Letter

# Rhodium (II)-Catalyzed Undirected and Selective C(sp2)-H Amination en Route to Benzoxazolones

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*ACS Catal.*, **Just Accepted Manuscript** • DOI: 10.1021/acscatal.6b02237 • Publication Date (Web): 29 Aug 2016

# Rhodium(II)-Catalyzed Undirected and Selective C($sp^2$)-H Amination en Route to Benzoxazolones

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*Supporting Information*

**ABSTRACT:** *Rhodium (II) can effectively promote the activation and cyclization of arylcarbamate substrates to yield benzoxazolones via an intramolecular nitrene C—H insertion reaction. Investigation of the substrate scope show that the reaction undergoes selective aromatic C($sp^2$)—H amination over more labile o-C($sp^3$)—H bonds. Observation of inverse secondary KIE ($P_H/P_D$ = 0.42±0.03) indicates involvement of aromatic electrophilic substitution mechanism for this aryl C—H amidation transformation.*

Direct functionalization of unactivated C—H bonds into C—N bonds are of immense interest and ideal organic transformations for the construction of N-containing heterocycles from cheap, and readily available raw materials.[1] An effective strategy for such transformation involves transition metal catalyzed direct C—H bond nitrene/ metal nitrenoid insertion, where relatively weaker C($sp^3$)—H bonds (3°>2°>1°) are preferentially activated *via* outer sphere C-H insertion mechanism.[2] In stark contrast, aryl C($sp^2$)—H amination *via* metal nitrenoid insertion garnered little attention due to lack of chemo/regioselectivity.[3] Notwithstanding, the recent developments of nitrene and metal nitrenoid insertion in aromatic C—H bonds *via* inner sphere mechanism which requires catalyst directing(chelating) groups),[4] aryl C($sp^2$)—H amination *via* "outer sphere mechanism" remains underdeveloped.[5-7] Moreover, the greatest challenge lies in the selective (chemo/regio) C—H bond functionalization. Among several catalytic systems developed till date for C—H bond nitrene/metal-nitrenoid insertion, only few reports describe preferential aromatic C($sp^2$)—H amidation in unactivated system over more labile and available *ortho*-C($sp^3$)—H bonds with poor chemo/regioselectivity, and very limited substrate scope. Notable ones include Au(III),[8a] Cu(I),[8b,c] and Fe(II) complex[8d] catalyzed intermolecular C-H amidation. Herein, we wish to report $Rh_2$(II)-catalyzed arylcarbamate system (**2**) which undergoes selective intramolecular aromatic C($sp^2$)—H amination/nitrenoid insertion *en route* to substituted benzoxazolones starting from ubiquitous phenols(**1**)(Figure 1).

Benzoxazolone moiety is an important privileged scaffold in medicinal chemistry which is endowed with broad spectrum of biological properties.[9] Besides, they also find usage as achiral template for enantioselective reaction.[10] Traditional methods to synthesize benzoxazolone nucleus includes cyclocarbonylation of 2-aminophenols with phosgene[11] and other carbonyl group donors.[12] Recent reports includes rearrangement of N-aryl-O-acylhydroxylamine,[13] N-alkyl-N-arylhydroxylamines[14] o-hydroxyl acetophenone[15a] to benzoxazolone core. Besides, Lie et al have also reported Cu catalyzed air oxidation of benzoxazole to benzoxazolone.[15b] However; all of the aforementioned methods suffer from various drawbacks, such as air sensitivity of o-aminophenols, toxicity of phosgene, high temperatures and pressures, along with undesirable side products. More so, they offer little diversity because each of them requires *o*-substituted (generally an amine or nitro group) phenols or their derivatives and their availability is often hampered by their multistep synthesis and non-selective transformations (non-regioselectivity and oversubstitution of the aromatic ring).[16]Therefore, to devise a straightforward synthesis of substituted benzoxazolones *via* direct C-H bond functionalization would be highly desirable because of the improved synthetic efficiency.

