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PII: S0040-4039(19)30845-7
DOI: https://doi.org/10.1016/j.tetlet.2019.151082
Reference: TETL 151082

To appear in: *Tetrahedron Letters*

Received Date: 19 July 2019
Revised Date: 9 August 2019
Accepted Date: 23 August 2019

Please cite this article as: Shi, Y., Zhou, Q., Du, F., Fu, Y., Du, Y., Fang, T., Chen, G., Iridium-catalyzed Intramolecular C–N and C–O/S Cross-Coupling Reactions: Preparation of Benzoazole Derivatives, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151082

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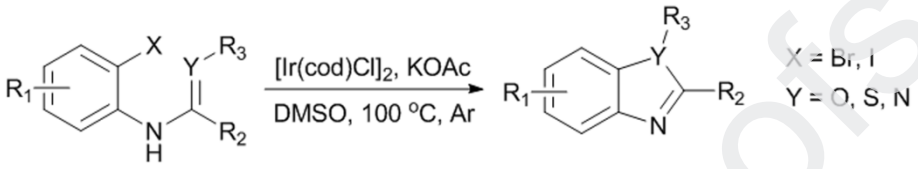

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Iridium-catalyzed Intramolecular C–N and C–O/S Cross-Coupling Reactions: Preparation of Benzoazole Derivatives

Yajie Shi [a], [†] Qifan Zhou [a], [†] Fangyu Du [a], Yang Fu [a], Yang Du [a], Ting Fang [a], Guoliang Chen [a*]

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Iridium
Catalysis
Intramolecular Cross-Coupling
Benzoazole

ABSTRACT

The iridium-catalyzed intramolecular arylcarbon-hetero cross-coupling reactions with *o*-haloarylamides or *o*-haloarylamidine have been effectively achieved using KOAc and just 1 mol % catalyst. The $[Ir(cod)Cl]_2$ was proved to be more potential for smoothly assembling functional structures benzimidazoles, benzoxazoles and benzothiazoles, which was superior to Cu- and Pd-catalyzed systems. Simultaneously, a concise and efficient synthesis of tafamidis was developed in 5-gram scale.

1. Introduction

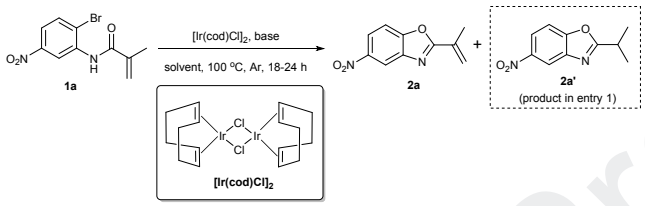
Benzoazole derivatives include benzoxazoles, benzimidazoles and benzothiazoles are ubiquitous structural motifs in numerous natural products,[1] biologically active compounds,[2] and fluorescent probes[3] or heat-resistant polymers.[4] Particularly, they are ubiquitous in pharmaceuticals and account for a large part of the bestseller drugs, such as omeprazole, nexium, protonix, famvir, vermox and priaxim.[5] For elaboration of these synthetically challenging molecules, several elegant methods have been described for construction of benzimidazoles and benzoxazoles over the past decades. Traditional approaches to build such structures often depend on condensations of 2-aminoaniline and 2-aminophenol with carboxylic acid or aldehydes.[6, 7] In 2007, Kaul et al. accomplished the synthesis of benzoxazoles [3] in excellent yield by condensation of carboxylic acid with *o*-aminophenol using *N*,*N*-dimethylchlorosulfitemethaniminium chloride as condensing reagent.[8] Wagner et al. reported the synthesis of benzimidazole using *o*-phenylenediamine and formic acid as starting material at 100 °C for 2 h.[9] However, these protocols generally suffered from harsh reaction conditions (strong acid or high temperature), the narrow substrates (not available to substituted 2-aminoanilines and 2-aminophenols) and with erratic yields, which seriously limited large-scale industrial applications. Recently, to overcome these drawbacks, transition-metal-catalyzed (e.g., Cu,[10] Fe,[11] Co,[12] Pd,[13] Ni[14]) cross-coupling reactions have been reported continuously for the formation of benzimidazoles benzoxazoles and benzothiazoles. In 2004, Altenhoff et al. first reported an efficient Cu-catalyzed formation of benzoxazoles from *o*-dihaloaromatic compounds and primary amides.[15] Subsequently, Canivet et al. described the Ni-catalyzed coupling reaction for assembly of benzoxazoles with aryl halides or arylboronic acids.[16] Weires et al. achieved the synthesis of benzimidazoles from *o*-nitroanilines using montmorillonite-K10 and Pd/C as cocatalyst.[17] These practical and flexible approaches catalyzed by transition-metal promote the reaction process, and open a new chapter in organic synthesis.

