C-H BOND HALOGENATION OF BENZOXAZINONES BY PALLADIUM CATALYSTS

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Abstract

In this research, palladium-catalyzed C-H bond halogenation of benzoxazinone derivatives has been achieved. This approach shows high regioselectivity and wide substrate scope, the products are obtained in moderate to good yields. The plausible mechanism was discussed, the reaction may have gone through a $Pd^{II}/Pd^{IV}/Pd^{II}$ process. This protocol provides a simple and effective synthesis pathway for various halogenated benzoxazinone derivatives.

Keywords: *Palladium catalyst; benzoxazinone; C-H activation; halogenation.*

1. Introduction

Benzoxazinone is an important nitrogen-containing heterocyclic compound and has many applications in pharmaceutical research [1]. Particularly, benzoxazinone derivatives exsite in a wide range of natural bioactive molecules, and exhibited different biological activities such as α-chymotrypsin inhibitor [2], anti-HCoV [3], high-density lipoprotein (HDL) elevator [4], inhibitor of C1r serine protease [5], elastate inhibitor [6], serine hydrolase inhibitors [7]. A few representative compounds are outlined in Figure 1. Therefore, developing a simple, efficient and environmentally benign process for synthesizing benzoxazinone derivatives has received extensive attention.

The functionalization of C-H bonds by using complex of transition metal as catalysts have become a reliable and powerful tool for valuable transformations [8]. These methods are simple to operate and significantly reduce by-products, improve economic atom for C-H functionalization reactions. This reaction was catalyzed efficiently by using complex of transition metals such as palladium, iridium, ruthenium, and rhodium. The majority of C-H functionalization has been achieved through catalysis of noble metals [9].

Recently, research on palladium-catalyzed C-H bond functionalization of benzoxazinone has been reported. The reactions that have successfully achieved conversion

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include acylation [10], acetoxylation and hydroxylation [11, 12], olefination [13], acetoxylation and halogenation [14], and amidation [15]. In order to expand the application of palladium-catalyzed C-H bond functionalization of benzoxazinone, and synthesize various biologically active halogenated products, we herein reported the palladium-catalyzed ortho-halogenation of benzoxazinone via C-H bond using NBS/NIS/NFSI as the halogenation reagent.

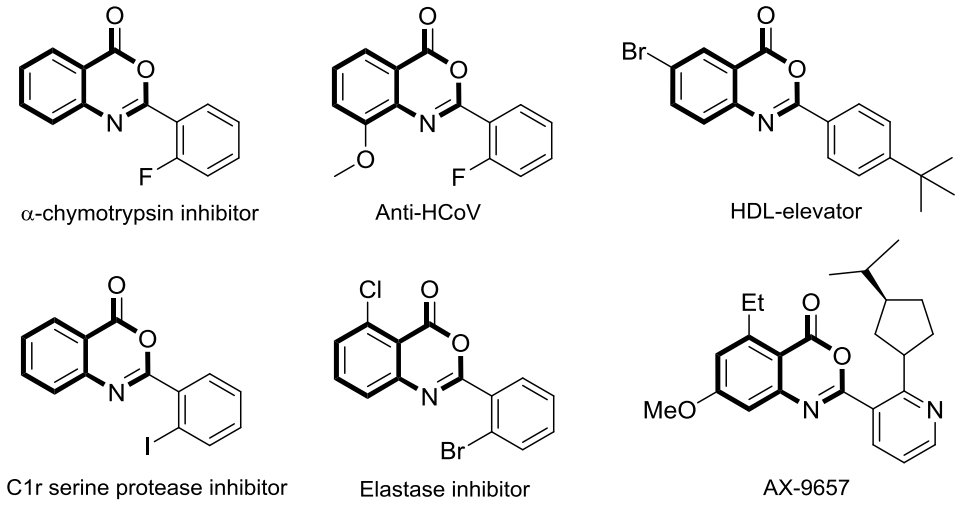


Fig. 1. Representative example of biologically active benzoxazinones.