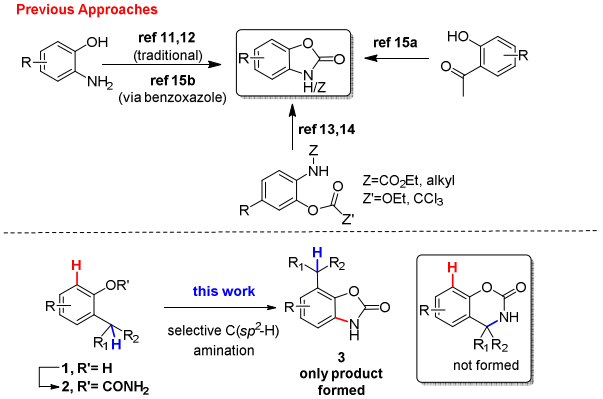
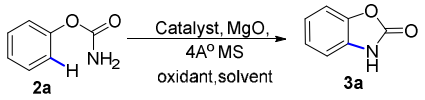



**Figure 1.** Selective C($sp^2$)—H amination approach to access substituted benzoxazolones

Our studies commenced with the treatment of O-phenyl carbamate **2a**, which was quantitatively obtained from corresponding phenol,[17] with different catalytic systems like Ag,[18] Pd,[4e] Cu,[19] Fe[20a] and Rh[2a] known to promote C-H nitrenoid insertion from amide precursors. Gratifyingly, after preliminary survey, Du Bois catalytic amination reaction condition $Rh_2(OAc)_4$, $PhI(OAc)_2$ with MgO and 4 A° MS in anhydrous dichloromethane (DCM) at 40°C, resulted in little product conversion **3a**(~15% yield). Further solvent screening at varying temperatures showed toluene to be the best solvent giving 100% conversion at 100°C with 85% yield in 6 h (see Table S1&S2 in ESI and entry 1, Table 1). Electronic nature of the carboxylate ligands displayed noteworthy effect on the activity of Rh(II) catalysis, where relatively electron rich carboxylates were able to promote aryl C—H amination quite effi-

ciently (entries 7, 10 and 11, Table 1) employing electron deficient carboxylate provided dismal yield of desired product (entry 8, Table 1).This is in contrast to their higher activity demonstrated for conversion of azide based nitrene substrates[5a] and aryl C($sp^2$)-H carbenoid insertion.[20b,c] $Rh_2(oct)_4$ performed slightly better than $Rh_2(OAc)_4$, perhaps due to better solubility at higher temperature. Decreasing the $Rh_2(OAc)_4$ catalyst loading (3 mol%) led to unconsumed starting material (entry 9, Table 1), moreover, increase in catalytic loading didn't improve the yield either(entry 2, Table 1). Inorganic oxidants screened ($K_2S_2O_8$, Oxone) (entries 3 and 4, Table 1) showed no product formation whereas other iodine based oxidants ($PhI(O_2CCF_3)_2$, $PhI(OPiv)_2$) (entries 5 and 6, Table 1) tested under otherwise similar conditions provided inferior product formation as compared to $PhI(OAc)_2$. Control reactions suggested the requirement of both oxidant ($PhI(OAc)_2$) and catalyst ($Rh_2(II)$), under inert atmosphere to promote this intramolecular aryl C—H amidation (entries 13 and 14, Table 1). Interestingly, there was no reaction between 2a and $PhI(OAc)_2$ without catalyst and both the starting materials remained intact even after ~24 h at 100°C in toluene, although with slight decomposition. This suggested the unique role of $Rh_2(II)$ catalyst in not only effecting the reaction between starting materials but also promoting intramolecular C—H amidation. Notably no C—H amidation of toluene was detected.[21a]