Because of increasing environmental pollution, chemists around the world are engaged in introducing the new concepts of green chemistry to minimize the damage and synthesize chemicals in an ecofriendly way.[18] In 2015, Nagarkar et al. synthesized 2-substituted benzoxazoles from substituted benzyl amines and *o*-nitrophenol as the starting materials, catalyzed by copper ferrite nanoparticles.[19] This protocol provided an alternative strategy for the synthesis of benzoxazoles. In 2014, Hao et al. reported the gold-catalyzed synthesis of benzimidazoles from 2-nitroanilines and CO_2 in the presence of H_2,[20] it provides a new route for synthesis of benzimidazoles, widens the CO_2 application in organic synthesis.

Iridium catalyst plays an important role in asymmetric allylic substitution reactions, [21] oxidation,[22] dehydrogenation,[23] due to its high catalytic activities, high yield and high stereoselectivity. The knowledge of iridium may be a great cross-coupling catalyst encouraged us to conduct further studies. We found that substituted benzoazole derivatives were readily obtained *via* intramolecular C-O/S or C-N coupling reactions of *o*-haloarylamides or *o*-haloarylamidine just by using $[Ir(cod)Cl]_2$ in 1 mol % catalytic loading in the presence of KOAc at moderate temperature. To our best knowledge, intramolecular Ir-catalyzed arylcarbon-heteroatom cross-coupling reactions are unprecedented. Herein, we wish to disclose these results.

As described in **Table 1**, we began by examining the intramolecular coupling reaction of *N*-(2-bromo-5-nitrophenyl)methacrylamide in the presence of $[Ir(cod)Cl]_2$ and sodium formate under argon atmosphere (**Table 1**, **entry 1**). Surprisingly, a reductive product of 2-isopropyl-5-nitrobenzo[*d*]oxazole **2a'** yielded in 74% without any desirable product. We reasoned that sodium formate acted as both alkali and hydrogen donor, causing the reductive product. Further studies revealed a significant effect of bases, with acetates proving to be optimal in terms of yield (**entries 2-5**). KOAc was found to be slightly better than NaOAc. Noteworthy was that a stronger base was disadvantageous to the smoothly formation of **2a**. Attempts to optimize the reaction through screening various solvents proved unsuccessful (**entries 6-10**). Polar aprotic solvent appeared to be feasible, with DMSO giving **2a** in excellent yield in shorter time (**entry 10**). To our delight, when the catalytic loading was reduced from 10 mol % to 1 mol %, there was no influence on the Ir-catalyzed reaction (**entries 11-12**). In addition, a scale-up experiment of 10 gram loading was carried out to provide **2a** in 93% yield, proving the stability of this catalytic system in a multi-gram scale (**entry 13**). It was noted that no Heck C-C coupling product was detected in the optimized experiment.

