EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Radical-Induced, Palladium-Catalyzed C-H activation: A New Approach to Functionalize 4H-Benzo[d][1,3]oxazin-4-one Derivatives with Toluenes, Aldehydes and Benzyl Alcohols

Authors: Prashant Kumar, Mohit Gupta, Vijay Bahadur, Virinder S. Parmar, and Brajendra Kumar Singh

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800263

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800263

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

FULL PAPER

Radical-Induced, Palladium-Catalyzed C-H activation: A New Approach to Functionalize 4*H*-Benzo[*d*][1,3]oxazin-4-one Derivatives with Toluenes, Aldehydes and Benzyl Alcohols

Prashant Kumar[a], Mohit Gupta[a], Vijay Bahadur[a,b], Virinder S. Parmar[a,c] and Brajendra K. Singh[a,*]

[a]Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

[b]SRM University Delhi-NCR, Sonepat, Haryana 131 029, India

[c]Department of Chemistry, Central University of Haryana, Mahendragarh, Haryana 123 031, India

[*]Corresponding-Author. Tel: +91-11-27666646, Ext: 136, Fax: +91-11-27667206, E-mail address: singhbk@chemistry.du.ac.in (Dr. Brajendra Kumar Singh); URL: http://people.du.ac.in/~singhbk/

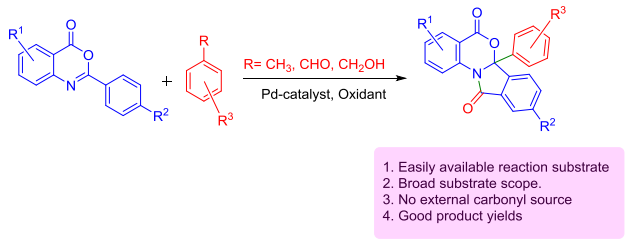
Abstract: In the present work, toluenes, aldehydes and benzyl alcohols have been exploited in the radical-induced direct functionalization of heterocyclic molecules, in particular 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives *via* the palladium-catalyzed C-H activation strategy. Greater stability, low toxicity and the easy access to toluenes, aldehydes and benzyl alcohols have made them suitable candidates for this transformation. The reaction in general proceeded smoothly and afforded the desired products in moderate to good yields with high functional group compatibility. Mechanistic investigations have illustrated the radical pathway and have highlighted the importance of both catalyst and oxidant.

Introduction

In the past decade, remarkable progress has been made on the transition metal catalyzed direct oxidative carbon-carbon and carbon-heteroatom bond formation reactions *via* the C-H activation strategies because of the accompanied atom-economy, fewer reaction steps and utilization of readily available cheap starting materials.[1] Amongst several substrates explored till date, toluenes, aldehydes and benzyl alcohols have gained considerable attention as elegant reaction partners in the direct functionalization of important organic molecules owing to their exceptional advantages such as high stability, low toxicity and easy availability.[2-4] Moreover, these substrates do not require any pre-functionalization when used as reaction coupling partners and thus have changed the landscape of organic synthesis.[5] Recently, they have been extensively employed in directing group assisted catalytic and selective acylation of numerous aromatic systems as they provide a sustainable strategy for atom-economical C-C bond formation protocols.[6] Although, tremendous progress has been made in the application of toluenes, aldehydes and benzyl alcohols in metal catalyzed C-H functionalization processes, however there are still several areas which need to be explored further towards their application in C-C and C-N bond formation reactions for the synthesis of structurally diverse interesting scaffolds.

4*H*-Benzo[*d*][1,3]oxazin-4-one represents ubiquitous and highly significant scaffold, widely spread in natural products, drugs and pharmacologically active compounds with interesting biological properties.[7] Interestingly, 4*H*-benzo[*d*][1,3]oxazin-4-one is a key pharmacophore of the drug (under phase-III clinical trial) cetilistat, being developed as an anti-obesity agent.[8] Some derivatives of 4*H*-benzo[*d*][1,3]oxazin-4-one have been found to display various biological activities such as antimicrobial,[9] inhibitors of HSV-1 protease,[10] inhibitors of human Chymase,[11] serine protease inhibitors,[12] potent inhibitors of DAPK (death-associated protein kinase),[13] inhibitors of leucocyte clarase, etc.[14] Although, the synthesis of 4*H*-benzo[*d*][1,3]oxazin-4-one and its derivatives[15] have received significant attention, however simple and general route for the direct functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-one is still unknown. In this regard, very recently, Majhi *et al.* have reported the first regioselective acylation of 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives with α-oxo carboxylic acids using Pd-catalyzed cyclic imine-N-directed C-H activation approach.[16] Although this group has developed a new strategy for the direct functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-ones, however the use of additional co-catalyst $AgNO_3$, low atom-economy and limited substrate scope is bottleneck to this protocol. Our group is currently involved in developing novel approaches

for sustainable chemical approaches towards the synthesis of bioactive molecules.[17] In continuation of this endeavor, we report herein (**Scheme 1**) a general, expedient and simple method for the direct C-H functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives using abundantly and easily available substrates such as toluenes, aldehydes and benzyl alcohols as reaction partners, Pd-catalyst and a radical-inducer oxidant to synthesize 6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones,[18] analogues of biologically significant molecules.[19]



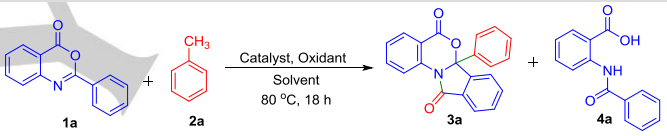
Scheme 1. Synthesis of 6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones by radical-induced catalytic direct C-H functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-ones.