**Table 1**. Optimization of aromatic C—H amidation[a]

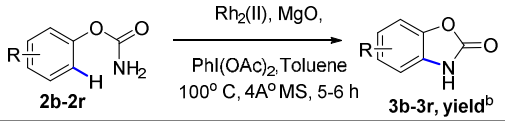


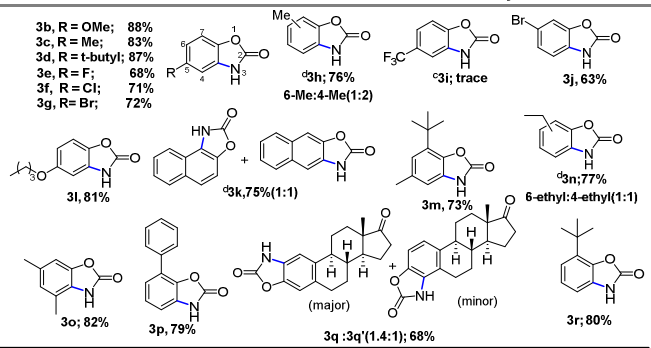

| Entry | Catalyst (mol%) | Oxidant (equiv) | Solvent | Temp(°C)/Time(h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Rh_2(OAc)_4$(5) | $PhI(OAc)_2$(1.2) | Toluene | 100/6 | 85(81)[c] |
| 2 | $Rh_2(OAc)_4$(10) | $PhI(OAc)_2$(1.2) | Toluene | 100/6 | 84 |
| 3 | $Rh_2(OAc)_4$(5) | $K_2S_2O_8$(5) | Toluene | 100/48 | nr |
| 4 | $Rh_2(OAc)_4$(5) | Oxone(5) | Toluene | 100/48 | nr |
| 5 | $Rh_2(OAc)_4$(5) | $PhI(O_2CCF_3)_2$(1.2) | Toluene | 100/24 | 14 |
| 6 | $Rh_2(OAc)_4$(5) | $PhI(OPiv)_2$(1.2) | Toluene | 100/24 | 10 |
| 7 | $Rh_2(oct)_4$(5) | $PhI(OAc)_2$(1.2) | Toluene | 100/12 | 86 |
| 8 | $Rh_2(O_2CCF_3)_4$(5) | $PhI(OAc)_2$(1.2) | Toluene | 100/48 | 10 |
| 9 | $Rh_2(OAc)_2$(3) | $PhI(OAc)_2$(1.2) | Toluene | 100/18 | 61[d] |
| 10 | $Rh_2(esp)_2$(5) | $PhI(OAc)_2$(1.2) | Toluene | 100/6 | 72 |
| 11 | $Rh_2(SDOSP)_4$(5) | $PhI(OAc)_2$(1.2) | Toluene | 100/6 | 77 |
| 12 | $Rh_2$(tpa)4(10) | $PhI(OAc)_2$(1.2) | Toluene | 100/48 | 79 |
| 13 | $Rh_2(OAc)_4$(0) | $PhI(OAc)_2$(1.2) | Toluene | 100/24 | nr |
| 14 | $Rh_2(OAc)_4$(5) | $PhI(OAc)_2$(0) | Toluene | 100/24 | nr |
| 15[e] | $Rh_2(OAc)_4$(5) | $PhI(OAc)_2$(1.2) | Toluene | 100/6 | (78)[e] |

[a]Reactions were conducted in a Schlenk tube under argon at 0.31 mmol scale with MgO (2.2 eq), 4 A° MS(200 wt%), solvent (2.0 mL)(see ESI for details).[b]NMR based yields (see ESI for details).[c]Isolated yield in parentheses.[d]20% starting material recovered.[e]7 mmol scale. nr= no reaction.