2. Experiment

Chemicals and reagents were purchased from Sigma Aldrich, Aladdin and used as such unless stated otherwise. The nuclear magnetic resonance (NMR) spectra have been recorded with Brucker Avance 400 spectrometers at University of Science and Technology Beijing. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ using TMS as internal standard, operating at 400 MHz and 101 MHz, respectively. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), m (multiplet). The melting point were determined on the Bibby Stuart melting point instrument (model: SMP11). Infrared spectroscopy has been recorded with Spectrum Two Perkin Elmer spectrometer. Unless otherwise noted, the purification was performed using column chromatography on silica gel.

General steps for the synthesis of 2-arylbenzoxazinones (1a-1d). To a mixture of anthranilic acid (50 mmol), Na_2CO_3 (125 mmol) in THF (50 mL), benzoyl chloride (100 mmol) was added drop wise at 0°C. After 10 min, the cold-bath was removed, and the mixture was stirred at room temperature overnight. After the reaction was complete, water (50 mL) was added, and the mixture was stirred for 10 min prior to filtration. After removal of the

solvent, the solid was washed with water and 50% aqueous CH_3OH respectively to get the desired product **1**.

Synthesis of 2-(2-bromophenyl)-4H-benzo[d][1,3]oxazin-4-one (2a). The substrate **1a** (0.3 mmol), NBS (1.2 equiv), $Pd(OAc)_2$ (10 mol%), $AgNO_3$ (50 mol%), DCE (3 mL) were added to a test tube, the mixture was stirred at 100 °C under air for 24 h. Upon completion, the mixture was cooled to room temperature, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on a silica gel using *n*-hexane/ethyl acetate as the eluent. The product **2a** as white solid (75.8 mg, 84% yield); Mp: 121 - 123°C; IR νmax (cm^{-1}): 2923, 1761, 1625, 1472, 1312, 1219, 1079, 996, 764, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.9 Hz, 1H), 7.89 (dd, *J* = 11.9, 4.6 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.61 (dd, *J* = 11.0, 4.2 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.40 (td, *J* = 7.8, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 157.2, 146.4, 136.7, 134.3, 132.4, 132.4, 131.5, 129.0, 128.6, 127.5, 127.4, 121.8, 117.0.

Synthesis of 2-(3-bromo-[1,1'-biphenyl]-4-yl)-4H-benzo[d][1,3]oxazin-4-one (2b). The synthesis steps are the same as synthesis of **2a**. The product **2b** as white solid (83,7 mg, 74 % yield); Mp: 137 - 139°C; IR νmax (cm^{-1}): 2917, 1758, 1609, 1464, 1304, 1211, 1057, 974, 723, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.9 Hz, 1H), 8.00 (dd, *J* = 4.8, 3.2 Hz, 2H), 7.89 (dd, *J* = 11.0, 4.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.69 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.62 (dd, *J* = 15.5, 7.8 Hz, 3H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.9, 146.5, 145.5, 138.5, 136.7, 132.9, 131.9, 130.6, 129.2, 129.0, 128.7 128.6, 127.5, 127.3, 126.1, 122.3, 117.0.

Synthesis of 3-bromo-2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl acetate (2c). The synthesis steps are the same as synthesis of **2a**. The product **2c** as white solid (70,2 mg, 65% yield); Mp: 130 - 132°C; IR νmax (cm^{-1}): 1761, 1630, 1465, 1327, 1014, 752, 668, 584; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.9 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 159.0, 154.4, 149.9, 146.0, 136.8, 132.1, 130.7, 129.4, 128.7, 127.4, 126.9, 122.6, 122.5, 117.1, 20.7.

Synthesis of 2-(2-bromophenyl)-5-chloro-4H-benzo[d][1,3]oxazin-4-one (2d). The synthesis steps are the same as synthesis of **2a**. The product **2d** as white solid; (75,8 mg, 75% yield); Mp: 170-172°C; IR νmax (cm^{-1}): 2976, 1776, 1661, 1483, 1309, 1232, 1041, 794; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.73 (m, *J* = 2.3 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.56 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.46 (m, 1H), 7.40 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 155.9, 148.9, 136.3, 136.2, 134.6, 132.7, 131.9, 131.6, 131.5, 127.6, 126.6, 121.9, 114.9.

