carbene C–H insertion of α-diazo-α(methoxycarbonyl) acetamides for the preparation of oxindoles (yield up to 79%) (Scheme 1b) [9c]. Both of these established approaches for the procurement of oxindole derivatives remain challenging in certain areas, such as requiring large amounts of catalyst or special reaction conditions.

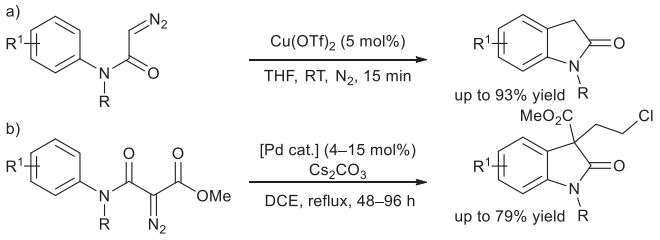
In the past several years, our group has been engaged in developing a Ru(II)-Pheox complex [11]. This catalyst was designed with a stereodirecting unit attached to the oxazoline ring and featuring various substituents on the ligand backbone to control the electron density on the metal center (Fig. 1).

Two factors cause different reactivities between Ru(II)–Pheox and traditional catalysts: (i) the design of the chiral ligand environment of the Ru(II)–Pheox catalyst, which allows much closer access to the substrate compared with traditional catalysts to provide a better reaction environment, and (ii) the strong electron-donating effect of the C_{sp2} anionic ligand on the Ru atom, which facilitates oxidative addition (usually the rate-limiting step of transition-metalcatalyzed reactions) [11b].

Moreover, we had achieved the highly regio- and enantioselective functionalization of unactivated primary C–H bonds, such as in the *N-tert*-butyl group of various diazoacetamides, using the Ru(II)-Pheox catalyst (Scheme 2a) [11g].

* Corresponding author.
E-mail address: iwasa@chem.tut.ac.jp (S. Iwasa).

https://doi.org/10.1016/j.tet.2020.131481
0040-4020/© 2020 Elsevier Ltd. All rights reserved.



Scheme 1. Transition metal-catalyzed C–H insertion reaction of diazoacetamides.

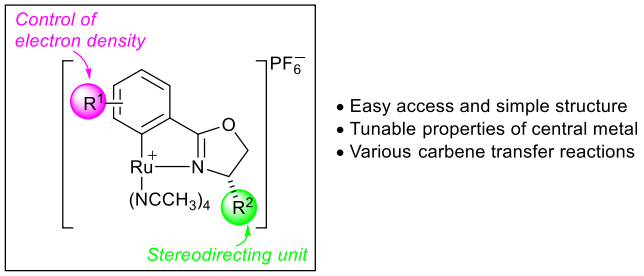
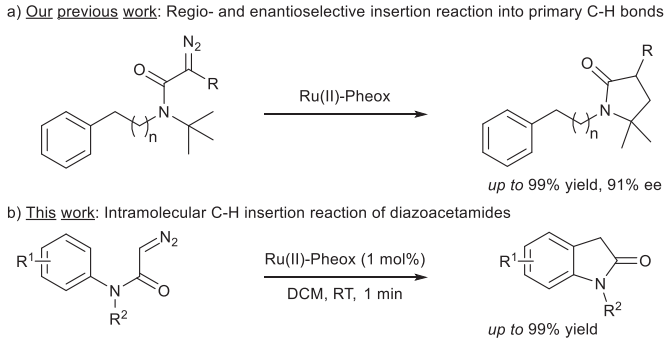


Fig. 1. Catalyst Ru(II)-Pheox.



Scheme 2. Intramolecular C–H insertion reaction of diazoacetamides catalyzed by Ru(II)-Pheox.

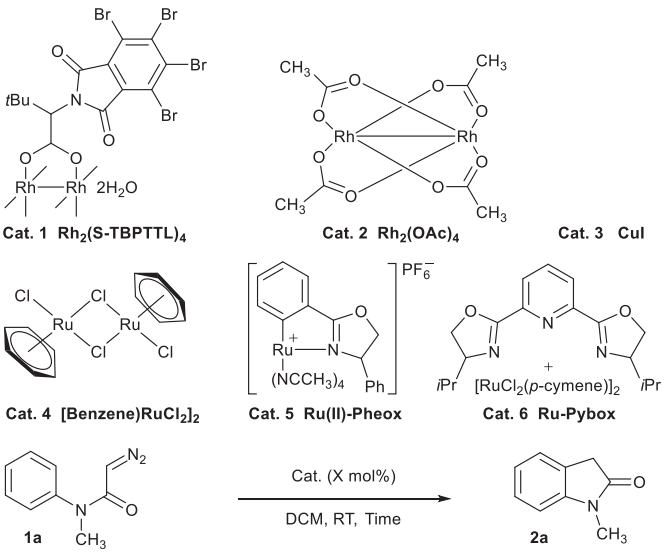
And in another our report, the oxindole derivatives particularly play an important role as starting materials for the synthesis of optically active spiro-cyclopropyl oxindole derivatives [11e].

Due to the interest in the catalytic C–H insertion reaction of diazoacetamide and the importance of the oxindole scaffold in natural product synthesis, we have recently described the results of experiments designed to probe the efficiency of Ru(II)-Pheox in the synthesis of oxindole. In this full paper, we describe in details the development of an intramolecular C-H insertion reaction of a variety of diazoacetamide derivatives in the presence of the Ru(II)-Pheox catalyst for the selective synthesis of oxindole derivatives (Scheme 2b), which based on our preliminary research in 2019 [11l].

2. Results and discussion

Initially, 2-diazo-*N*-methyl-*N* phenylacetamide **1a** was chosen as the model substrate to screen the reaction conditions based on various catalysts. The results are shown in Table 1. Oxindole **2a** was obtained at 91% yield and under the catalysis of 1 mol% Rh_2(S-TBPTTL)$_4$ [12] (Cat. 1) at room temperature (entry 1). For another Rh_2(II) complex, $Rh_2(OAc)_4$ [13] (Cat.2), the intramolecular C–H

Table 1
Catalyst screening experiments.