Scale up of this reaction led to no significant change in isolated yield (entry 15, Table 1).With optimal reaction conditions in hand we investigated the scope of substrates. To test the steric and electronic influences on the C—H bond functionalization process and demonstrate the potential of this approach to provide benzoxazolones with substitution patterns that would be less readily accessible by traditional routes, various substituted carbamates were synthesized and subjected to optimized reaction condition. As indicated from results obtained in **Table 2**, varied substituents like halogens, alkyl, aryl and methoxy groups were well tolerated under the reaction condition. Significant electronic effect was observed on 4-substituted carbamates, where substrates with electron donating substitutents (alkoxy, Me, *t*-butyl) cyclized efficiently to provide desired products in good to excellent yields (entries **3b-3d** and **3l**), while electron withdrawing substituted (F, Cl, Br) substrates provided diminished yields of their respective benzoxazolones (entries **3e-3g**).Halogenated benzoxazolones thus obtained provides additional handle for further diversification thereof. However, only trace amount of desired product was observed from substrate with strong electron withdrawing group (entry **3i**). Employment of other catalysts was unsuccessful in promoting the C-H bond amidation on this substrate (data not shown). Subjecting dialkyl substituted carbamates under optimized reaction condition furnished product **3m** and **3o** in very good yields.[21b] Further, to observe the steric effect on the C-H bond amination mediated cyclization process, *m*-substituted carbamates were tested.

**Table 2.** Scope of $Rh_2(II)$ catalyzed C($sp^2$)—H amination on substituted arylcarbamates[a]



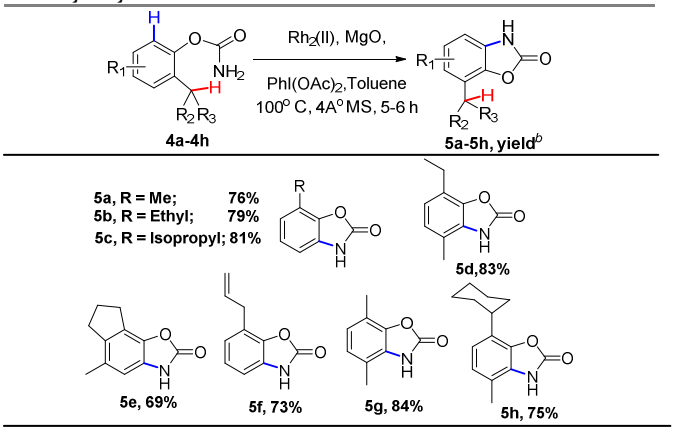




[a]Reactions were conducted in a Schlenk tube under argon at 0.31 mmol scale in Toluene with $Rh_2(OAc)_4$(5 mol%), $PhI(OAc)_2$(1.2 eq), MgO (2.2 eq), 4 A° MS(200wt%).[b]Isolated yields.[c] Observed from crude NMR. [d]Regioselectivity determined from NMR spectroscopy.

Moderate regioselectivity (1:2) was observed on *m*-methyl substituted carbamate with major C—H amination product obtained from sterically more congested C-H site in good yields (entry **3h**). Substrates with *m*-ethyl and 2-naphthol derived carbamate furnished the regioisomeric products **3n** and **3k** respectively in 1:1 ratio. Surprisingly, only single isomer (from sterically less encumbered C-H site) was isolated from the reaction of *m*-bromo substituted carbamate (entry **3j**).Excellent regioselectivity was demonstrated on o-phenyl substituted substrate, providing the cyclized product **3p**, in very good yield. Subsequently, in order to probe the chemoselective potential of this transformation we subjected various o-alkyl substituted carbamates (**Table 3**) with 1°, 2°, and 3° C—H bonds under cyclization condition. Remarkably, only the o-aryl C—H amidation products were obtained in excellent yields(entries **5a-5c**).This is in contrast to a previous report where no aryl C—H amination product was observed from o-alkyl substituted sulfamates with $Rh_2(II)$ catalyst under similar reaction conditions, instead exclusive formation of C($sp^3$)—H aminated product was observed.[22a] When o-allyl substituted carbamate, which potentially has three sites for N insertion, was subjected to oxidative

reaction condition, it selectively gave only five membered benzoxazolone product (entry **5f**) with very good yield.[22b] The product **5f** having tethered double bond thus provides additional site for further synthetic manipulations. Furthermore, differently substituted di-alkyl carbamates gave good to excellent yields of their respective benzoxazolones (entries **5d, 5e, 5g** and **5h**).Thus,these examples represents one of the rare systems with preferential *aromatic C($sp^2$)—H bond nitrenoid insertion over more labile o-substitutent C($sp^3$)—H bond.* Note worthily, during the course of substrate investigation we observed that carbamate with electron donating substituents reacted more efficiently and provided higher yields than electron withdrawing substituted carbamates. Also, substrates with bulkier alkyl groups (*t*-butyl) provided higher yields than substrates with smaller alkyl groups.