Although, few reports are available towards the synthesis of similar types of compounds, however these protocols suffer from several serious limitations such as pre-functionalization of starting materials, poor substrate scope, use of ligand and toxic reagents like CO gas, etc.[20] To the best of our knowledge, this is the first report exploiting toluenes, aldehydes and benzyl alcohols for the direct functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives involving a simple and general radical promoted, Pd-catalyzed protocol.

Results and Discussion

We began our investigation by testing the reaction between commercially available or easily prepared 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**, 0.5 mmol) [16] and toluene (**2a**) (2 mL, 15 mmol) using 3 mol% of $Pd(OAc)_2$ and 70% aqueous t*ert*-butyl hydrogen peroxide solution (TBHP) (6 mmol) as a radical initiator oxidant in 1,2-dichloroethane (DCE, 0.5 mL). These reactants were stirred at 80 °C for 18 h. The experimental result revealed that the product **3a** could be obtained in 32% yield along with a highly valuable hydrolyzed product[21] **4a** (28%) (**Table 1**, **entry 1**). The formation of the product **3a** encouraged us to make the reaction conditions better to furnish improved product yield by firstly screening several solvents. Disappointingly, none of the screened solvents gave improved yield (**Table 1**, **entries 2-8**). However, when toluene was used as solvent, slight improvement in the product yield was observed (**Table 1**, **entry 9**). Subsequently, various oxidants were screened (**Table 1**, **entries 10-14**) and we observed that TBHP is the most effective oxidant (**Table 1**, **entry 9**). Moreover, amongst other screened oxidants such as TBPB, $K_2S_2O_8$, DTBP and H_2O_2, etc., only TBPB provided the desired product **3a** in 7% yield along with 45% hydrolyzd product (**Table 1**, **entries 11**). Rest of the oxidants yielded only the hydrolyzed product along with the starting materials and failed to deliver the desired product **3a** (**Table 1**, **entries 12-14**). Further, various salts of metals like Pd, Cu, Ni and Co were screened to influence this transformation (**Table 1**, **entries 15-20**). None of them, except palladium salts yielded the desired product. Amongst the screened Pd-salts, $Pd(OAc)_2$ showed the best result and yielded the desired product **3a** in 40% yield (**Table 1**, **entry 9**). It is interesting to mention here that in all the screened systems, formation of the hydrolyzed product **4a** was observed (**Table 1**).

Table 1. Optimization of reaction conditions.[a]



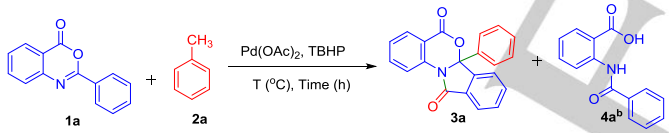
Entry	Catalyst (mol%)	Oxidant (mmol)	Solvent	Yield (%)[b] **3a**	Yield[b] (%) **4a**
1	$Pd(OAc)_2$	TBHP	DCE	32	28
2	$Pd(OAc)_2$	TBHP	DCM	16	35
3	$Pd(OAc)_2$	TBHP	CH_3CN	-[c]	15
4	$Pd(OAc)_2$	TBHP	1,4-Dioxane	30	25
5	$Pd(OAc)_2$	TBHP	DMSO	-[d]	10
6	$Pd(OAc)_2$	TBHP	DMF	-[d]	12
7	$Pd(OAc)_2$	TBHP	H_2O	-[c]	10
8	$Pd(OAc)_2$	TBHP	EtOH	-[c]	10
9	$Pd(OAc)_2$	TBHP	-[e]	40	20
10	$Pd(OAc)_2$	TBHP[f]	-[e]	33	30
11	$Pd(OAc)_2$	TBPB	-[e]	7	45
12	$Pd(OAc)_2$	DTBP	-[e]	-[d]	30
13	$Pd(OAc)_2$	H_2O_2	-[e]	-[d]	35
14	$Pd(OAc)_2$	$K_2S_2O_8$	-[e]	-[d]	20
15	$PdCl_2$	TBHP	-[e]	27	15
16	$Pd(TFA)_2$	TBHP	-[e]	31	20
17	CuO	TBHP	-[e]	-[d]	35
18	$Cu(OAc)_2.H_2O$	TBHP	-[e]	-[d]	40
19	$CoCl_2$	TBHP	-[e]	-[d]	45
20	$NiCl_2$	TBHP	-[e]	-[d]	45

[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) (0.5 mmol), toluene (**2a**) (2 mL, 15 mmol), catalyst (3 mol%), oxidant (6 mmol)

in the indicated solvent (0.5 mL) was stirred at 80 °C for 18 h; [b]isolated yields; [c]product was obtained in traces; [d]desired product **3a** formation was not observed, only the starting materials and hydrolyzed product **4a** were obtained after 24 h; [e]toluene (2 mL, 15 mmol) was used as solvent; [f]TBHP in decane.

We also evaluated the effect of catalyst concentration to improve the yield of compound **3a** and observed that the product yield significantly increased from 40% to 62% on increasing the concentration of $Pd(OAc)_2$ from 3 mol% to 5 mol% (**Table 2**, **entry 1**). However, further increase in the catalyst concentration had an adverse effect on the reaction (**Table 2**, **entry 2**). Then the role of the reaction temperature was explored. On increasing the reaction temperature, the product yield increased and at 120 °C, the targeted product **3a** was obtained in 75% yield along with 7% of hydrolyzed produt **4a** (**Table 2**, **entries 3** and **4**), however any further increase in temperature retarded the product yield (**Table 2**, **entries 5** and **6**). Further, the effect of reaction time, concentration of TBHP and toluene was examined. Any change, increase or decrease either in reaction time or in TBHP concentration had an adverse effect on the outcome of the reactions (**Table 2**, **entries 7-11**). Moreover, decreasing the amount of toluene decreased the product yield (**Table 2**, **entry 12**).