Entry	X [mol%]	Cat.	Time [min]	Yield[a] [%]	TON[b]	TOF[c] [min^{-1}]
1	1	Cat. 1	10	91	91	9.1
2	1	Cat. 2	1440	83	83	0.1
3	1	Cat. 3	4320	30	30	–
4	1	Cat. 4	30	92	92	3.1
5	1	Cat. 5	1	96	96	96
6	1	Cat. 6	10	83	83	8.3
7	0.5	Cat. 5	1	78	156	156
8	0.1	Cat. 5	60	58	580	9.7

[a] Isolated yield.
[b] TON = moles of desired product (**2a**)/moles of catalyst.
[c] TOF = TON/reaction time (min).

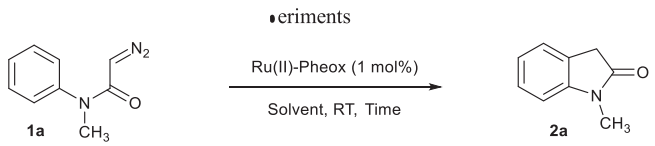
insertion reaction also dominated, producing **2a** at 83% yield after 24 h (entry 2).

Subsequently, the CuI [14] catalyst (Cat. 3) was also tested for this transformation. In this case, the reaction proceeded very gradually (72 h), and the yield of **2a** decreased dramatically to 30% (Table 1, entry 3). In addition, Ru complexes are well known to be good catalysts for carbene-transfer reactions [11b,15]. Thus, the Ru(II) complexes were also examined to improve reaction performance (Table 1, entries 4–8). When Ru-Pybox [16] was used, product **2a** was formed in 83% yield (Table 1, entry 6). In the case of the [(benzene)$RuCl_2]_2$ [17,18] complexes, the yield of **2a** increased slightly to 92%. However, the reaction time was relatively long (30 min) (Table 1, entry 4). The Ru(II)-Pheox [11] catalyst with various loadings was tested for the intramolecular C–H insertion reaction (Table 1, entries 5 and 7–8). Reducing the Ru(II)-Pheox loading from 1 to 0.1 mol% resulted in relatively high TON (up to 580) and TOF (up to 156 min^{-1}) values with yields of 58% and 78%, respectively (Table 1, entries 7, 8). In the presence of 1 mol% Ru(II)-Pheox, the reaction of diazoacetamide **1a** proceeded smoothly at room temperature, delivering the corresponding **2a** oxindole products at a high yield of 96% (Table 1, entry 5).

To get additional details of this reaction, the influence of various solvents (such as tetrahydrofuran, acetone, methanol, toluene, acetonitrile, dimethyl sulfoxide, and dichloromethane) on this intramolecular C-H insertion reaction of diazoacetamides was examined. The results are shown in Table 2. And dichloromethane (DCM) was demonstrated to be the best solvent for this Ru(II)-Pheox catalyzed reaction [11l]

Based on the optimized reaction conditions for the

Table 2
Solvent screening experiments [11].



Entry	Solvent	Time [min]	Yield [%][a]
1	Tetrahydrofuran	1	91
2	Acetone	1	79
3	Methanol	1	82
4	Toluene	1	86
5	Acetonitrile	10	78
6	Dichloromethane	1	96
7	Dimethyl sulfoxide	240	_

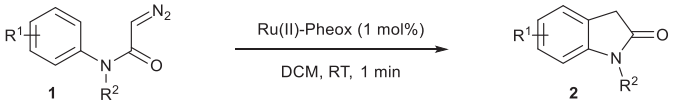
[a] Isolated yield.

intramolecular C–H insertion of diazoacetamide (Table 2, entry 6), the substrate scope was subsequently examined.

As shown in Table 3, all various R^1 substituents at different positions of the phenyl group were also well-tolerated, producing **2a**–**n** in 91–99% yields. Substitution with R^1 was an electron-donating group (e.g., 4-OCH_3, 2-OCH_3, and 3-CH_3) on the *N*-phenyl has a strong impact on the reaction (Table 3, entries 2, 7, and 8). The corresponding oxindole products were obtained in excellent yields.

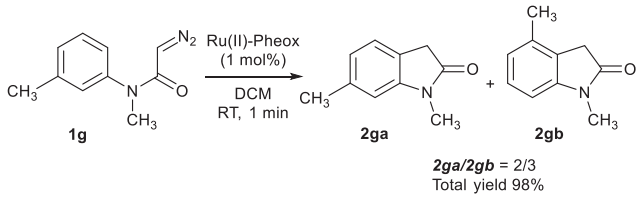
In addition, compared to substitution with an electron-donating group, the efficiency of the intramolecular reaction of substitution bearing an electron-withdrawing group (namely H, 4-Cl, 4-Br, 4-NO_2, 2-Br, and 2-I) slightly decreased with yields of 93–99% (Table 3, entries 1, 3–6, and 9–10). As a plausible explanation, the substituent changes the electronic properties of the benzene ring. Nucleophilic substituents are regarded as electronic-donating groups, which increase the electropositivity of the aryl group and improve the reactivity in the intramolecular ArC_{sp2}-H insertion reaction. In contrast, electrophilic substituents are regarded as electron-withdrawing groups, which decrease the electropositivity of the aryl group.

Table 3
Ru(II)-Pheox-catalyzed intramolecular C–H insertion reactions of diazoacetamides.