Table 1. Optimization Studies for the Ir-catalyzed C-O Cross-coupling of *N*-(2-iodophenyl)benzamide [a]



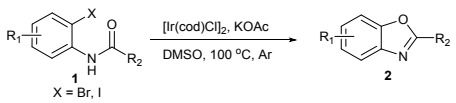
Entry	Base	Solvent	Catalytic Loading (mol %)	Time (h)	**2a** (%)[b]
1	HCOONa	DMA	10	24	0[c]
2	KOAc	DMA	10	20	79
3	NaOAc	DMA	10	20	70
4	K_2CO_3	DMA	10	20	26
5	NaOH	DMA	10	20	trace
6	KOAc	Toluene	10	20	13
7	KOAc	CH_3CN	10	20	70
8	KOAc	1,4-dioxane	10	20	56
9	KOAc	2-propanol	10	20	63
10	KOAc	DMSO	10	12	90
11	KOAc	DMSO	1	10	91
12	KOAc	DMSO	0.1	18	76
13[d]	KOAc	DMSO	1	24	93

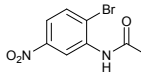
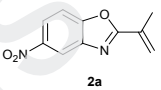
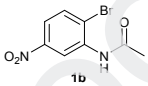
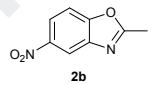
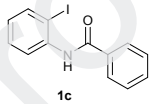
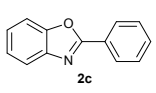
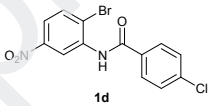
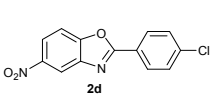
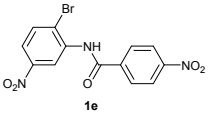
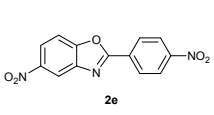
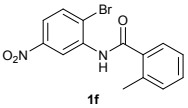
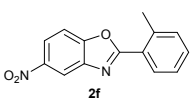
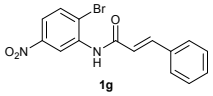
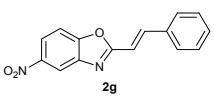
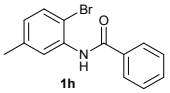
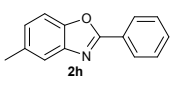
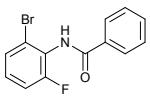
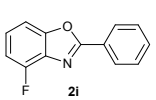
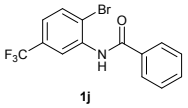
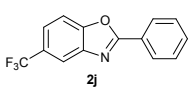
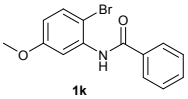
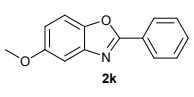
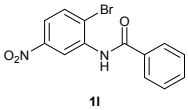
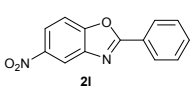
[a] Standard conditions: **1a** (1.00 mmol), base (3.0 mmol), solvent (5 mL), under argon atmosphere, 100 °C. [b] Isolated yield after silica gel column chromatography. [c] **2a'** was obtained in 74% yield. [d] The loading of **1a** was 10 gram.

With optimized conditions in hand, we explored the scope of the Ir-catalytic coupling reactions of 2-haloarylamides in the presence of potassium acetate (**Table 2**). Various 2-haloarylamides were converted to corresponding benzoxazoles under the optimal reaction conditions in from good to excellent yields, 63-91%. Not surprisingly, aryl bromides and aryl iodides were both participated in this system. The 2-haloarylamides bearing electron-withdrawing groups provided superior conversion than those carrying electron-donating substitutes (**2k** vs. **2l**). Furthermore, the sterically hindered 2-methylbenzamide derivative afforded **2f** in 71% yield, appearing to prove that this reaction was sensitive to steric hindrance. In addition, when the

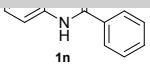
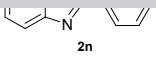
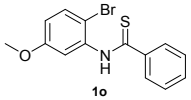
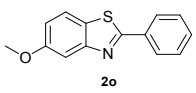
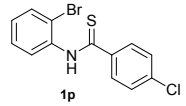
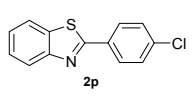
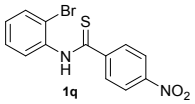
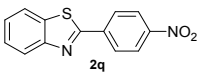
ed O-cyclization products were obtained in moderate yield (**entries 4, 5**). Notably, when amino groups were substituted by α,β-unsaturated acyl groups, the desired C-O coupling product **2a** and **2g** was afforded smoothly in 91% and 74% yield, with no Heck C-C coupling reaction occurred (**entries 1 and 7**). The synthesis of benzothiazoles also follows a similar regularity with benzoxazoles (**entry13-16**).