Table 2. Effect of temperature, time and concentration of $Pd(OAc)_2$ and TBHP on the reaction yield.[a]

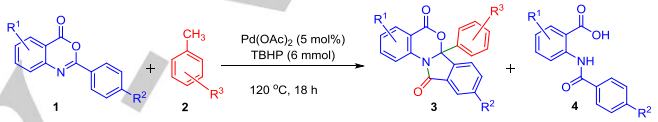


Entry	$Pd(OAc)_2$ (mol %)	TBHP (mmol)	Time (h)	Temp. (°C)	Yield (%)[c] **3a**
1	5	6	18	80	62
2	7	6	18	80	53
3	5	6	18	95	66
4	**5**	**6**	**18**	**120**	**75[d]**
5	5	6	18	130	71
6	5	6	18	150	61
7	5	6	15	120	68
8	5	6	24	120	63
9	5	4	18	120	65
10	5	5	18	120	67
11	5	8	18	120	72
12	5	6	18	120	69[e]

[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) (0.5 mmol), toluene (**2a**) (2 mL, 15 mmol), $Pd(OAc)_2$ as indicated, 70% aqueous TBHP as indicated was stirred at given temperature and time; [b]formation of **4a** was obsereved in all the screened systems; isolation was not attempted; [c]isolated yields; [d]**4a** was isolated in 7% yield; [e]1.5 mL (11 mmol) of toluene was used.

With the aim to generalize and expand the substrate scope of this newly developed protocol, different toluene derivatives were treated with 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**Table 3**). All the toluene derivatives yielded the targeted products in good yields and unsubstituted toluene provided the highest product yield (75%) among all the screened toluene derivatives (**Table 3**, **entry 1**). This protocol nicely tolerated both kinds of substituents, i.e. electron withdrawing as well as electron donating functional groups on the benzene ring (**Table 3**, **entries 2-6**).

Table 3. Substrate scope of toluenes and 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones.[a,b]



Entry	R^1	R^2	R^3	Product	Yield (%)[c] **3/4**
1	H	H	H	**3a/4a**	75/7
2	H	H	2-Cl	**3b/4a**	52/16
3	H	H	4-Cl	**3c/4a**	54/14
4	H	H	2-F	**3d/4a**	56/13
5	H	H	4-F	**3e/4a**	65/14
6	H	H	4-OCH_3	**3f/4a**	52/18
7	5-Br	H	H	**3g/4b**	60/19
8	4-Br	H	H	**3h/4c**	52/18
9	H	4-Cl	H	**3i/4d**	38/22
10	H	4-CH_3	H	**13j/4e**	64/19

[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones (**1**) (0.5 mmol), toluenes (**2**) (2 mL, 15 mmol), $Pd(OAc)_2$ (5 mol%); 70% aqueous TBHP (6 mmol) was stirred at 120 °C temperature for 18h; [b]isolated yields.

It was observed that the *para*-halo substituted toluenes provide better product yield as compared to *ortho*-halo substituted toluenes and that could be because of steric hindrance caused by the substituent at the *ortho*-position (**Table 3**, **entries 2-5**). It was further noticed that the fluoro derivatives were more effective as compared to chloro ones and that could be because of higher electronegativity of fluorine. The substrate scope of variously substituted 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with toluene was also investigated and we found that 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one derivatives have good compatibility under these reaction conditions. The substituents such as Br, Cl and Me on the aromatic ring furnished the target compounds in

moderate to good yields (**Table 3**, **entries 7-10**). The structures of the compounds **3a** and **3f** were also confirmed by the single crystal X-ray analysis (**Figure 1**).

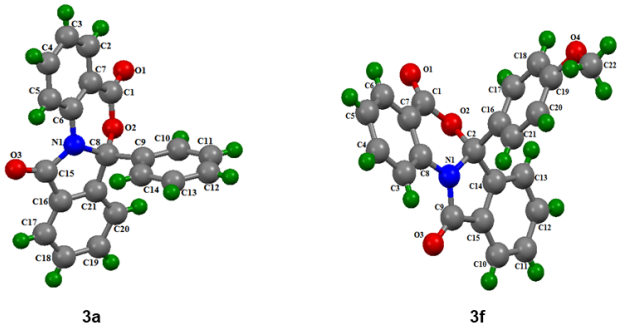
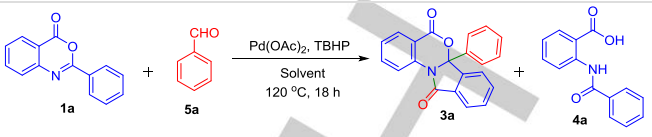


Figure 1. Single crystal X-ray structures of compounds **3a** and **3f**.

Encouraged by these results, we further explored the compatibility of this protocol with various aldehydes. In this regard, primarily, we optimized the reaction conditions by varying only solvents and concentration of TBHP to achieve better product yields (**Table 4**). To our delight, best reaction condition was obtained when 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) (0.5 mmol) was reacted with benzaldehyde (**5a)** (0.55 mmol) using $Pd(OAc)_2$ (5 mol%), TBHP (5 mmol) in 1,4-dioxane (2 mL) at 120 ^oC for 18 h which yielded the target compound in 79% yield (**Table 4**, **entry 7**). With this gratifying result, numerous benzaldehydes substituted by electron donating groups as well as electron withdrawing groups were reacted with 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) and all these fruitfully provided the target compounds in good yields, regardless of the position of the substituents on the phenyl ring of benzaldehydes (**Table 5**). The poor yield in case of chlorine and bromine substituted benzaldehydes in comparison to the fluorine substituted benzaldehydes could be attributed to higher electronegativity of fluorine (**Table 5**, **entries 3**, **5**, **11-13**, **15** and **16**). Not merely monosubstituted benzaldehydes, but disubstituted benzaldehydes also were well tolerated under these conditions (**Table 5**, **entries 2**, **3** and **13-17**). When aliphatic aldehydes such as cyclohexanecarbaldehyde and isovaleraldehyde were allowed to react with 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**), the desired products were obtained in 48% and 33% yield, respectively (**Table 5**, **entries 18** and **19**), which indicated that the reaction condition is not limited to aromatic aldehydes.