Entry	1	R^1	R^2	2	Yield [%][a]
1[11]	**1a**	H	CH_3	**2a**	96
2[11]	**1b**	4-OCH_3	CH_3	**2b**	99
3[11]	**1c**	4-Cl	CH_3	**2c**	94
4[11]	**1d**	4-Br	CH_3	**2d**	93
5[11]	**1e**	4-I	CH_3	**2e**	99
6[11]	**1f**	4-NO_2	CH_3	**2f**	94
7[11]	**1g**	3-CH_3	CH_3	**2g**	98
8	**1h**	2-OCH_3	CH_3	**2h**	93
9	**1i**	2-Br	CH_3	**2i**	98
10	**1j**	2-I	CH_3	**2j**	97
11	**1k**	H	H	**2k**	_
12[11]	**1l**	H	C_6H_5	**2l**	99
13	**1m**	H	CH_2CH_3	**2m**	94
14	**1n**	H	$CH(CH_3)_2$	**2n**	91
15	**1o**	H	$CH_2C_6H_5$	**2o**	95

[a] Isolated yield.



Scheme 3. Intramolecular C–H insertion reaction of diazoacetamide, 1g, catalyzed by Ru(II)-Pheox.

Switching the substrate to **1g** (R^1 = 3-CH_3) 2-diazo-*N*-methyl-*N*-(*m*-tolyl)acetamide dramatically changed the reaction, affording the corresponding product, **2g**. Two regiomers of **2g** were generated in a ratio of **2ga**/**2gb** = 2/3 and with high overall yield (Scheme 3).

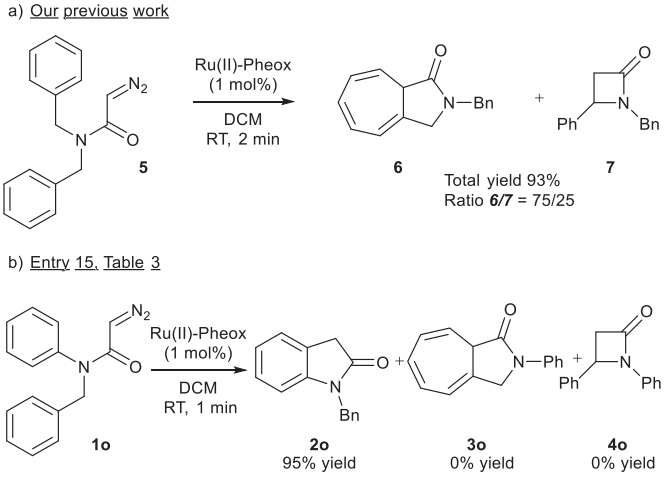
Furthermore, the *N*-substituent effect was also evaluated under reaction conditions similar to that of the intramolecular C–H insertion reaction. When substituting R^2 = H, diazo (**1k**) could not be converted into the desired oxindole because it was prevented by the dimerization reaction (Table 3, entry 11).

However, the steric-demanding R^2 (-C_6H_5, $-CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2C_6H_5$) substituents were compatible. The efficient synthesis of oxindole still held an excellent yield of 99% (entry 12).

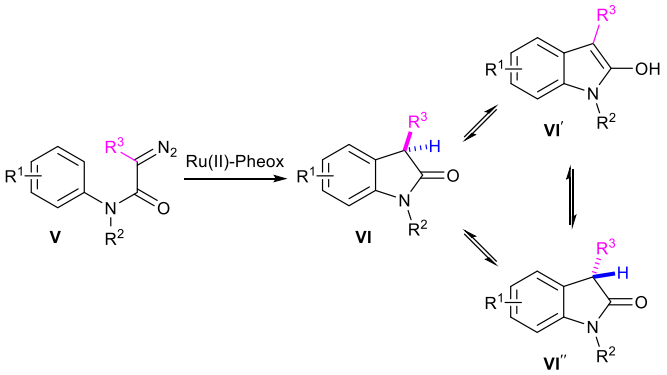
When substituting R^2 = -CH_2CH_3 and $-CH(CH_3)_2$, in which the newly introduced methyl groups provided additional competitive alkyl C–H insertion sites, the reactions occurred selectively at the desired ArC_{sp2}-H position and led to the products, **2m** and **2n**, in decreased yields (94% and 91%, respectively), probably due to the steric hindrance (Table 3, entries 13–14).

In 2019, our previous report [11j] demonstrated the efficient conversion of diazo compound **5** into a mixture of Buchner reaction product γ-lactam **6** and C–H insertion reaction product β-lactam **7** at room temperature using the Ru(II)–Pheox catalyst (Scheme 4a). There is intense competition between the reactive sites of *N*,*N*-dibenzyl-2-diazoacetamide **5**. Therefore, products **6** and **7** could be obtained in the yields of 75% and 25%, respectively. Compared to compound **5**, diazoacetamide **1o** (entry 15, Table 3) exhibited a highly regioselective intramolecular aromatic C–H insertion reaction (Scheme 4b), and only oxindole derivative **2o** was formed in 95% yield.

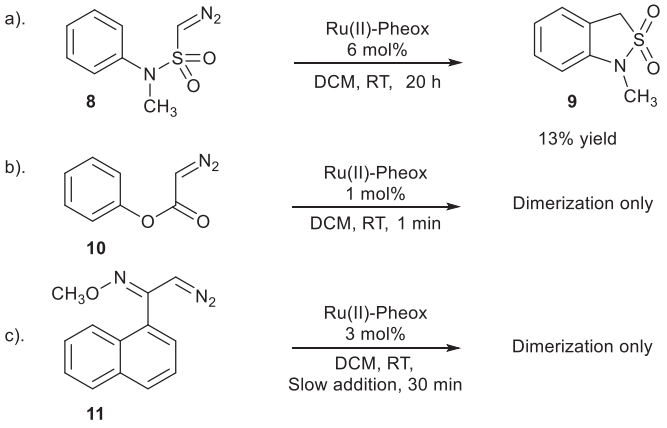
On another hand, with this system intramolecular aromatic C–H



Scheme 4. Ru(II)-Pheox catalyzed decomposition of diazoacetamides.