Synthesis of 2-(2-iodophenyl)-4H-benzo[d][1,3]oxazin-4-one (2e). The synthesis steps are the same as synthesis of **2a**, NIS (0.36 mmol, 1.2 equiv) instead of NBS. The product **2e** as pale yellow solid (67.0 mg, 64% yield); Mp: 120 - 122°C; IR νmax (cm^{-1}): 3059, 1749, 1623, 1468, 1318, 1215, 1032, 1004, 768, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.88 (dd, *J* = 17.1, 7.8 Hz, 2H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 157.8, 146.3, 141.2, 136.7, 135.5, 132.3, 130.9, 129.0, 128.7, 128.2, 127.4, 117.0, 94.6.

Synthesis of 2-(2-fluorophenyl)-4H-benzo[d][1,3]oxazin-4-one (2f). The synthesis steps are the same as synthesis of **2a**, NFSI (0.6 mmol, 2 equiv) instead of NBS. The product **2f** as white solid (39,8 mg, 55% yield); Mp: 115 - 117°C; IR νmax (cm^{-1}): 2925, 1759, 1622, 1487, 1319, 1236,1027, 761, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.6, 146.5, 136.7, 133.5, 132.5, 131.5, 131.1, 130.3, 129.0, 128.5, 127.5, 126.9, 117.0.

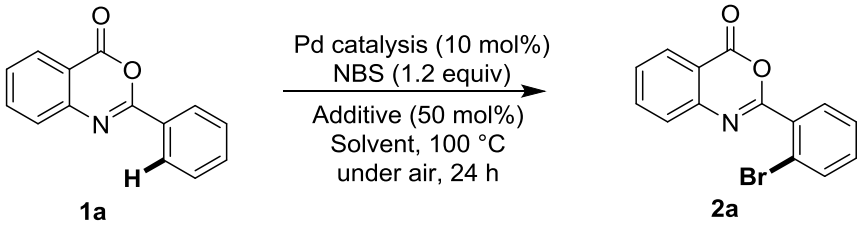
3. Results and discussion

The reaction of benzoxazinone (**1a**) and N-bromosuccinimide (NBS) was chosen for screening the optimal reaction conditions. The work content of this section has been preliminarily introduced in our previous article [14], the results were shown in Table 1.

When the reaction was carried out in DCE at 100°C for 24 h and using $PdCl_2$ (10 mol%) and $AgNO_3$ (50 mol%) as catalyst and additive, the brominated product **2a** was obtained in 68% yield (Table 1, entry 1). Replacing $PdCl_2$ with $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ the yield of compound **2a** did not increase, while $Pd(OAc)_2$ can significantly increase the yield of the product to 84% (Table 1, entries 2-4), the reason may be that the -OAc group as a ligand is more suitable for this conversion. Increasing the amount of the catalyst did not bring an evident improvement of the yield (Table 1, entry 5), while the amount of the catalyst decreased to 5 mol%, the yield dramatically decreased (Table 1, entry 6). However, the reaction cannot proceed without the presence of palladium salt catalyst (Table 1, entry 7).

Another factor to influence this reaction was the solvent. The solvents tested include: THF, CH_3CN, CH_3NO_2, toluene, DMF, DMSO, C_6H_5Cl, etc. The results indicate that only the solvents CH_3NO_2 or C_6H_5Cl gave lower yields, while the other solvents simply did not allow the reaction to proceed smoothly (Table 1, entries 8-15).

Table 1. Optimization of reaction conditions[a]



