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An Easy Access to Oxime ethers by Pd-Catalyzed C–O Cross-Coupling of Activated Aryl bromides with Ketoximes and Chalcone oximes

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Summary of main observation and conclusion An efficient Pd-catalyzed method for C–O cross-coupling of ketoximes and chalcone oximes with activated aryl bromides and bromo-chalcones has been developed. All oxime ethers were obtained in good to excellent yields by [(π-allyl)PdCl]$_2$/*t*BuXPhos (**L7**) catalyst system. TrixiePhos (**L11**) was also found to be effective for the oxime coupling. This method offers an easy and smooth coupling of chalcone oximes with activated aryl bromides and bromo-chalcones which has not been previously explored .

Background and Originality Content

Oxime ethers are one of the most important structural motifs in organic chemistry which continue to beguile the chemists' interest thanks to their pharmaceutical and agricultural applications.[1] Examples concerning the biological importance of oxime ethers (**Figure 1**) are as potent inhibitors of transthyretin amyloid fibril formation,[1a] antibiotic (Cefmenoxime,[1b] Aztreonam,[1c] Roxithromycin),[1d] anti-inflammatory (Ridogrel),[1e] antifungal (Oxiconazole),[1f] neuroleptic activity,[1g] immunosuppressive agents,[1h] antihistamine (**1a**),[1i] therapeutic agent for insomnia (Eplivanserin) (**1b**),[1j,k] melanin-concentrating hormone1 receptor antagonists (**1c**),[1l] antiplasmodial property,[1m] monamine oxidase and Acethylcholinesterase inhibitors (**1d**),[1n] insecticidal,[1o] fungicidal,[1p,q] herbicidal,[1r] etc. Moreover, oxime ethers are served as important and versatile intermediates in the synthesis of various structural motifs.[2] The O-aryl oxime ethers have been paid much interest due to their accessibility to myriad of medicinally and synthetically important organic compounds[2] such as benzoxazole,[3a-c] dihydrobenzofuran,[3d,e] benzofurans,[3e-h,m] phenols,[3i] quinolines,[3j] 3-Aminobenzisoxazoles,[3k] pyrroles,[3l] etc.

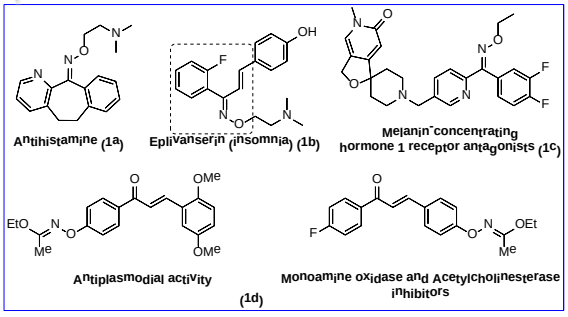
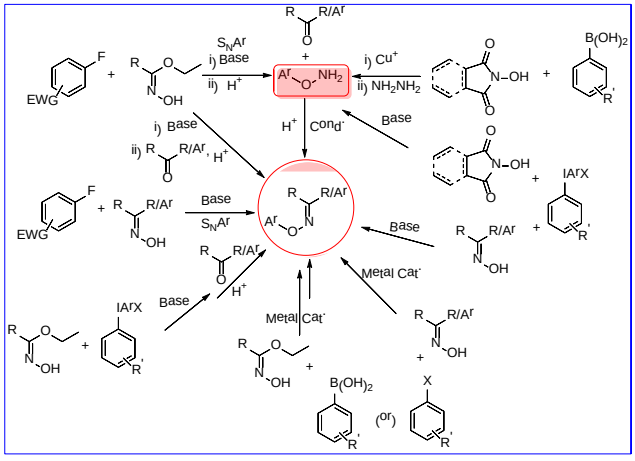


Figure 1 Examples of pharmaceutical molecules containing oxime ethers structural motif

Moreover, *O*-aryl oxime ethers could also be used as a ligand in Pd-catalyzed Suzuki-Miyaura coupling reaction to synthesize biaryls.[4] Conventionally, the synthesis of *O*-aryl oxime ethers were achieved by i) condensation of *O*-aryloxyamines with carbonyl compounds,[1a,3e,f,5] and ii) *O*-arylation of oximes with activated nitro- or fluoroarene derivatives in the presence of a strong base *via* S_NAr type process.[1a,3e,5a,6]

The *O*-aryloxyamines could be obtained from an amine exchange reaction of 2,4-dinitrophenoxyamine with phenols[3f,7] and *O*-arylation of ethyl acetohyroxamate,[1a,5d,8] or *N*-protected hydroxylamine[9] by S_NAr type process, and subsequent hydrolysis with acid (**Scheme 1**).