Scheme 5. Keto-enol tautomerism of compound VI.



Scheme 6. Intramolecular C–H insertion reaction using various diazo compounds.

insertion of diazoacetamide, the chiral induction could not remained. The corresponding oxindole **VI** can be rationalized to **VI′**, **VI"** by a keto-enol tautomerism causing racemization at C-3 (Scheme 5) [20].

Furthermore, intramolecular aromatic C–H insertion reactions using various diazo were also investigated (Scheme 6). The aromatic C ($_{sp2}$)-H insertion of diazosulfonamide **8** occurred after 20h, giving to benzo-γ-sultam **9** in 13% yield (Scheme 6a). However, the phenyl diazoacetate **10** and the diazooxime **11** gave only dimers (Scheme 6b and 6c).

A plausible mechanism is outlined in Fig. 2. The interaction of diazo amide **I** with the Ru(II)-Pheox catalyst produces Ru-carbene complex **II.** The lone pair of electrons on the nitrogen in amides is delocalized into the carbonyl, forming a partial double bond between *N* and carbonyl carbon. *N*-unsubstituted diazoacetamide (**1k**) is a linear structure that has no advantage for the intramolecular C–H insertion reaction.

However, the steric hindrance of the R^2 group in the other cases allows the carbene to get close to the benzene ring and favors aromatic C–H insertion reaction to afford the intermediate **III**. The last step of the mechanism is the reductive elimination of Ru, and it leads to oxindole **IV** with the regeneration of the catalyst.

3. Conclusion

In summary, we successfully developed an operationally simple protocol to regioselectively synthesize substituted oxindoles. In the presence of Ru(II)-Pheox, the intramolecular C–H insertion

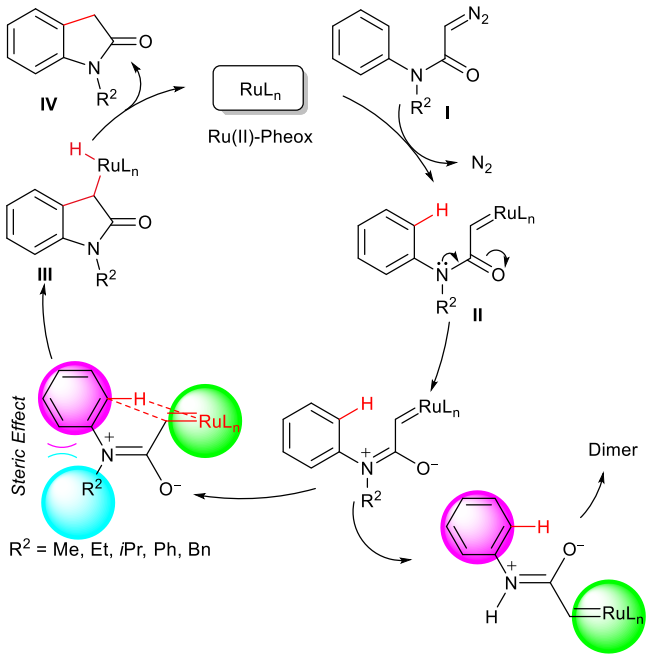


Fig. 2. A plausible mechanism of the intramolecular C–H reaction of diazoacetamide I catalyzed by Ru(II)-Pheox.

reaction proceeds smoothly under mild conditions, providing the corresponding oxindole derivatives in excellent yield (up to 99%). No other side reactions related to metal-carbene reactivity, such as dimerization, aromatic ring expansion, and C_{sp3}-H on amide nitrogen insertion reaction, were observed.

4. Experimental section

4.1. General

All reactions were performed under an atmosphere of argon unless otherwise noted. DCM was purchased from Kanto Chemical Co., Inc. All reactions were monitored by thin-layer chromatography (TLC). Glass plates with a layer thickness of 0.2 mm were precoated with silica gel Merck KGaA 60 F_{254}. The products were visualized either by ultraviolet (UV) light irradiation or by treatment with a phosphomolybdic acid solution or by treatment with a *p*-anisaldehyde solution. Flash column chromatography was performed using silica gel (Merck, Art. No. 7734). Hydrogen-1 nuclear magnetic resonance (^{1}H NMR) (500 MHz, 400 MHz) and carbon nuclear magnetic resonance (^{13}C NMR) (125 MHz, 100 MHz) spectra were recorded on a JEOL JNM-ECX500, JEOL JNM-ECS400 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane (0.00 ppm) in $CDCl_3$. Elemental analyses were measured on Yanaco CHN CORDER MT-6.

4.2. Typical procedure for the synthesis of 2-diazo-N-methyl-N phenylacetamide (*1a*), [11l]

Bromoacetyl bromide (0.95 mL, 11 mmol) was added dropwise at 0 °C to a suspension of K_2CO_3 (1.66 g, 12 mmol) and *N*-methylaniline (1.07 g, 10 mmol) in DCM (20 mL). The reaction mixture was stirred at room temperature for 30 min. Subsequently, the mixture was extracted three times with DCM (20 mL × 3), dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was obtained and used in the next step without purification. The

resulting bromoacetamide and *N,N′*-ditosylhydrazine (5.1 g, 15 mmol) were dissolved in THF (20 mL) and cooled to 0 °C, and thereafter, DBU (3 mL, 20 mmol) was added dropwise and stirred for 30 min at 0 °C. After quenching with saturated aqueous $NaHCO_3$ and extracting with diethyl ether (20 mL × 3) three times, the organic phase was dried over Na_2SO_4 and evaporated to obtain the crude product. Purification was performed by flash column chromatography on silica gel eluted with *n*-Hexane/EtOAc (1/5 (*v/v*)) to obtain 2-diazo-*N*-methyl-*N* phenylacetamide (0.96 g, 55% yield) as yellow oil **1a.** The NMR (^{1}H and ^{13}C) and infrared (IR) data agree with the reported values [6a, 11l].