1a **2a**

Entry	**Catalysis** (x mol%)	**Additive** (50 mol%)	**Solvent**	**Yield**[b] **%**
1	$PdCl_2$ (10)	$AgNO_3$	DCE	68
2	$Pd_2(dba)_3$ (10)	$AgNO_3$	DCE	49
3	$Pd(PPh_3)_4$ (10)	$AgNO_3$	DCE	67
4	**$Pd(OAc)_2$ (10)**	**$AgNO_3$**	**DCE**	**84**
5	$Pd(OAc)_2$ (20)	$AgNO_3$	DCE	84
6	$Pd(OAc)_2$ (5)	$AgNO_3$	DCE	55
7	-	$AgNO_3$	DCE	-
8	$Pd(OAc)_2$ (10)	$AgNO_3$	THF	-
9	$Pd(OAc)_2$ (10)	$AgNO_3$	CH_3CN	trace
10	$Pd(OAc)_2$ (10)	$AgNO_3$	CH_3NO_2	20
11	$Pd(OAc)_2$ (10)	$AgNO_3$	Toluene	trace
12	$Pd(OAc)_2$ (10)	$AgNO_3$	DMF	-
13	$Pd(OAc)_2$ (10)	$AgNO_3$	DMSO	-
14	$Pd(OAc)_2$ (10)	$AgNO_3$	C_6H_5Cl	37
15	$Pd(OAc)_2$ (10)	$AgNO_3$	Dioxane	-
16	$Pd(OAc)_2$ (10)	KNO_3	DCE	45
17	$Pd(OAc)_2$ (10)	$NaNO_3$	DCE	53
18	$Pd(OAc)_2$ (10)	$NaNO_2$	DCE	60
19	$Pd(OAc)_2$ (10)	$AgNO_2$	DCE	70
20	$Pd(OAc)_2$ (10)	$Cu(NO_3)_2.H_2O$	DCE	trace
21	$Pd(OAc)_2$ (10)	TFA	DCE	15
22	$Pd(OAc)_2$ (10)	AcOH	DCE	21
23[c]	$Pd(OAc)_2$ (10)	$AgNO_3$	DCE	32
24[d]	$Pd(OAc)_2$ (10)	$AgNO_3$	DCE	82
25	$Pd(OAc)_2$ (10)	-	DCE	22
26[e]	$Pd(OAc)_2$ (10)	$AgNO_3$	DCE	82
27[f]	$Pd(OAc)_2$ (10)	$AgNO_3$	DCE	54

[a]*Reaction conditions*: **1a** (0.3 mmol, 1.0 equiv), NBS (0.36 mmol, 1.2 equiv), Pd catalysis (0.03 mmol, 10 mol%), additive (0.15 mmol, 50 mol%), solvent (3.0 mL), under air, 100°C, 24 h. [b]Isolate yield. [c]$AgNO_3$ (10 mol%). [d]$AgNO_3$ (100 mol%). [e]Temp = 120°C. [f]Temp = 80°C.

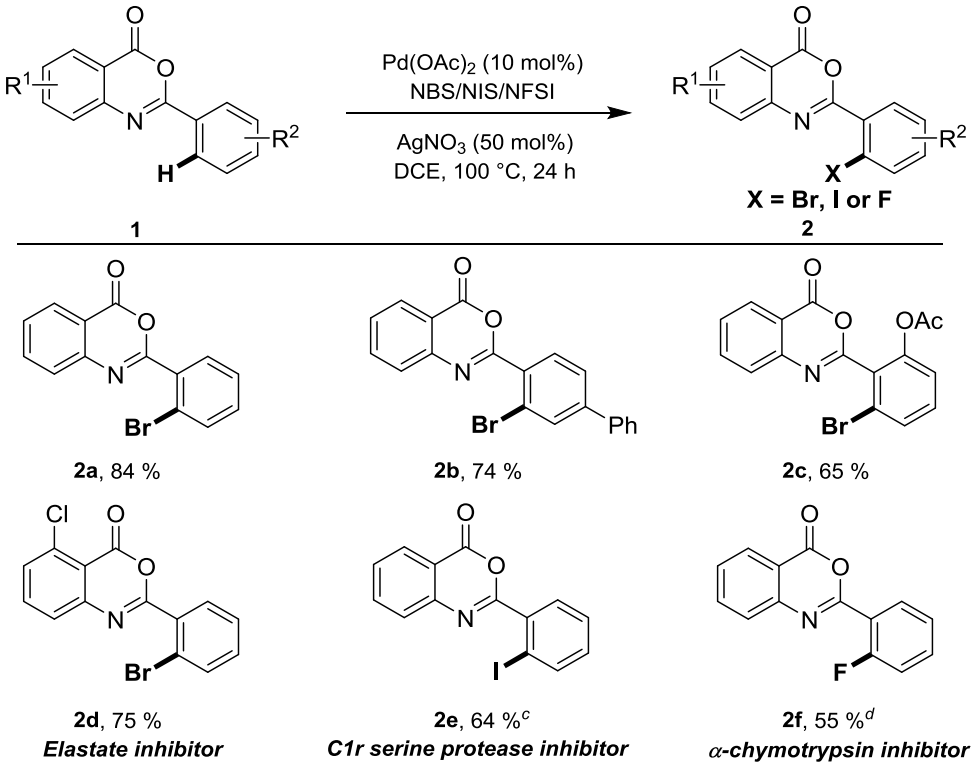
After obtaining the optimal catalyst and solvent, we investigated the effect of additives on the reaction. When different nitrates and nitrites, such as KNO_3, $NaNO_3$, $AgNO_2$, and $NaNO_2$ were used as additives for the reaction, only moderate yields were