Table 4. Optimization of reaction conditions for aldehydes.[a]

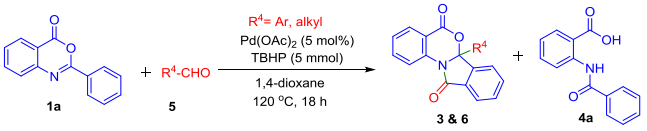


Entry	Solvent[b]	Oxidant (mmol)	Yield (%)[b] **3a**	Yield (%)[b] **4a**
1	DCE	6	55	17
2	DCE	5	62	14
3	DCE	4	64	14
4	DCE	2	59	18
5	DCE	4	45[d]	20
6	1,4-dioxane	4	55	20
7	1,4-dioxane	5	79	3

[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) (0.5 mmol), benzaldehyde (**5a**) (0.55 mmol), catalyst (5 mol%), 70% aqueous TBHP in the indicated solvent was stirred at 120 ^oC temperature for 18 h; [b]2mL of solvents was used; [c]isolated yields; [d]under nitrogen atmosphere.

Further, the substrate scope for the functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones was investigated with benzyl alcohols. Delightfully, when 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) was treated with benzyl alcohol (**7a**) under the same reaction conditions as were used for aldehydes, the target product was obtained in 57% yield (**Scheme 2**, **compound 3a**). Encouraged by this result, we next explored the structural diversity of benzyl alcohols in this protocol. Various benzyl alcohols yielded the desired products in significant yields (**Scheme 2**). Notably, substituted 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one also led to the product formation in 49% yield when reacted with benzyl alcohol (**7a**) (**Scheme 2**, **compound 3j**).

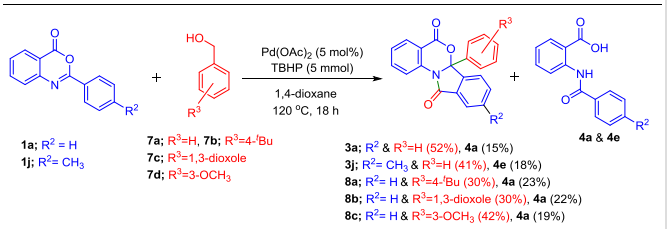
Table 5. Substrate scope of aldehydes.[a,b]



Entry	R^4	Product	Yield (%)[c]	Yield (%)[c] **4a**
1	Ph	**3a**	79	3
2	2-Cl-Ph	**3b**	58	15
3	4-Cl-Ph	**3c**	60	15
4	2-F-Ph	**3d**	58	17
5	4-F-Ph	**3e**	66	12
6	4-OCH_3-Ph 4	**3f**	69	10
7	4-CH_3-Ph	**6a**	62	17
8	3,4-di-CH_3-Ph	**6b**	53	19
9	3,4-di-OCH_3-Ph	**6c**	57	17
10	3-Cl-Ph	**6d**	37	26

11	2-Br-Ph	**6e**	22	31
12	4-Br-Ph	**6f**	30	27
13	2,4-di-F-Ph	**6g**	70	13
14	2,6-di-F-Ph	**6h**	58	17
15	4-Cl-2-F-Ph	**6i**	53	19
16	4-Br-2-F-Ph	**6j**	48	14
17	3,4-di-Cl-Ph	**6k**	21	38
18	cyclohexyl	**6l**	48	17
19	isobutyl	**6m**	33	21

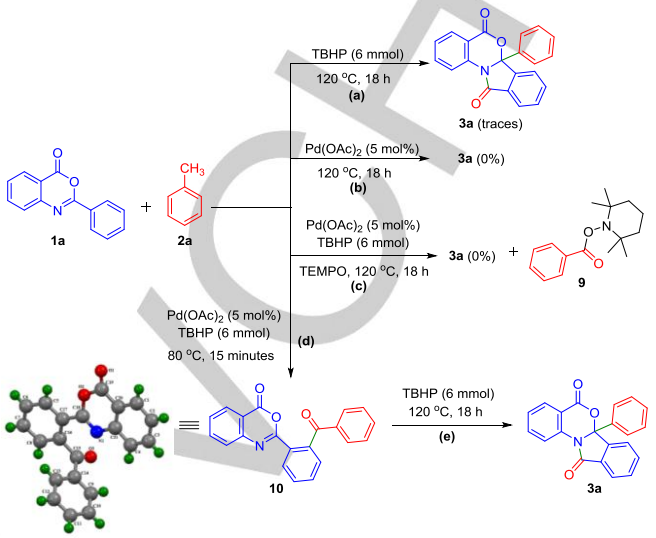
[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones (**1a**) (0.5 mmol), aldehydes (**5**) (0.55 mmol), $Pd(OAc)_2$ (5 mol%), 70% aqueous TBHP solution (5 mmol) was stirred at 120 °C temperature for 18 h; [b]isolated yields.



Scheme 2. Substrate scope of benzyl alcohols.[a,b]

[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones (**1**) (0.5 mmol), benzyl alcohols (**7**) (0.55 mmol), $Pd(OAc)_2$ (5 mol%), 70% aqueous TBHP solution (5 mmol) was stirred at 120 °C temperature for 18 h; [b]isolated yields are given in parentheses.