*4.2.1. 2-Diazo-N-(4-methoxyphenyl)-N-methylacetamide (**1b**)*

Yellow powder. 66% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11l].

*4.2.2. 2-Diazo-N-(4-chlorophenyl)-N-methylacetamide **(1c)***

Yellow powder. 49% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11l].

*4.2.3. 2-Diazo-N-(4-bromophenyl)-N-methylacetamide **(1d)***

Yellow powder. 50% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11l].

*4.2.4. 2-Diazo-N-(4-iodophenyl)-N-methylacetamide **(1e)***

Yellow powder. 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (ddd, J = 8.79, 2.29, 2.29 Hz, 2H), 6.97 (ddd, J = 9.94, 2.29, 2.29 Hz, 2H), 4.54 (s, 1H), 3.29 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.61, 142.85, 138.98, 92.64, 47.72, 37.24 ppm. IR (neat) ν 3075, 2105, 1621, 1483, 1281, 787 cm^{-1}. HRMS (DART) calcd for $C_9H_8N_3OI$ [M+H]+: 301.9795 found: 301.9790.

*4.2.5. 2-Diazo-N-(4-nitrophenyl)-N-methylacetamide **(1f)***

Yellow powder. 53% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11l].

*4.2.6. 2-Diazo-N-methyl-N-(m-tolyl)acetamide **(1g)***

Yellow oil. 64% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [6a, 11l].

*4.2.7. 2-Diazo-N-(2-methoxyphenyl)-N-methylacetamide **(1h)***

Yellow powder. 43% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (ddd, J = 7.84, 7.84, 1.91 Hz, 1H), 7.06 (dd, J = 7.64, 1.91 Hz, 1H), 6.89 (ddd, J = 15.67, 7.64, 1.53 Hz, 2H), 4.54 (s, 1H), 3.76 (s, 3H), 3.13 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.27, 155.46, 131.04, 129.84, 129.48, 121.04, 112.22, 55.62, 46.74, 35.77 ppm. IR (neat) ν 3067, 2103, 1626, 1419, 1242, 751 cm^{-1}. HRMS (DART) calcd for $C_{10}H_{11}N_3O_2$[M+H]+: 206.0923 found: 206.0929.

*4.2.8. 2-Diazo-N-(2-bromophenyl)-N-methylacetamide **(1i)***

Yellow powder. 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 13.76, 7.26 Hz, 2H), 7.41–7.39 (m, 1H), 7.31–7.26 (m, 2H), 4.31 (s, 1H), 3.25 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.77, 141.58, 134.16, 130.40, 130.28, 129.20, 123.77, 47.38, 35.84 ppm. . IR (neat) ν 3067, 2108, 1627, 1420, 1289, 767 cm^{-1}. HRMS (DART) calcd for $C_9H_8N_3OBr$ [M+H]+: 253.9923 found: 253.9929.

*4.2.9. 2-Diazo-N-(2-iodophenyl)-N-methylacetamide **(1j)***

Yellow powder. 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.64, 1.53 Hz, 1H), 7.42 (ddd, J = 7.64, 7.64, 1.53 Hz, 1H), 7.27 (dd, J = 7.64, 1.53 Hz, 1H), 7.09 (ddd, J = 7.64, 7.64, 1.53 Hz, 1H), 4.25 (s, 1H), 3.22 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.69, 145.11, 140.50, 130.37, 130.22, 129.67, 99.87, 47.72, 36.07 ppm. IR (neat) ν 3065, 2100, 1634, 1467, 1256, 798 cm^{-1}. HRMS (DART) calcd for $C_9H_8N_3OI$ [M+H]+: 301.97969 found: 301.97903.

*4.2.10. 2-Diazo-N-phenylacetamide **(1k)***

Yellow oil. 48% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [19].

*4.2.11. 2-Diazo-N,N-diphenyl-acetamide **(1l)***

Yellow oil. 49% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [19].

*4.2.12. 2-Diazo-N-ethyl-N-phenylacetamide **(1m)***

Yellow oil. 56% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dt, J = 7.84, 1.91 Hz, 2H), 7.33 (dt, J = 7.64, 1.91 Hz, 1H), 7.16 (dd, J = 8.03, 1.15 Hz, 2H), 4.36 (s, 1H), 3.79 (d, J = 7.26 Hz 1H), 3.77 (d, J = 7.26 Hz, 1H), 1.11 (t, J = 7.26 Hz, 3H), ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.43, 141.46, 129.81, 128.64, 128.21, 47.48, 44.12, 13.44 ppm. IR (neat) ν 3059, 2106, 1621, 1401, 1257, 700 cm^{-1}. HRMS (DART) calcd for: $C_{10}H_{11}N_3O$ [M+H]+: 190.0980 found: 190.0980.

*4.2.13. 2-Diazo-N-isopropyl-N-phenylacetamide **(1n)***

Yellow oil. 55% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–736 (m, 3H), 7.11–7.09 (m, 2H), 5.01 (sep., 1H), 4.13 (s, 1H), 1.06 (d, J = 6.88 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.53, 137.85, 130.76, 129.23, 128.82, 47.57, 46.47, 21.26 ppm. IR (neat) ν 3067, 2103, 1624, 1394, 1118, 704 cm^{-1}. HRMS (DART) calcd for: $C_{11}H_{13}N_3O$ [M+H]+: 204.1137 found: 204.1136.

*4.2.14. 2-Diazo-N- benzyl-N-phenylacetamide **(1o)***

Yellow oil. 52% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [6a].

4.3. Typical procedure for intramolecular C–H insertion reaction of diazo-N-phenyl-N-methylacetamide [11l]

A solution of diazoacetamides (0.2 mmol) in DCM (2.0 mL) was added to a stirred mixture of Ru(II)-Pheox catalyst (1.30 mg, 0.002 mmol) in DCM (1.0 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 1 min. Upon completion, the solvent was removed and the residue was purified by flash column chromatography on silica gel eluted with n–Hexane/EtOAc (1/3 (*v/v*)) to give the desired product. The regioselective ratios were determined from the crude ^{1}H NMR spectra.