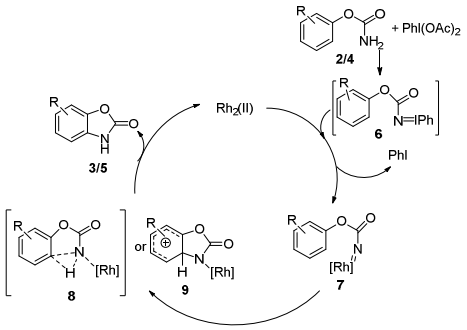
**Table 3.** Scope of $Rh_2$(II) catalyzed C($sp^2$)—H amination on o-alkyl arylcarbamates[a]



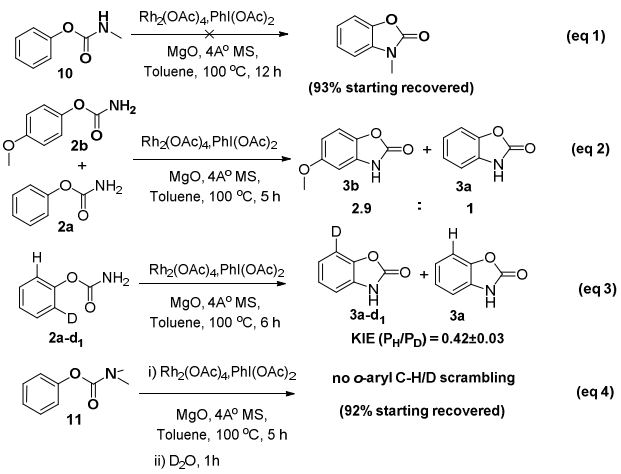

[a]Reactions were conducted in Schlenk tube under argon at 0.31 mmol scale in Toluene with $Rh_2(OAc)_4$(5 mol%), $PhI(OAc)_2$(1.2 eq), MgO (2.2 eq), 4A° MS(200 wt%). [b]Isolated yields.

It is pertinent to mention here, that the high regio- and chemoselectivity of these $Rh_2$(II) promoted C—H bond amidations on substrates capable of forming benzoxazinone as well as aziridine derivatives (entries **5a-5c** and **5f**) provides possible evidence against free nitrene intermediates. This is in contrast to the indiscriminate free nitrene insertion of formylnitrenes observed upon photolytic or thermolytic decomposition of substituted phenylazidoformates.[23,24a] In addition, no product formation from N-methyl O-phenyl carbamate, **10** under similar reaction conditions, further indicated involvement of potential Rh-nitrenoid intermediate for aromatic C—H bond amidation, as **10** is incapable of generating nitrene intermediate.[4e,25a] Based on our observation in this report and previous literature reports,[5,20b,25b,c] we believe that initial co-ordination of $Rh_2$(II) with *in situ* generated iminoiodinane, **6** would lead to Rh–nitrenoid intermediate species **7**,which could potentially undergo *o*-C—H bond nitrenoid insertion either *via* concerted asynchronous pathway through **8**,or by stepwise[24b] electrophilic substitution pathway through arenium ion intermediate **9** (Scheme 1).

To gain some mechanistic insight of this $Rh_2$(II) catalyzed intramolecular aryl C-H bond amination, a one pot competition reaction between an electron rich system (**2b**) and electron neutral system (**2a**) provided their respective benzoxazolone products in the ratio of 2.9:1(eq 2, Scheme 2; see ESI for details), indicating beneficial effect of electron donating groups on the current intramolecular C—H bond amination system and putative involvement of aromatic electrophilic mechanism. Further, to probe the electronic nature of the nitrene intermediate, a Hammett analysis for the relative rate of aromatic C—H nitrenoid insertion on different *p*-substituted (**2b, 2c, 2e, 2f**) versus unsubstituted carbamate (**2a**) was performed under standard reaction condition. Obtention of near linear correlation of corresponding log(kAr/kPh) against Hammet constant($\sigma^p$) with slight negative slope value ($\rho$ = -0.20)(see ESI for details), indicated involvement of positive transition state and thus favoring aromatic electrophilic substitution mechanism (see Figure S3, ESI).[25b]