Table 2. Ir-Catalyzed Synthesis of Benzoxazole Derivatives [a]



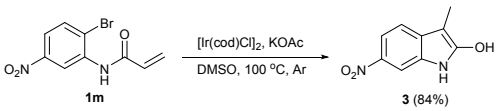
Entry	Substrates	Product	Yield (%) [b]
1			91
2			89
3			82
4			74
5			72
6			71
7			74[c]
8			73
9			78[d]
10			84[d]
11			75[d]
12			90

Entry	Substrates	Product	Yield (%) [b]

13	 1n	 2n	89
14	 1o	 2o	80
15	 1p	 2p	85
16	 1q	 2q	79

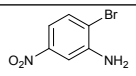
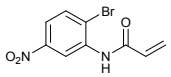
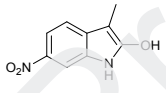
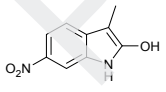
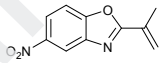
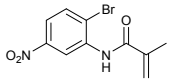
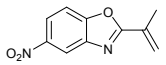
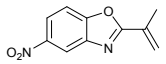
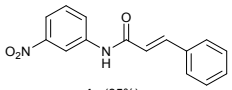
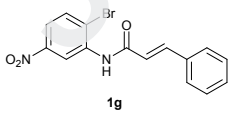
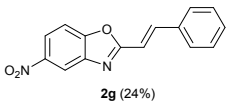
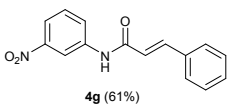
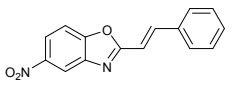
[a] Standard conditions: **1** (1.00 mmol), $[Ir(cod)Cl]_2$ (0. 01 mmol), KOAc (3.0 mmol), DMSO (5 mL), under Ar, 10 h, 100 °C. [b] Isolated yield after chromatography. [c] 15 h. [d] 13 h.

Scheme 1. Ir-Catalyzed Heck Reaction of *N*-(2-Bromo-5-nitrophenyl)acrylamide



1m — 3 (84%)

Table 3. Intramolecular Cross-coupling of Acryl Substituted *o*-Bromoaniline Catalyzed *via* $Pd(OAc)_2$, CuI and $[Ir(cod)Cl]_2$, respectively.

Substrate	Catalyst [a]	Product [b]
	$Pd(OAc)_2$ (0.01 mmol)	 **4m** (68%)
 **1m**	CuI (0.20 mmol)	 **3** (60%)
	$[Ir(cod)Cl]_2$ (0.01 mmol)	 **3** (84%)
	$Pd(OAc)_2$ (0.01 mmol)	 **2a** (42%)
 **1a**	CuI (0.20 mmol)	 **2a** (85%)
	$[Ir(cod)Cl]_2$ (0.01 mmol)	 **2a** (91%)
	$Pd(OAc)_2$ (0.01 mmol)	 **4g** (85%)
 **1g**	CuI (0.20 mmol)	 **2g** (24%)
		 **4g** (61%)
	$[Ir(cod)Cl]_2$ (0.01 mmol)	 **2g** (74%)

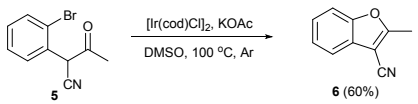
[a] Standard conditions: 1(1.00 mmol), cat., KOAc (3.00 mmol), DMSO (4 mL), under Argon, 100 °C. [b] Isolated yield after silica gel column chromatography.