observed (Table 1, entries 16-19). When $Cu(NO_3)_2.H_2O$ replaced $AgNO_3$, only trace product formation was obtained (entry 20). In many literatures, adding a small amount of acid as an additive is the key to the success of the reaction, but the effect is not ideal in this system. If a small amount of TFA or AcOH is added as an additive, the reaction yield decreases instead (Table 1, entries 21-22).

The reason may be that the addition of acid leads to the hydrolysis of the benzoxazinone substrate and ring opening. Increasing or decreasing the amount of $Ag(NO)_3$ will result in a decrease in product yield (Table 1, entries 23-25). At the same time, we also carried out the reaction under the conditions of different temperature and time. When the reaction temperature was increased to 120°C, did not bring an evident improvement of the yield (Table 1, entry 26), while the reaction was carried out at 80°C, the substrate conversion was incomplete and the yield decreased (Table 1, entry 27).

Finally, the optimized reaction conditions for bromination of 2- phenylbenzoxazinone were determined as follows: $Pd(OAc)_2$ (10 mol%) as the catalyst, $Ag(NO)_3$ (50 mol%) as an additive and DCE as the solvent, at 100°C under air for 24 h.

Table 2. Substrate scope of direct halogenation of 2-arylbenzoxazinones [a, b]

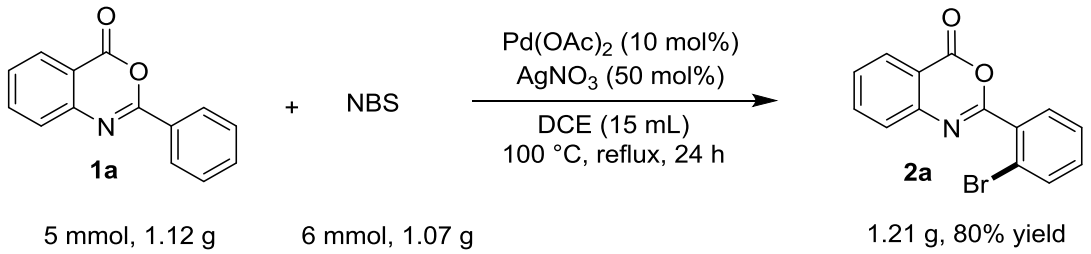


[a]*Reaction conditions*: **1** (0.3 mmol), NBS (0.36 mmol, 1.2 equiv), $Pd(OAc)_2$ (10 mol%), $AgNO_3$ (50 mol%) in DCE (3.0 mL), under air, 100°C for 24 h.

[b]Isolated yield. [c]NIS (0.36 mmol, 1.2 equiv) instead of NBS. [d]NFSI (0.6 mmol, 2 equiv) instead of NBS.

Based on the optimized reaction conditions, several brominated benzoxazinone derivatives **2a-2d** were successfully prepared in moderate to good yields (Table 2). In addition to bromination, we also studied the application of reaction conditions for iodization and fluorination reactions using N-iodosuccinimide (NIS) or N-fluorobenzenesulfonimide (NFSI) instead of NBS. We successfully synthesized iodine and fluorine derivatives of 2-phenylbenzoxazinone with moderate yields (Table 2, **2e-2f**).

In order to further investigate the application prospects of the above reaction methods, we have expanded the dosage of substrates to the order of grams (Scheme 1). The results suggested that the scale-up of the reaction dosage did not affect the reaction yield, the yield of brominated products can still reach 80%. Therefore, the method we have explored has practical application prospects, providing a new route for the synthesis of halogenated 2-arylbenzoxazinone compounds.