*4.3.1. 1-Methylindolin-2-one **(2a)***

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of diazo-*N*-phenyl-*N*-methylacetamide **1a** (29.4 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 (*v/v*)) to give 1-methylindolin-2-one **(2a)** as white powder. 96% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11l, 19].

*4.3.2. 5-Methoxy-1-methylindolin-2-one **(2b)***

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(4-methoxyphenyl)-*N*-methylacetamide **1b** (40.8 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 (*v/v*)) to give 5-methoxy-1-methylindolin-2-one **(2b)** as white powder. 99% yield. NMR (^{1}H, ^{13}C), IR and HRMS data agree with reported values [10, 11l].

*4.3.3. 5-Chloro-1-methylindolin-2-one (**2c**)*

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(4-

chlorophenyl)-*N*-methylacetamide 1c (41.7 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 5-chloro-1-methylindolin-2-one (2c) as white powder. 94% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11].

4.3.4. 5-Bromo-1-methylindolin-2-one (2d)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(4-bromophenyl)-*N*-methylacetamide **1d** (41.7 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 5-bromo-1-methylindolin-2-one (**2d**) as white powder. 93% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [10, 11].

4.3.5. 5-Iodo-1-methylindolin-2-one (2e)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(4-iodophenyl)-*N*-methylacetamide **1e** (54.6 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 5-iodo-1-methylindolin-2-one (**2e**) as white powder. 99% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.41 Hz, 1H), 7.51 (s, 1H), 6.58 (d, J = 8.41 Hz, 1H), 3.48 (s, 2H), 3.16 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.27, 144.76, 136.79, 133.13, 126.91, 110.14, 84.84, 35.42, 26.18 ppm. IR (neat) ν 2935, 1696, 1364, 1100, 810 cm^{-1}. HRMS (DART) calcd for C_9H_8NOI [M+H]+: 273.9722 found: 273.9728.

4.3.6. 5-Nitro-1-methylindolin-2-one (2f)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(4-nitrophenyl)-*N*-methylacetamide **1f** (43.8 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 5-nitro-1-methylindolin-2-one **(2f)** as white powder. 94% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [11].

4.3.7. 1,6-Dimethylindolin-2-one (2ga), 1,4-dimethylindolin-2-one (2gb)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(3-methylphenyl)-*N*-methylacetamide **1g** (37.8 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 1,6-dimethylindolin-2-one (**2ga**), 1,4-dimethylindolin-2-one (**2gb**) as yellow powder. 98% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [10, 11].

4.3.8. 7-Methoxy-1-methylindolin-2-one (2h)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(2-methoxyphenyl)-*N*-methylacetamide **1h** (35.6 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 7-methoxy-1-methylindolin-2-one (**2h**) as yellow powder. 93% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98–6.95 (m, 1H), 6.86–6.84 (m, 2H), 3.85 (s, 1H), 3.48 (s, 2H), 3.48 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.20, 145.37, 133.11, 125.97, 122.46, 117.07, 111.54, 55.67, 35.62, 28.50 ppm. IR (neat) ν 2978, 1694, 1467, 1253, 754 cm^{-1}. HRMS (DART) calcd for $C_{10}H_{11}NO_2$ [M+H]+: 178.0863 found: 178.0868.

4.3.9. 7-Bromo-1-methylindolin-2-one (2i)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(2-bromophenyl)-*N*-methylacetamide **1i** (45.2 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 7-bromo-1-methylindolin-2-one (**2i**) as yellow powder. 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.03 Hz, 1H), 7.16 (d, J = 8.03 Hz, 1H), 6.89–6.86 (m, 1H), 3.59 (s, 3H), 3.53 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.41, 142.25, 133.62, 127.30, 123.44, 102.21, 35.78, 29.75 ppm. IR (neat) ν 2943, 1716, 1462, 1332, 794 cm^{-1}. HRMS (DART) calcd for C_9H_8NOBr [M+H]+: 225.9860 found: 225.9867.

4.3.10. 7-Iodo-1-methylindolin-2-one (2j)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-(2-Iodophenyl)-*N*-methylacetamide **1j** (54.6 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 7-iodo-1-methylindolin-2-one (**2j**) as yellow powder. 97% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.03, 1.15 Hz, 1H), 7.18 (dd, J = 7.64, 1.15 Hz, 1H), 6.73 (t, J = 7.64 Hz, 1H), 3.58 (s, 3H), 3.49 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.14, 145.89, 140.23, 127.48, 124.19, 124.11, 71.97, 36.12, 29.54 ppm. IR (neat) ν 2942, 1706, 1455, 1333, 766 cm^{-1}. HRMS (DART) calcd for $C_{10}H_{11}NO$[M+H]+: 273.9721 found: 273.9728.

4.3.11. 1-Phenylindolin-2-one (2l)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*,*N*-diphenylacetamide **1l** (47.5 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 1-phenylindolin-2-one (**2l**) as white powder, 99% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [10, 11].

4.3.12. 1-Ethylindolin-2-one (2m)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-ethyl-*N*-phenylacetamide **1m** (32.4 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 1-ethylindolin-2-one (**2m**) as white powder. 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J = 16.82, 8.03 Hz, 2H), 7.01 (t, J = 7.26 Hz, 1H), 6.83 (d, J = 8.03 Hz, 1H), 3.75 (q, J = 7.26 Hz, 2H), 3.49 (s, 2H), 1.25 (t, J = 7.26 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.79, 144.05, 127.89, 124.85, 124.58, 122.20, 108.28, 35.94, 34.72, 12.76 ppm. IR (neat) ν 2978, 1699, 1466, 1245, 749 cm^{-1}. HRMS (DART) calcd for $C_{10}H_{11}NO$ [M+H]+: 162.0914 found: 162.0928.