Based on these findings, *N*-(2-bromo-5-nitrophenyl)acrylamide was reacted in this catalytic system to C-C coupling reaction. Interestingly, a C-C coupling product **3** was solely constructed in 84% yield with no detectable C-O coupling product. On the other hand, 2-hydroxyindole compound **3** which was traditionally obtained *via* deamination cyclisation from *N*'-arylpropionic acid hydrazide[24] or condensation from *N*-(2-chloroaryl)-*N*-methylacetamide.[25] Accordingly, $[Ir(cod)Cl]_2$ might be a useful catalyst to build such structures. Compared with the results of **entries 7, 12** in **Table 1** and **Scheme 1**, it was found that the C-H at the alpha position was readily activated by Ir catalyst, leading to C-C coupling reaction, when the α,β-unsaturated alkenyl linking to carbonyl was not conjugated with an aryl group. Contrarily, the C-O coupling product was mainly obtained when there was no such easily activated C-H at α position.

To cast about for the orderliness, the intramolecular cross-coupling of acryl substituted *o*-bromoaniline was proceeded by utilizing $Pd(OAc)_2$, CuI and $[Ir(cod)Cl]_2$ as catalyst under the basic conditions, respectively. As described in **Table 3**, when the hydrogen of α position in acryloyl group was substituted by methyl, the Heck reaction did not occur in these three systems, with only affording the C-O coupling product **2a**. Moreover, $[Ir(cod)Cl]_2$ was more superior than the other two catalyst. $Pd(OAc)_2$- and CuI- catalyzed coupling reactions both yielded an amount of debromination by-product **4g** when using the less active cinnamoyl substituted *o*-haloaniline as substrate,[12] and CuI- catalyzed system could give **2g** in just 24% yield. However, Ir- catalyzed coupling reaction was capable to afford **2g** in 74% yield without **4g** observed. The same result was achieved in Cu- and Ir- catalyzed coupling reactions of acryl substituted *o*-halogenated aniline, with cleanly providing Heck C-C coupling product **3**. Interestingly, the utilization of palladium catalyst led to hydrolysis product **4m**. Arguably, $[Ir(cod)Cl]_2$ was proved to be a more potential and efficient agent for C-O coupling reaction than $Pd(OAc)_2$ and CuI.

Inspired by the successful formation of benzoxazole, the Ir-catalytic system was performed by using 2-(2-bromophenyl)-3-oxobutanenitrile as substrate (**Scheme 2**). Results showed that the C-O coupling product **6** was isolated in 60% yield, indicating that $[Ir(cod)Cl]_2$-catalytic system may be applied as a novel practical and flexible method to build benzofuran structures.

Scheme 2. Ir-catalyzed system for assembly of 2-Methylbenzofuran-3-carbonitrile [a,b]

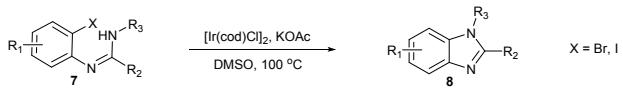


5 — 6 (60%)

[a] Standard conditions: **5** (1.00 mmol), $[Ir(cod)Cl]_2$ (0. 01 mmol), KOAc (3.0 mmol), DMSO (5 mL), under Argon, 100 °C. [b] Isolated yield after silica gel column chromatography.

The reaction also enjoys wide substrate scope with respect to *o*-haloarylamidine, as summarized in **Table 4**. The amidines **7a-m** were then investigated for the cyclization reaction under the optimized conditions, using 1 mol % $[Ir(cod)Cl]_2$ at 100 °C in the presence of KOAc in DMSO under Argon. The reactions occurred in an intramolecular manner to provide the corresponding substituted benzimidazoles **8a-m** in 75-91% yields and consumed short reaction time. Interestingly, the substrates with R_3= alkyl substituents enhanced reactivity compared to R_3= aryl groups. These results clearly suggested that this protocol could be used for the synthesis of the substituted 2-alkyl and 2-aryl benzimidazoles in high yield.