Scheme 1 Previous synthetic routes to oxime ethers

Other methods describing the synthesis of alkoxy and aryloxyamines are the oxyaziridines as aminating agent for a wide range of alcohols as nucleophile.[10]

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In the recent past, several other improved methods for the synthesis of *O*-aryloxyamines developed are i) copper-catalyzed coupling of phenylboronic acids with *N*-hydroxyphthalimide,[11] ii) base promoted *O*-arylation of *N*-hydroxyphthalimide and *N*-hydroxysuccinimide with diaryliodonium salts[12] and subsequent cleavage with hydrazine, hydroxylamine or ammonia, and iii) *O*-arylation of ethyl acetohydroxamate or oximes either with aryl coupling partner under Pd-catalyzed C–O coupling methodology[1m,3m] or with diaryl iodonium salts under basic condition (**Scheme 1**).[3f] However, the synthesis of *O*-aryl oxime ethers by direct coupling of aryl halides with ketoxime was not well explored and is highly inviting and only one method available was reported by Maitra et al. .[13a] This method described the copper-catalyzed coupling of aryl iodides with oximes in moderate to good yields but the functional group tolerance of aryl iodides, and aryl bromides has not been fully explored and also required to carry out at reflux temperature of toluene. After the pioneering work of Maitra et al., several other groups reported the methods for the direct coupling of oximes with phenyl boronic acids, under different conditions using copper catalyst,[13b-f] and diaryliodonium salts under basic conditions (**Scheme 1**).[3f,g,14] Therefore, the synthesis of *O*-aryl oxime ethers reported so far, despite their generality, requires multistep synthesis that includes the synthesis of starting materials such as arylboronic acids or diaryliodonium salts, which are usually obtained from aryl halides and commercially these starting materials are relatively expensive when compared with corresponding aryl halides.

Although general and efficient Pd-catalyzed methods for the direct coupling of aryl halides with ethyl acetohydroximate were reported,[1m,3m] no Cu or Pd-catalyzed direct coupling of aryl bromides with ketoximes is available to date. Moreover, the reaction of chalcone oximes with i) arylboronic acids, under copper catalyzed conditions,[15a,b] and ii) diaryliodonium salts under basic conditions led to *N*-arylation products predominantly over *O*-arylation products (Scheme 2). [15c]

Scheme 2 Reactions of chalcone oximes with arylboronic acids and diaryliodonium salts

In the latter method, D. L. Mo et al. observed a mixture of *O*- (55%) and *N*-arylation (34%) of chalcone oxime and decided to switch the selectivity from *O*- to *N*-arylation process.[15c] Therefore, the *O*-arylation of chalcone oxime is not fully explored at all and no methods are available for this coupling to date.

Herein, in the light of the above, we report an efficient Pd-catalyzed method for *O*-arylation of ketoximes and chalcone oximes with aryl bromides and bromo-chalcones.[15d]

Results and Discussion

Finding practicable supporting phosphine ligands for Pd-catalyzed *O*-arylation of acetophenone oxime with 4-bromoacetophenone was starting point of our investigation. The commercially available Buchwald and Beller type ligands shown in Figure 2 were employed for this *O*-arylation process.

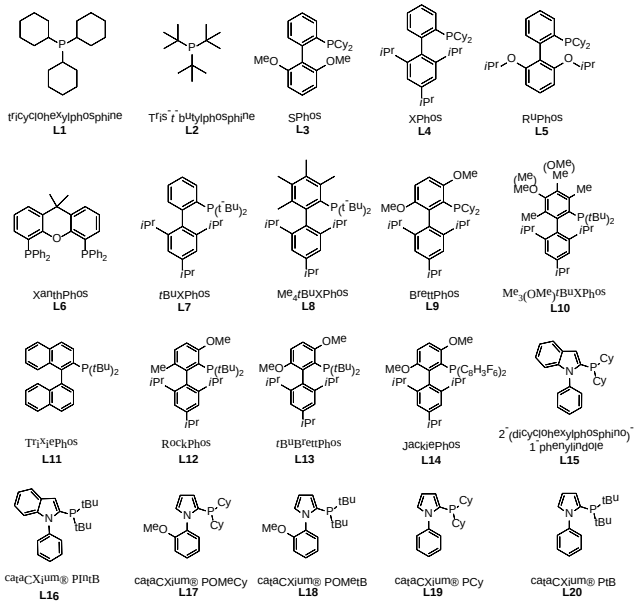


Figure 2 Structure of ligands used for Pd-catalyzed *O*-arylation of acetophenoneoxime.