4.3.13. 1-Isopropylindolin-2-one (2n)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-isopropyl-*N*-phenylacetamide **1n** (35.2 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 1-isopropylindolin-2-one (**2n**) as white powder. 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.01–6.98 (m, 2H), 4.67 (seq, J = 6.88 Hz, 1H), 3.48 (s, 2H), 1.46 (d, J = 6.88 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.79, 143.88, 127.60, 125.09, 124.64, 121.81, 109.92, 43.59, 36.03, 19.40 ppm. IR (neat) ν 2973, 1709, 1485, 1246, 749 cm^{-1}. HRMS (DART) calcd for $C_{11}H_{13}NO$ [M+H]+: 176.1071 found: 176.1074.

4.3.14. 1-Benzylindolin-2-one (2o)

This compound was prepared according to the typical procedure for intramolecular C–H insertion reaction of 2-diazo-*N*-benzyl-*N*-phenylacetamide **(1o)** (50.2 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/*n*-Hexane (1/3 *(v/v)*) to give 1-benzylindolin-2-one **(2o)** as white

powder. 95% yield. NMR (^{1}H, ^{13}C), IR data agree with reported values [6a].

*4.3.15. 1-Diazo-N-methyl-N-phenylmethanesulfonamide **(8)***

Yellow powder. NMR (^{1}H, ^{13}C), IR data agree with reported values [21a].

*4.3.16. 1-Methyl-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide **(9)***

The investigated compound was obtained according to the known procedure [21c].

*4.3.17. Phenyl 2-diazoacetate **(10)***

Yellow oil. NMR (^{1}H, ^{13}C), IR data agree with reported values [21b].

*4.3.18. (Z)-2-diazo-1-(naphthalen-1-yl)ethan-1-one O-methyl oxime **(11)***

Yellow oil. NMR (^{1}H, ^{13}C), IR data agree with reported values [11i].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by Japan Society for the Promotion of Science. The Grants-in-Aid for Scientific Research (C) (20K05583).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131481.

References

[1] (a) S.S. Rindhe, B.K. Karale, R.C. Gupta, M.A. Rode, Indian J. Pharmaceut. Sci. 73 (2011) 292–296;
(b) A.L. Davis, D.R. Smith, T.J. McCord, J. Med. Chem. 16 (1973) 1043–1045;
(c) M.S. Estevao, L.C. Carvalho, L.M. Ferreira, E. Fernandes, M.M.B. Marques, Tetrahedron Lett. 52 (2011) 101–106.

[2] (a) C. Crestini, R. Saladino, Synth. Commun. 24 (1994) 2835–2841;
(b) D. Kungumathilagam, K. Karunakaran, Asian J. Chem. 25 (2013) 4311–4314;
(c) D.I. Perez, M.M. Grau, I.W.C.E. Arends, F. Hollmann, Chem. Commun. 44 (2009) 6848–6850;
(d) R. Shintani, M. Inoue, T. Hayashi, Angew. Chem. Int. Ed. 45 (2006) 3353–3356;
(e) I.D. Hills, G.C. Fu, Angew. Chem. Int. Ed. 42 (2003) 3921–3924;
(f) S. Shaw, A.P. Aleman, E. Vedejs, J. Am. Chem. Soc. 125 (2003) 13368–13369.

[3] (a) A.B. Dounay, K. Hatanaka, J.J. Kodanko, M. Oestreich, L.E. Overman, L.A. Pfeifer, M.M. Weiss, J. Am. Chem. Soc. 125 (2003) 6261–6271;
(b) A. Pinto, Y. Jia, L. Neuville, J. Zhu, Chem. Eur J. 13 (2007) 961–967.

[4] (a) E.J. Hennessy, S.L. Buchwald, J. Am. Chem. Soc. 125 (2003) 12084–12085;
(b) A.H. Beckett, R.W. Daisley, J. Walker, Tetrahedron 24 (1968) 6093–6109;
(c) D. Ben-Ishai, N. Peled, I. Sataty, Tetrahedron Lett. 21 (1980) 569–572.

[5] (a) T. Ye, M.A. McKervey, Chem. Rev. 94 (1994) 1091–1160;
(b) A. Ford, H. Miel, A. Ring, C.N. Slattery, A.R. Maguire, M.A. McKervey, Chem. Rev. 115 (2015) 9981–10080.

[6] (a) M.P. Doyle, M.S. Shanklin, H.Q. Pho, S.N. Mahapatro, J. Org. Chem. 53 (1988) 1017–1022;
(b) S. Miah, A.M.Z. Slawin, C.J. Moody, S.M. Sheehan, J.P. Marino Jr., M.A. Semones, A. Padwa, I.C. Richards, Tetrahedron 52 (1996) 2489–2514.

[7] W.W. Chan, T.L. Kwong, W.Y. Yu, Org. Biomol. Chem. 10 (2012) 3749–3755.

[8] H.L. Wang, Z. Li, G.W. Wang, S.D. Yang, Chem. Commun. 47 (2011) 11336–11338.

[9] (a) Z.S. Chen, X.H. Duan, P.X. Zhou, S. Ali, J.Y. Luo, Y.M. Liang, Angew. Chem. Int. Ed. 51 (2012) 1370–1374;
(b) D. Solé, F. Pérez-Janer, I. Fernández, Chem. Commun. 53 (2017) 3110–3113;
(c) D. Solé, F. Pérez-Janer, A. Amenta, M.L. Bennasar, I. Fernández, Molecules 24 (2019) 3551–3567.

[10] P. Garg, S.D. Jadhav, A. Singh, Asian J. Org. Chem. 6 (2017) 1019–1023.