Scheme 1. Gram-scale reaction

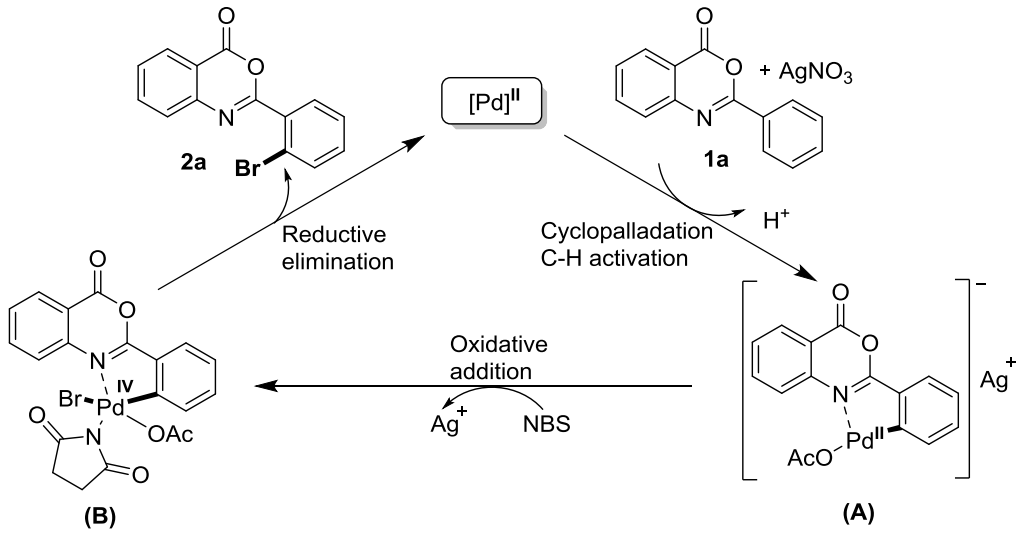


Fig. 2. Possible reaction mechanism.

Based on the previous report [10-15], we hypothesize a possible reaction mechanism in Fig. 2. The reaction may have gone through a $Pd^{II}/Pd^{IV}/Pd^{II}$ process. Firstly, the palladium metal catalyst complexes with 2-phenylbenzoxazinone **1a** to generate intermediate (**A)**, which is a cyclopalladation process. Then, intermediate (**A)** combines with NBS to form intermediate (**B)**, while Pd metal is also oxidized from II valence to IV valence. Finally, intermediate (**B)** undergoes reductive elimination to afford bromated 2-arylbenzoxazinone products **2a** and regenerated II valent palladium, then starting a new catalytic cycle.

4. Conclusion

In summary, we have studied an effective palladium-catalyzed method for halogenation of the C-H bond. The reaction conditions have been investigated, and the optimal reaction conditions are $Pd(OAc)_2$ (10 mol%) as the catalyst, $Ag(NO)_3$ (50 mol%) as an additive and DCE as the solvent, at 100°C under air for 24 h. Successfully synthesized 6 halogenated benzoxazinone derivatives with moderate to good yields. Additionally, this transformation can also be scaled up to the gram level. This method provides an efficient approach for the synthesis of halogenated benzoxazinone compounds.

Acknowledgement

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XÚC TÁC PALLADIUM HOẠT HÓA LIÊN KẾT C-H THỰC HIỆN PHẢN ỨNG HALOGEN HÓA TRÊN CƠ CHẤT BENZOXAZINONE

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Tóm tắt: Trong nghiên cứu này, phản ứng palladium hoạt hóa liên kết C-H tiến hành halogen hóa trên cơ chất benzoxazinone đã được thực hiện thành công. Phương pháp này cho thấy tính chọn lọc vị trí cao, phạm vi cơ chất rộng, các sản phẩm thu được đạt hiệu suất trung bình đến cao. Cơ chế của phản ứng đã được nhóm tác giả đề xuất, phản ứng có khả năng đã trải qua quá trình tuần hoàn $Pd^{II}/Pd^{IV}/Pd^{II}$. Nghiên cứu này đã cung cấp một phương pháp mới đơn giản và hiệu quả để tổng hợp các dẫn xuất halogen của hợp chất benzoxazinone.

Từ khóa: *Xúc tác palladium; benzoxazinone; hoạt hóa liên kết C-H; halogen hóa.*

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