The ligand screening reaction was carried out under conditions, $[(\pi\text{-allyl})PdCl]_2$ (1.0 mol %), ligands, **L1–L20** (2.5 mol %), in toluene (2.0 mL), at 60 °C and is summarized in table 1. The only ligand *t*BuXPhos (**L7**) gave the *O*-arylation product **1** in 72% yields with complete conversion in short reaction time (Entry 7). The ligand TrixiePhos (**L11**) gave the desired product in poor yield (Entry 11, 53%) with 65% conversion even after 17 h. The ligands cataCXium®PIntB (**L16**), and cataCXium®PtB (**L20**), produced promising results in our previous report for the coupling of bromo-chalcones with ethyl acetohydroxamate,[1m] were unsuccessful in the present coupling reaction. It is important to note that other promising ligands such as BrettPhos (**L9**),[16a,b] RockPhos (**L12**),[16f] *t*BuBrettPhos (**L13**)[16g] in the C–O cross-coupling reactions were also unsuccessful to couple 4-bromoacetophenone with acetophenones oxime. This due to the fact that the property of the ligands and their complexes directs different mechanistic reductive elimination pathway from nucleophile to nucleophile. Some ligands do not facilitate the reductive-elimination step and hence no reaction.[16a,h]

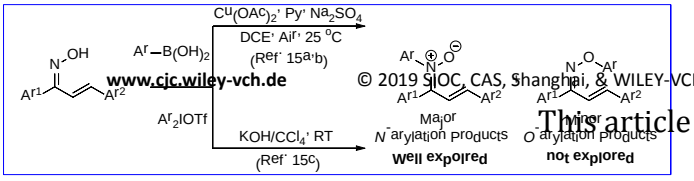
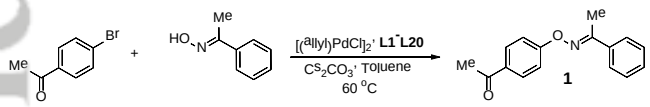


Table1. Ligand Evaluation[a]

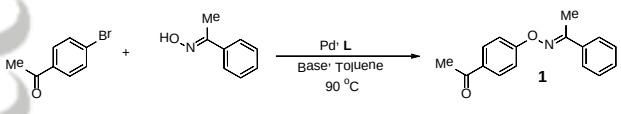


Entry	Ligand	Reaction Time (h)	Conv. (%)[b]	Yield (%)[c]	Entry	Ligand	Reaction Time (h)	Conv. (%)[b]	Yield (%)[c]
1	**L1**	17	ND	NR	11	**L11**	17	65	53
2	**L2**	17	ND	NR	12	**L12**	17	66	12
3	**L3**	17	ND	NR	13	**L13**	17	ND	NR
4	**L4**	17	ND	NR	14	**L14**	17	ND	NR
5	**L5**	17	ND	NR	15	**L15**	17	ND	NR
6	**L6**	17	ND	NR	16	**L16**	17	60	25
7	**L7**	3	100	**72**	17	**L17**	17	ND	NR
8	**L8**	17	ND	NR	18	**L18**	17	64	26
9	**L9**	17	ND	NR	19	**L19**	17	ND	NR
10	**L10**	17	ND	NR	20	**L20**	17	59	14

[a]Reaction Conditions: 4′-Bromoacetophenone (0.5 mmol, 1.0 eq.), acetophenoneoxime (0.55 mmol, 1.1 eq.), Cs_2CO_3 (0.75 mmol, 1.5 eq.), [(π-allyl)PdCl]$_2$ (1.0 mol %), Ligand, **L1**–**L20** (2.5 mol %), toluene (2.0 mL), 60 °C, Ar atm.. [b]Based on starting material recovered. [c]Isolated yield. ND = Not Determined. NR = No Reaction.