[11] For synthesis and characterization of catalysts Ru(II)-Pheox, see: (a) A.M. Abu-Elfotoh, K. Phomkeona, K. Shibatomi, S. Iwasa, Angew. Chem. Int. Ed. 49 (2010) 8439–8443. For selected Ru(II)-Pheox catalyzed reaction, see:;
(b) S. Chanthamath, S. Iwasa, Acc. Chem. Res. 49 (2016) 2080–2090;
(c) Y. Nakagawa, S. Chanthamath, I. Fujisawa, K. Shibatomi, S. Iwasa, Chem. Commun. 53 (2017) 3753–3756;
(d) Y. Nakagawa, Y. Imokawa, I. Fujisawa, N. Nakayama, H. Goto, S. Chanthamath, K. Shibatomi, S. Iwasa, ACS Omega 3 (2018) 11286–11289;
(e) M. Tone, Y. Nakagawa, S. Chanthamath, I. Fujisawa, N. Nakayama, H. Goto, K. Shibatomi, S. Iwasa, RSC Adv. 8 (2018) 39865–39869;
(f) Y. Nakagawa, N. Nakayama, H. Goto, I. Fujisawa, S. Chanthamath, K. Shibatomi, S. Iwasa, Chirality 31 (2019) 52–61;
(g) Y. Nakagawa, S. Chanthamath, Y. Liang, K. Shibatomi, S. Iwasa, J. Org. Chem. 84 (2019) 2607–2618;
(h) C.T.L. Le, S. Ozaki, S. Chanthamath, K. Shibatomi, S. Iwasa, Org. Lett. 20 (2018) 4490–4494;
(i) L.D. Ho, N. Otog, I. Fujisawa, S. Iwasa, Org. Lett. 21 (2019) 7470–7474;
(j) N.T.T. Phan, M. Tone, H. Inoue, I. Fujisawa, S. Iwasa, Chem. Commun. 55 (2019) 13398–13401;
(k) H. Inoue, N.T.T. Phan, I. Fujisawa, S. Iwasa, Org. Lett. 22 (2019) 1475–1479;
(l) N.T.T. Phan, M. Tone, H. Inoue, K. Shibatomi, S. Iwasa, Key Engineering Materials 840 (2020) 251–256.

[12] (a) K. Goto, K. Takeda, M. Anada, K. Ando, S. Hashimoto, Tetrahedron Lett. 52 (2011) 4200–4203;
(b) T. Goto, K. Takeda, N. Shimada, H. Nambu, M. Anada, M. Shiro, K. Ando, S. Hashimoto, Angew. Chem. Int. Ed. 50 (2011) 6803–6808;
(c) F.G. Adly, A. Ghanem, Chirality 26 (2014) 692–711.

[13] (a) F.A. Cotton, B.G. DeBoer, M.D. LaPrade, J.R. Pipal, D.A. Ucko, Acta Crystallogr. 27 (1971) 1664–1671;
(b) G.A. Rempel, P. Legzdins, H. Smith, G. Wilkinson, D.A. Ucko, Inorg. Synth. 13 (1972) 90–91.

[14] (a) H.D. Hardt, A.Z. Pierre, Anorg. Allg. Chem. 402 (1973) 107–112;
(b) G.B. Kauffman, L.Y. Fang, N. Viswanathan, G. Townsend, Inorg. Synth. 22 (1983) 101–103;
(c) D.A. Keen, S.J. Hull, Phys. Condens. Matter 7 (1995) 5793–5804;
(d) K. Sonogashira, T. Yatake, Y. Tohda, S. Takahashi, N.J.C.S. Hagihara, Chem. Commun. (J. Chem. Soc. Sect. D) 9 (1977) 291–292.

[15] (a) W.H. Cheung, S.L. Zheng, W.Y. Yu, G.C. Zhou, C.M. Che, Org. Lett. 5 (2003) 2535–2538;
(b) G. Maas, Chem. Soc. Rev. 33 (2004) 183–190;
(c) M.K.W. Choi, W.Y. Yu, C.M. Che, Org. Lett. 7 (2005) 1081–1084;
(d) V.K.Y. Lo, Z. Guo, M.K.W. Choi, W.Y. Yu, J.S. Huang, C.M. Che, J. Am. Chem. Soc. 134 (2012) 7588–7591;
(e) M. Chu, R. Li, J. Chen, X. Wu, Y. Zhao, S. Liu, W. Hu, Org. Lett. 19 (2017) 1290–1293.

[16] H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, Bull. Chem. Soc. Jpn. 68 (1995) 1247–1262.

[17] (a) M.A. Bennett, T.N. Huang, T.W. Matheson, A.K. Smith, Inorg. Synth. 21 (1982) 74–78;
(b) J. Canivet, B. Therrien, G. Süss-Fink, Acta Crystallogr. 61 (2005) 1090–1091.

[18] C. Prandi, E.G. Occhiato, S. Tabasso, P. Bonfante, M. Novero, D. Scarpi, M.E. Bova, I. Miletto, Eur. J. Org Chem. 20 (2011) 3781–3793.

[19] (a) T. Hashimoto, N. Uchiyama, K. Maruoka, J. Am. Chem. Soc. 44 (2008) 14380–14381;
(b) N. Döben, H. Yan, M. Kischkewitz, J. Mao, A. Studer, Org. Lett. 20 (2018) 7933–7936.

[20] A. Scala, M. Cordaro, G. Grassia, A. Piperno, G. Barberi, A. Cascio, F. Risitano, Bioorg. Med. Chem. 22 (2014) 1063–1069.

[21] (a) A. Bubyrev, D. Dar'in, G. Kantin, M. Krasavin, Eur. J. Org Chem. (2020) 4112–4115;
(b) T. Toma, J. Shimokawa, T. Fukuyama, Org. Lett. 9 (2007) 3195–3197;
(c) J.F. Bunnett, T. Kato, R.R. Flynn, J.A. Skorcz, J. Org. Chem. 28 (1963) 1–6.