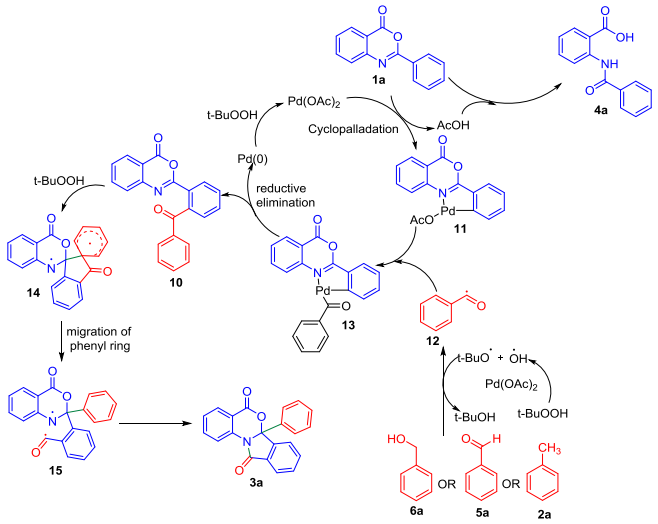
In order to predict and postulate the plausible reaction pathway, some control experiments were carried out using 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) and toluene (**2a**) (**Scheme 3**). Initially, we carried out a blank experiment where the reaction contents were stirred in the absence of the catalyst (**Scheme 3**, **a**) and the desired product was detected in trace amounts on TLC. Subsequently, when the reaction was carried out in the absence of the oxidant TBHP (**Scheme 3**, **b**), the reactants remained unchanged. Moreover, addition of radical scavenger TEMPO to the reaction mixture under the optimized reaction conditions yielded the TEMPO-trapped intermediate **9** (**Scheme 3**, **c**). Under this condition no desired product formation was observed, which clearly demonstrates that the reaction is progressing through a free radical pathway. Furthermore, when the reaction between 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) and toluene (**2a**) was carried out at 80 °C, compound **10**[16] was obtained after 15 minutes (**Scheme 3**, **d**) which got converted into the product **3a** when reaction was continued further. Moreover, to ascertain that the reaction product formation involves the migration of phenyl ring and proceeds through the formation of compound **10**, the compound **10** was further treated with TBHP at 120 °C for 18 h and the reaction yielded the product **3a** (**Scheme 3**, **e**), that supported our hypothesis.



Scheme 3. Control experiments.

On the basis of above control experiments and literature reports,[16] a plausible mechanism has been proposed as shown in **Scheme 4**. We believe that initially, the complex **11** is formed by the *ortho*-palladation of compound **1a** with $Pd(OAc)_2$ with the liberation of AcOH, which resulted in the hydrolysis of compound **1a** into **4a**. At the same time, acyl radical **12** is generated from the other reactant viz toluene or aldehyde or benzyl alcohol in the presence of TBHP. This step is followed by the reaction of complex **11** and the acyl radical which leads to the formation of complex **13** containing either palladium (III) or palladium (IV). Thereafter, complex **13** undergoes reductive elimination process to give compound **10**. It is presumed that compound **10** may then undergo aryl ring migration[22] in the presence of oxidant TBHP *via* the intermediate **14** and forms a bi-radical compound **15** which then undergoes C-N bond formation to give the final compound **3a**.

10.1002/ejoc.201800263



Scheme 4. Plausible mechanism.

Conclusions

To summarize, we have developed a "Pd-catalyzed, free radical promoted efficient and general protocol" for the direct functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives by C-H activation process. In this strategy, non-toxic and readily available toluenes, aldehydes and benzyl alcohols were used as reaction partners that proficiently resulted in the formation of the final products in good yields. Mechanistic studies revealed that both $Pd(OAc)_2$ and TBHP were very important for this transformation and reaction proceeded through radical pathway. This protocol provides a new direction to the applicability of toluenes, aldehydes and benzyl alcohols in the functionalization of heterocyclic molecules by sustainable C-H activation strategies.

Experimental Section

General procedure for the synthesis of 3
An oven dried 10 mL reaction tube with a small stirring bar was charged with a mixture of 4*H*-benzo[*d*][1,3]oxazin-4-one (1) (0.5 mmol), toluene (2) (2 mL, 15 mmol), $Pd(OAc)_2$ (5 mol%) and 70% aqueous TBHP solution (6 mmol). The tube was capped tightly and heated at 120 °C for 18 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled upto ambient temperature and passed through a short plug of celite and washed with EtOAc (3 x 10 mL). The combined organic filtrate was further diluted with 30 mL EtOAc and washed with 20 mL saturated $NaHCO_3$ solution 2 times, followed by distilled water (2 x 15 mL). The organic layer was separated, dried over solid anhydrous Na_2SO_4 and concentrated on a rotary evaporator to obtain the crude product which was further purified on a silica gel column using hexane/ethyl acetate (8:2) as eluent to give the pure targeted product 3.

General procedure for the synthesis of 6
An oven dried 10 mL reaction tube with a small stirring bar was charged with a mixture of 4*H*-benzo[*d*][1,3]oxazin-4-one (1) (0.5 mmol), aldehyde (4) (0.55 mmol), $Pd(OAc)_2$ (5 mol%), 70% aqueous TBHP solution (5 mmol) and 1,4-dioxane (2 mL). The tube was capped tightly and heated at 120 °C for 18 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled upto ambient temperature and passed through a short plug of celite, washed with EtOAc (3 x 10 mL). The combined organic filtrate was further diluted with 30 mL EtOAc and washed with 20 mL saturated $NaHCO_3$ solution two times, followed by distilled water (2 x 15 mL). The organic layer was separated, dried over solid anhydrous Na_2SO_4 and concentrated on a rotary evaporator to obtain the crude product which was further purified on a silica gel column using hexane/ethyl acetate (8:2) as eluent to give the pure targeted product 6.