With this practicable ligand **L7**, we further optimized the reaction conditions such as temperature, Pd source, base, and solvent (Table 2). Initially, the efficiency of the ligand, **L7** was checked at a bit higher temperature, 90 °C. Surprisingly, the ligands, **L7**, afforded the desired product **1** in excellent yield, 96% (Table 2; Entry 1). With this interesting result, we further engaged in carrying out the coupling reaction using other two ligands **L11**, and **L16** with moderate results (Table 1) to check the effect of temperature. To our surprise, the ligand TrixiePhos (**L11**) was also successful towards the coupling with a significant improvement in the yield of the product **1**, 83% (Table 2; Entry 2), whereas the ligand **L16** did not afford a significant improvement in the yield of the product **1** (Table 2; Entry 3). The reduction of catalyst [(π-allyl)PdCl]$_2$ loading from 1.0 to 0.5 mol % with **L7** (Entry 4) was unsuccessful.

Table 2 Optimization of reaction conditions[a]

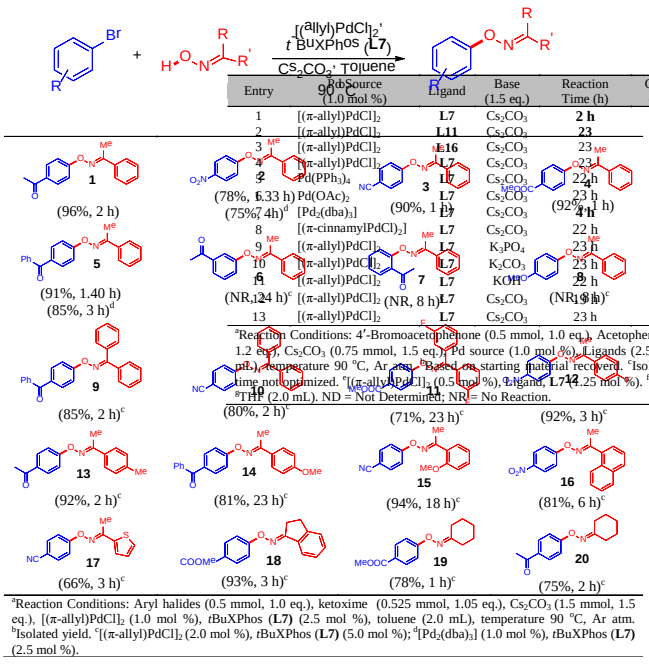


Entry	Pd Source (1.0 mol %)	Ligand	Base (1.5 eq.)	Reaction Time (h)	Conv. (%)[b]	Yield (%)[c]
1	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	**2 h**	**100**	**96**
2	[(π-allyl)PdCl]$_2$	**L11**	Cs_2CO_3	**23**	**100**	**83**[d]
3	[(π-allyl)PdCl]$_2$	**L16**	Cs_2CO_3	23	66	41
4	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	23	62	26[e]
5	$Pd(PPh_3)_4$	**L7**	Cs_2CO_3	22 h	ND	NR
6	$Pd(OAc)_2$	**L7**	Cs_2CO_3	23 h	ND	NR
7	$[Pd_2(dba)_3]$	**L7**	Cs_2CO_3	**4 h**	**100**	**92**
8	[(π-cinnamylPdCl)$_2$]	**L7**	Cs_2CO_3	22 h	ND	NR
9	[(π-allyl)PdCl]$_2$	**L7**	K_3PO_4	23 h	84	42
10	[(π-allyl)PdCl]$_2$	**L7**	K_2CO_3	23 h	71	47
11	[(π-allyl)PdCl]$_2$	**L7**	KOH	22 h	ND	NR
12	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	19 h	73	56[f]
13	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	23 h	ND	NR[g]

[a]Reaction Conditions: 4′-Bromoacetophenone (0.5 mmol, 1.0 eq.), Acetophenoneoxime (0.6 mmol, 1.2 eq.), Cs_2CO_3 (0.75 mmol, 1.5 eq.), Pd source (1.0 mol %), Ligands (2.5 mol %), toluene (2.0 mL), temperature 90 °C, Ar atm. [b]Based on starting material recovered. [c]Isolated yields. [d]Reaction time not optimized. [e][(π-allyl)PdCl]$_2$ (0.5 mol %), Ligand, **L7** (1.25 mol %). [f]1,4-Dioxane (2.0 mL); [g]THF (2.0 mL). ND = Not Determined; NR = No Reaction.