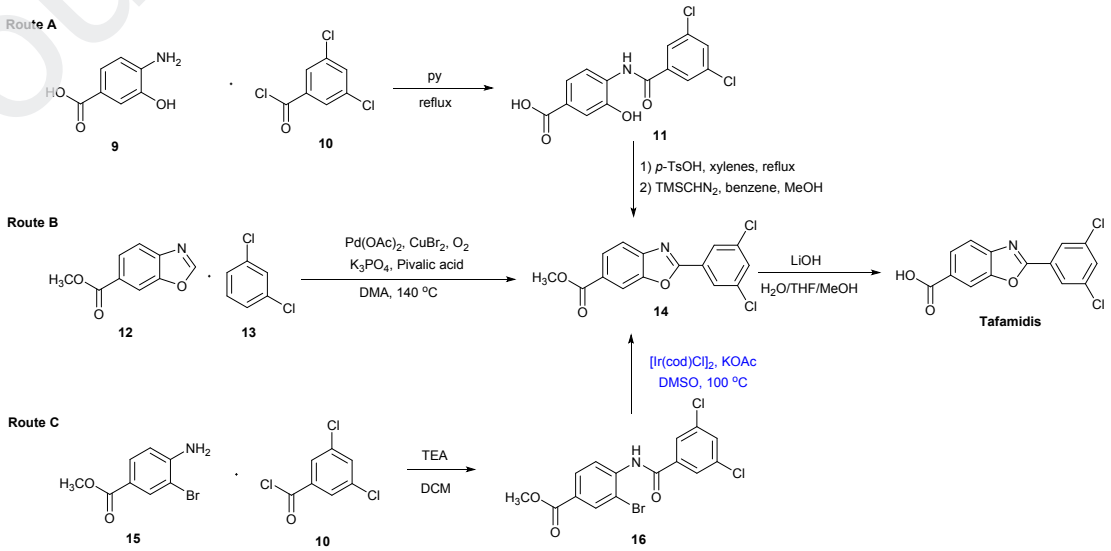
Table 4. Ir-Catalyzed Synthesis of Benzimidazole Derivatives [a]



Entry	Substrates	Product	Yield (%) [b]	Entry	Substrates	Product	Yield (%) [b]
1	7a	8a	89	8	7h	8h	83
2	7b	8b	91	9	7i	8i	79
3	7c	8c	82	10	7j	8j	84
4	7d	8d	75	11	7k	8k	80
5	7e	8e	85	12	7l	8l	90
6	7f	8f	88	13	7m	8m	87
7	7g	8g	80				

[a] Standard conditions: **7** (1.00 mmol), $[Ir(cod)Cl]_2$ (0. 01 mmol), KOAc (3.0 mmol), DMSO (5 mL), 6 h, under Ar. [b] Isolated yield after silica gel column chromatography.