General procedure for the synthesis of 8
An oven dried 10 mL reaction tube with a small stirring bar was charged with a mixture of 4*H*-benzo[*d*][1,3]oxazin-4-one (1) (0.5 mmol), benzyl alcohol (6) (0.55 mmol), $Pd(OAc)_2$ (5 mol%), 70% aqueous TBHP solution (5 mmol) and 1,4-dioxane (2 mL). The tube was capped tightly and heated at 120 °C for 18 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled upto ambient temperature and passed through a short plug of celite, washed with EtOAc (3 x 10 mL). The combined organic filtrate was further diluted with 30 mL EtOAc and washed with 20 mL saturated $NaHCO_3$ solution two times, followed by distilled water (2 x 15 mL). The organic layer was separated, dried over solid anhydrous Na_2SO_4 and concentrated on a rotary evaporator to obtain the crude product which was further (8:2) purified on a silica gel column using hexane/ethyl acetate as eluent to give the pure targeted product.

Acknowledgements

The authors acknowledge the financial assistance from the University of Delhi (India) under its strengthening R & D Doctoral Research Programme and the DST-DU Purse Grant Phase-II. P.K. is thankful to the University Grants Commission (UGC, New Delhi, India) for providing a Junior Research Fellowship.

Keywords Free radical, C-H activation, Direct functionalization, 6a-Phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones, Cetilistat

1. a) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900-2936; b) X.

Zhu, S. Chiba, *Chem. Soc. Rev.* **2016**, *45*, 4504-4523; c) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107-1295.

2. a) H. Aruri, U. Singh, S. Kumar, M, Kushwaha, A. P. Gupta, R. A. Vishwakarma, P. P. Singh, *Org. Lett.* **2016**, *18*, 3638-3641; b) C. Li, T. Jin, X. Zhang, C. Li, X. Jia, J. Li, *Org. Lett.* **2016**, *18*, 1916-1919; c) L. Yang, L. Han, B. Xu, L. Zhao, J. Zhou, H. Zhang, *Asian J. Org. Chem.* **2016**, *5*, 62-65; c) D. Huw ML, D. Morton, *J. Org. Chem.* **2016**, *81*, 343-350; d) C. Xiaopei, X. Cui, Y. Wu, *Org. Lett.* **2016**, *18*, 2411-2414; e) J. Gu, Z. Fang, Y. Yang, Z. Yang, L. Wan, X. Li, P. Wei, K. Guo*, RSC Adv.* **2016**, *6*, 89413-89416; f) R. Santhoshkumar, S. Mannathan, C. H. Cheng, *J. Am. Chem. Soc.* 2015, *137*, 16116-16120; g) A. J. Rawlings, L. J. Diorazio, M. Wills, *Org. Lett.* **2015**, *17*, 1086-1089.
3. a) X. Mi, C. Wang, M. Huang, Y. Wu, Y. Wu, *J. Org. Chem.* **2015**, *80*, 148-155; b) L. Hou, X. Chen, S. Li, S. Cai, Y. Zhao, M. Sun, X. J. Yang, *Org. Biomol. Chem.* **2015**, *13*, 4160-4164; c) T. Xiong, Q. Zhang, *Chem. Soc. Rev*. **2016**, *45*, 3069-3087; d) J. Zhao, P. Li, C. Xia, F. Li, *Chem. Commun.* **2014**, *50*, 4751-4754; e) J. M. Hoover, B. L. Ryland, S. S. Stahl, *J. Am. Chem. Soc*. **2013**, *135*, 2357-2367; f) J. Park, A. Kim, S. Sharma, M. Kim, E. Park, Y. Jeon, Y. Lee, J. H. Kwak, Y.H. Jung, I.S. Kim, *Org. Biomol. Chem.* **2013**, *11*, 2766-2771.