**Scheme 1**. Putative mechanism for aryl C($sp^2$)—H amidation




**Scheme 2.** Mechanistic investigation experiments

In order to assess whether cleavage of C—H bond is a rate limiting step in this proposed model, we subjected the deuterium probe **(2a-$d_1$)** under standard cyclization condition. Observation of inverse secondary kinetic isotope effect ($P_H/P_D$ = 0.42±0.03) (eq 3, Scheme 2, see ESI for details), indicated that this intramolecular C—H amidation is occuring *via* stepwise mechanism and rules out involvement of C—H bond cleavage in rate determining step. Furthermore, no *o*-H/D scrambling was observed upon $D_2O$ quench of reaction with N,N-dimethyl O-phenyl carbamate **11**, (eq 2, Scheme 2, see ESI for details), which clearly rules out inner sphere activation mechanism, and suggests that the excellent chemoselectivity observed on *o*-alkyl substituted substrates toward exclusive aromatic C-H amination could possibly be the result of more conformationally favourable 5-membered benzoxazolone ring. Finally, we demonstrated the potential of this direct C($sp^2$) —H amidation on a natural scaffold, estrone derived

carbamate **2q**, which gave the regioisomeic products **3q** in 1.4:1 ratio with 68% yield. Thus setting up the platform for utilization of this methodology for late stage C($sp^2$) —H bond amidation(entry 3q, Table 2).

In conclusion, we have developed an highly efficient, two step strategy to access diverse privileged benzoxazolone scaffolds with practical yields *via* C-H bond activation using inexpensive $Rh_2$(II) catalyst.This study also provides first time report of excellent chemoselective aryl C($sp^2$)—H bond amidation via nitrenoid insertion over more readily available and accessible *o*-C($sp^3$)—H bonds using *non-directed approach*. Further, the current system leverages the chemical tool box of $Rh_2$(II) catalyzed transformations with the potential to be utilized in other analogous systems to achieve different biologically relevant scaffolds besides utilization of this strategy to access benzoxazole embedded natural products, which is currently underway in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

## ACKNOWLEDGMENT

This work was supported by the DST INSPIRE fund GAP0548 and CSIR fund CSC0301. RS thanks DST (Department of Science and Technology) for INSPIRE faculty award. We are grateful to Dr Ajay Kumar Srivastava for helpful discussions. Dr UVR Vijay Saradhi, CSIR-IICT is highly acknowledged for providing HRMS data. Director, IICT is gratefully acknowledged for his constant motivation and providing necessary infrastructure.

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(21)(a)$^1$H NMR of the crude reaction mixture did not show any aminated toluene; b) Formation of dimer was observed when the reaction was run at 130 $^{o}$C for 18 h with excess $PhI(OAc)_2$(1.5 eq);see ESI for details.

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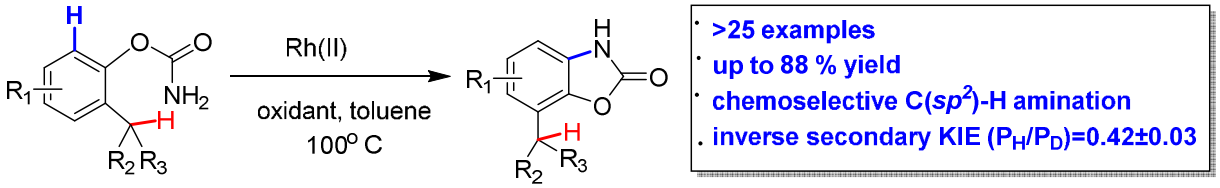


KEYWORDS: C-H amination, O-phenyl carbamates, benzoxazolone, chemoselective, nitrene insertion