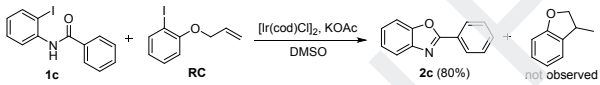
Scheme 3 Synthetic routes to tafamidis



preparation of drugs and some key intermediates, the synthetic usage of this reaction was demonstrated by direct assembly of one drug. Tafamidis[26] is a transthyretin amyloid inhibitor developed by Pfizer, which was approved by E.U. in 2011. In 2019, it was approved in Japan and the U.S. for the treatment of transthyretin amyloid cardiomyopathy. Traditional synthesis methods of key ester intermediates were showed as follows (**Scheme 3**). The key intermediate **11** was cyclized in the presence of *p*-TsOH·H_2O in refluxing xylene, followed by methylation with Me_3SiCHN_2 in benzene/MeOH affords the desired benzoxazole methyl ester **14** (Route A).[27] Alternatively, methyl 1,3-benzoxazole-6-carboxylate (**12**) condensed with 1,3-dichlorobenzene (**13**) using $Pd(OAc)_2$, $CuBr_2$, O_2, K_3PO_4 and pivalic acid in DMA at 140°C, giving ester **14** in 43% yield (Route B).[28] However, these routes suffered from high temperature or many additives which limit large-scale industrial applications. In our protocol (Route C), the key intermediate **16** could be readily cyclized in the presence of $[Ir(cod)Cl]_2$ to afford the desired product **14** in 52% yield. The coupling reaction was run at medium temperature (100 °C), using 1% loading catalyst, and giving target compound in moderate yield. The unreacted starting material could be recycled and used again, which showed potential application prospects in large-scale production.

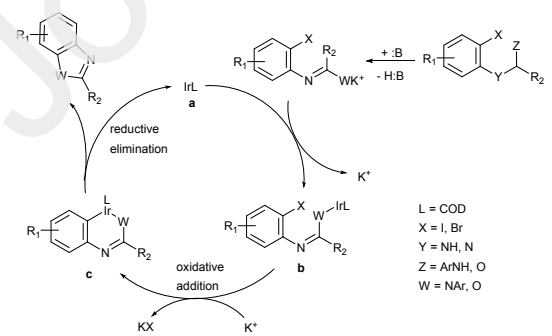
To gain insight into the mechanism of the cross coupling reactions with iridium as catalyst, we have selected one of 2-haloarylamides and used the radical clock (RC) 1-allyloxy-2-iodobenzene[29] as substrate in the coupling reactions under standard condition (**Scheme 4**). Result showed that RC did not affect the reaction process, which implying the absence of radical intermediates. This radical clock experiment indicated $[Ir(cod)Cl]_2$-catalyzed cross coupling reactions might suffer conventional oxidative addition and reductive elimination process.

Scheme 4 Cross-coupling Reaction Using RC as Substrate



By an analogy with other Cu- and Co-catalyzed C-O or C-N bond formations, [5,9] the plausible mechanism for the Iridium-catalyzed cross-coupling reaction was as follows (**Scheme 5**). In the presence of base, the initial coordination to iridium in **b** was supported by the lack of reactivity of the halo substituents at other positions in the ring under the iridium-catalyzed conditions. Subsequently, an oxidative addition with dehalogenation occurred to provide intermediate **c,** which could complete the catalytic cycle by reductive elimination of the heterocycle.

Scheme 5. Proposed Catalytic Cycle for the Iridium-catalyzed C-N and C-O Cross-coupling Reactions



In summary, we have developed an efficient iridium-catalyzed intramolecular C-N and C-O/S cross-coupling reaction to assemble numerous benzoxazoles, benzothiazoles, benzimidazoles, or benzofurans. Importantly, compared to Cu- and Pd-catalyzed C-N or C-O bond formations, Ir-catalyzed system could play a catalytic role with just 1 mol % catalyst loading and conveniently produce desired compounds without generating any debromination by-products. Simultaneously, a concise and efficient synthesis of tafamidis was developed in 5-gram scale. Applications of $[Ir(cod)Cl]_2$ to other coupling reactions, along with detailed mechanistic studies, are currently underway in our laboratory.

Acknowledgments

This work was financially supported by Liaoning Provincial Natural Science Foundation of China (No. 201602707).

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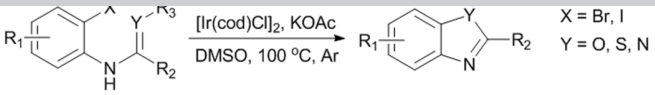
Supplementary Material

Experimental procedures and copies of ESI MS, ^{1}H NMR spectra for all new products.



O/S Cross-Coupling Reactions.
Benzoazole derivatives are readily available using this method.
Iridium catalyst can be effective with just 1 mol % catalyst loading.
Iridium performs better with low reactivity substrates than Cu or Pd.
One drug was prepared using this method.