4. a) H. Hikawa, H. Suzuki, Y. Yokoyama, I. Azumaya, *Catalysts* **2013**, *3*, 486-500; b) J. Zhang, S.H. Hong, *Org. Lett.* **2012**, *14*, 4646-4649; c) Y. S. Bao, C. Y. Chen, Z. Z. Huang, *J. Org. Chem.* **2012**, *77*, 8344-8349; d) J. C. Leung, M. J. Krische, *Chem. Sci.* **2012**, *3*, 2202-2209; e) M. C. Willis, *Chem. Rev.* **2010**, *110,* 725-748; f) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem Rev*. **2010**, *110*, 624-655; g) M. A. Garralda, *Dalton Trans.* **2009**, *19*, 3635-3645; h) P. A. Slatford, M. K. Whittlesey, J. M. Williams, *Tetrahedron Lett.* **2006**, *47*, 6787-6789.
5. a) B. Suchand, G. Satyanarayana, *J. Org. Chem.* **2016**, *81*, 6409-6423; b) M. Lanzillotto, L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *ACS Sustainable Chem. Eng.* **2015**, *3*, 2882-2889; c) L. Wang, J. Cao, Q. Chen, M. He, *J. Org. Chem.* **2015**, *80*, 4743-4748; d) T. K. Achar, P. Mal, *J. Org. Chem.* **2015**, *80*, 666-672; e) X. H. Ouyang, R. J. Song, Y. Li, B. Liu, J. H. Li, *J. Org. Chem.* **2014**, *79*, 4582-4589; f) S. K. Santra, A. Banerjee, B. K. Patel, *Tetrahedron* **2014**, *70*, 2422-2430; g) S. K. Rout, S. Guin, A. Banerjee, N. Khatun, A. Gogoi, B. K. Patel, *Org. Lett.* **2013**, *15*, 4106-4109; h) L. Wang, D. L., Priebbenow, L. H. Zou, C. Bolm, *Adv. Synth. Catal.* **2013**, *355*, 1490-1494; i) C. W. Chan, Z. Zhou, W. Y. Yu, *Adv. Synth. Catal.* **2011**, *353*, 2999-3006.
6. a) M. Adib, R. Pashazadeh, S. Rajai-Daryasarei, R. Kabiri, S. J. A. Gohari, *Synlett* **2016**, *27*, 2241-2245; b) C. Premi, S. S. Patel, N. Jain, *Eur. J. Org. Chem.* **2016**, 3788-3795; c) F. Luo, J. Yang, Z. Li, H. Xiang, X. Zhou, *Eur. J. Org. Chem.* **2015**, 2463-2469; d) F. Xiao, S. Chen, H. Huang, G. J. Deng, *Eur. J. Org. Chem.* **2015**, 7919-7925; e) P. He, Q. Tian, C. Kuang, *Synthesis* **2015**, *47*, 1309-1316; f) Y. Zheng, W. B. Song, S. W. Zhang, L. J. Xuan, *Tetrahedron* **2015**, *71*, 1574-1580; g) H. Song, D. Chen, C. Pi, X. Cui, Y. Wu, *J. Org. Chem.* **2014**, *79*, 2955-2962; h) J. Zhao, P. Li, C. Xia, F. Li, *Chem. Commun.* **2014**, *50*, 4751-4754; i) Y. Wu, P.Y. Choy, F. Mao, F.Y. Kwong, *Chem. Commun.* **2013**, *49*, 689-691; j) J. Weng, Z. Yu, X. Liu, G. Zhang, *Tetrahedron Lett*. **2013**, *54*, 1205-1207; k) Z. Yin, P. Sun, *J. Org. Chem.* **2012**, *77*, 11339-11344; l) Y. Yuan, D. Chen, X. Wang, *Adv. Synth. Catal.* **2011**, *353*, 3373-3379; m) O. Basle, J. Bidange, Q. Shuai, C. J. Li, *Adv. Synth. Catal.* **2010**, *352*, 1145-1149.
7. a) P. M. Chandrika, T. Yakaiah, A. R. R. Rao, B. Narsaiah, N. C. Reddy, V. Sridhar, J. V. Rao, *Eur. J. Med. Chem.* **2008**, *43*, 846-852; b) A. M. F. Eissa, R. J. El-Sayed, *Heterocycl. Chem.* **2006**, *43*, 1161-1168; c) M. Pietsch, M. Gütschow, *J. Med. Chem.* **2005**, *48,* 8270-8288; d) J. C. Powers, J. L. Asgian, Ö. D. Ekici, K. E. James, *Chem. Rev.* **2002**, *102*, 4639-4750; e) U. Neumann, N. M. Schechter, M. Gütschow, *Bioorg. Med. Chem.* **2001**, *9*, 947-954; f) R. L. Stein, A. M. Strimpler, B. R. Viscarello, R. A. Wildonger, R. C. Mauger, D. A. Trainor, *Biochemistry* **1987**, *26*, 4126-4130; g) L. Hedstrom, A. R. Moorman, J. Dobbs, R. H. Abeles, *Biochemistry* **1984**, *23*, 1753-1759.
8. a) Y. Yamada, T. Kato, H. Ogino, S. Ashina, K. Kato, *Horm. Metab. Res.* **2008**, *40*, 539-543; b) R. Padwal, *Curr. Opin. Investig. Drugs* **2008**, *9*, 414-421; c) P. Kopelman, A. Bryson, R. Hickling, A. Rissanen, S. Rossner, S. Toubro, P. Valensi, *Int. J. Obes.* **2006**, *31*,

494-499; d) J. C. Halford, *Curr. Opin. Investig. Drugs* **2006**, *7*, 312-318.

9. A. M. F. Eissa, R. El-Sayed, *J. Heterocycl. Chem.* **2006**, *43*, 1161-1168.
10. R. L. Jarvest, M. J. Parratt, C.M. Debouck, J. G. Gorniak, L. J. Jennings, H. T. Serafinowska, J. E. Strickler, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2463-2466.
11. U. Neumann, N. M. Schechter, M. Gütschow, *Bioorg. Med. Chem.* **2001**, *9*, 947-954.
12. M. Gütschow, U. Neumann, Bioorg. Med. Chem. 1997, 5, 1935-1942.
13. M. Okamoto, K. Takayama, T. Shimizu, A. Muroya, T. Furuya, *Bioorg. Med. Chem.* **2010**, *18*, 2728-2734.
14. A. Krantz, R. W. Spencer, T. F. Tam, T. J. Liak, L. J. Copp, E. M. Thomas, S. P. Rafferty, *J. Med. Chem.* **1990**, *33*, 464-479.
15. a) L. Wang, Y. B. Xie, N. Y. Huang, J. Y. Yan, W. M. Hu, M. G. Liu, M. W. Ding, *ACS Catal.* **2016**, *6*, 4010-4016; b) J. M. Wang, X. Jiang, Y. Zhang, Y. M. Zhu, J. K. Shen, *Tetrahedron Lett.* **2015**, *56*, 2349-2354; c) M. Yamashita, A. Iida, *Tetrahedron* **2014**, *70*, 5746-5751; d) M. Yamashita, A. Iida, *Tetrahedron Lett.* **2014**, *55*, 2991-2993; e) W. Li, X. F. Wu, *J. Org. Chem.* **2014**, *79*, 10410-10416; f) Q. Liu, P. Chen, G. Liu, *ACS Catal.* **2013**, *3*, 178-181; g) X. F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 12599-12602; h) L. Xue, L. Shi, Y. Han, C. Xia, H.V. Huynh, F. Li, *Dalton Trans.* **2011**, *40*, 7632-7638; i) X. F. Wu, J. Schranck, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, *17*, 12246-12249; j) R. Giri, J. K. Lam, J. Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 686-693; k) J. Salvadori, E. Balducci, S. Zaza, E. Petricci, M. Taddei, *J. Org. Chem.* **2010**, *75*, 1841-1847; l) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 1830-1833.
16. B. Majhi, D. Kundu, T. Ghosh, B. C. Ranu, *Adv. Synth. Catal.* **2016**, *358*, 283-295.
17. a) P. Kumar, A. K. Singh, V. Bahadur, C. Len, N. G. J. Richards, V. S. Parmar, E. V. Van der Eycken, B. K. Singh, *ACS Sustainable Chem. Eng.* **2016**, *4*, 2206-2210; b) U. K. Sharma, N. Sharma, Y. Kumar, B. K. Singh, E. V. Van der Eycken, *Chem. Eur. J.* **2016**, *22*, 481-485; c) P. Kumar, A. Matta, S. Singh, J. Van der Eycken, C. Len, V. S. Parmar, E. V. Van der Eycken, B. K. Singh, *Synth. Commun.* **2017**, *47*, 756-763; d) M. Gupta, P. Kumar, V. Bahadur, K. Kumar, V. S. Parmar, B. K. Singh, *Eur. J. Org. Chem.* DOI: 10.1002/ejoc.201701764.
18. a) P. Aeberli, W. J. Houlihan, *J. Org. Chem.* **1968**, *33*, 2402-2407; b) E. Abramowitz, M. Lachen, *J. Chem. Soc.* **1965**, 2165-2173.
19. a) K. S. Kumar, P. M. Kumar, K. A. Kumar, M. Sreenivasulu, A. A. Jafar, D. Rambabu, G. R. Krishna, C. M. Reddy, R. Kapavarapu, K. Shivakumar, K. K. Priya, *Chem. Commun.* **2011**, *47*, 5010-5012; b) Y. Ishihara, Y. Kiyota, *Chem. Pharm. Bull.* **1990**, *38*, 3024-3030; c) W. Hoelzl, B. Rotzinger, US Patent WO2013139799 A1 **2013**.
20. a) X. Wang, J. Gallardo-Donaire, R. Martin, *Angew. Chem. Int. Ed.* **2014**, *53*, 11084-11087; b) K. Natte, J. Chen, H. Li, H. Neumann, M. Beller, X. F. Wu, *Chem. Eur. J.* **2014**, *20*, 14184-14188; c) E. V. Gromachevskaya, A. V. Fin'ko, A. V. Butin, K. S. Pushkareva, V. D. Strelkov, L. I. Isakova, G. D. Krapivin, *Chem. Heterocyc. Compd.* **2013**,*49*, 1331-1344; d) J. Khalafy, R. H. Prager, *Aust. J. Chem.* **1998**, *51*, 925-930.
21. a) K. Bharathimohan, T. Ponpandian, A. A. Jafar, *Eur. J. Org. Chem.* **2017**, 2806-2813; b) Y. Wu, C. Jiang, D. Wu, Q. Gu, Z. Y. Luo, H. B. Luo, *Chem. Commun.* **2016**, *52*, 1286-1289; c) J. S. Pap, A. Matuz, G. Baráth, B. Kripli, M. Giorgi, G. Speier, J. Kaizer, *J. Inorg. Biochem.* **2012**, *108*, 15-21; d) S. Hinsberger, K. Hüsecken, M. Groh, M. Negri, J. Haupenthal, R. W. Hartmann, *J. Med. Chem.* **2013**, *56*, 8332-8338; e) B. U. Emenike, A. T. Liu, E. P. Naveo, J. D. Roberts, *J. Org. Chem.* **2013**, *78*, 11765-11771.
22. a) Z. M. Chen, X. M. Zhang, Y. Q. Tu, *Chem. Soc. Rev.* **2015**, *44*, 5220-5245; b) R. J. Song, Y. Q. Tu, D. Y. Zhu, F. M. Zhang, S. H. Wanga, *Chem. Commun.* **2015**, *51*, 749-752; c) J. Zhao, H. Fang, R. Song, J. Zhou, J. Han, Y. Pan, *Chem. Commun.* **2015**, *51*, 599-602.
23. CCDC 1528977 and CCDC 1527628 contains the supplementary crystallographic data for the compounds **3a** and **3f**, respectively for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

10.1002/ejoc.201800263

WILEY-VCH

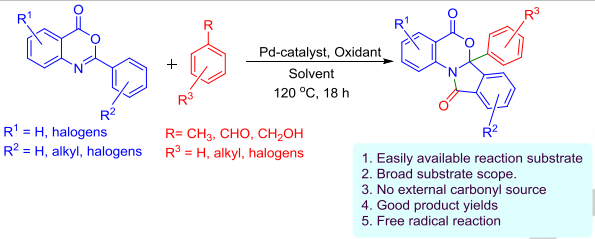
FULL PAPER

10.1002/ejoc.201800263

WILEY-VCH

FULL PAPER

Toluenes, aldehydes and benzyl alcohols have been exploited in radical-induced direct functionalization of 4*H*-benzo[*d*][1,3]oxazin-4-one derivatives *via* the palladium-catalyzed C-H activation strategy. Mechanistic investigations have illustrated the radical pathway and have highlighted the importance of both catalyst and oxidant.



*Prashant Kumar, Mohit Gupta, Vijay Bahadur, Virinder S. Parmar and Brajendra K. Singh**

Page No. – Page No.
Radical-Induced, Palladium-Catalyzed C-H activation: A New Approach to Functionalize 4*H*-Benzo[*d*][1,3]oxazin-4-one Derivatives with Toluenes, Aldehydes and Benzyl Alcohols