Other Pd catalysts with the ligand **L7** were also checked towards the coupling (Entries 5-8), showed that the only catalyst $[Pd_2(dba)_3]$ as effective as [(π-allyl)PdCl]$_2$ catalyst in the coupling reaction and afforded the desired product in excellent yield 92% (Entry 7). Further feasibility studies with various bases (Entries 9-11), and solvents (Entries 12, and 13) were also unsuccessful. As a result, the ligand (**L11**) and the catalyst $[Pd_2(dba)_3]$ were also found to be effective towards the *O*-arylation of acetophenone oxime.

With those optimized reaction conditions in hand, we were pleased to examine the generality of the coupling of aryl bromides with structurally diversified ketoximes (Table 3). First, we continued *O*-arylation of acetophenone oxime with different electronic nature of aryl bormides. Aryl bromides with electron-withdrawing group at 4-position gave the desired products **1**-**5** in good to excellent yields under optimized conditions with 1 mol % Pd catalyst. However, the catalyst system was failed to give the coupled products, **6** – **8** by coupling of acetophenone oxime with aryl bromides, such as 2′- and 3′-bromoacetophenones, and 4-bromoanisole even in higher catalyst loading and at 90 °C, which reveals that the catalyst system allows the C–O reductive elimination step via electronic pathway.[16a-e] We then continued the *O*-arylation of various ketoximes with activated aryl bromides. The C–O coupling of 4-bromobenzophenone with benzophenone oxime under optimized conditions was incomplete (40% conv.) with 1 mol % Pd catalyst while the same was successful at 2.0 mol % catalyst loading reveals that the higher catalyst loading is required for other ketoximes. All other structurally diversified ketoximes were then



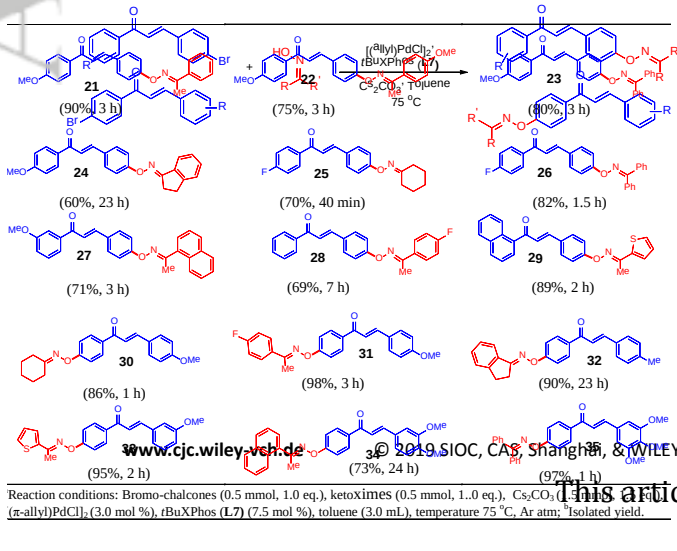
Entry	Pd Source (1.0 mol %)	Ligand	Base (1.5 eq.)	Reaction Time (h)	Conv. (%)[b]	Yield (%)[c]
1	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	**2 h**	**100**	**96**
2	[(π-allyl)PdCl]$_2$	**L11**	Cs_2CO_3	**23**	**100**	**83**[d]
3	[(π-allyl)PdCl]$_2$	**L16**	Cs_2CO_3	23	66	41
4	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	23	62	26[e]
5	$Pd(PPh_3)_4$	**L7**	Cs_2CO_3	22 h	ND	NR
6	$Pd(OAc)_2$	**L7**	Cs_2CO_3	23 h	ND	NR
7	$[Pd_2(dba)_3]$	**L7**	Cs_2CO_3	**4 h**	**100**	**92**
8	[(π-cinnamylPdCl)$_2$]	**L7**	Cs_2CO_3	22 h	ND	NR
9	[(π-allyl)PdCl]$_2$	**L7**	K_3PO_4	23 h	84	42
10	[(π-allyl)PdCl]$_2$	**L7**	K_2CO_3	23 h	71	47
11	[(π-allyl)PdCl]$_2$	**L7**	KOH	22 h	ND	NR
12	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	19 h	73	56[f]
13	[(π-allyl)PdCl]$_2$	**L7**	Cs_2CO_3	23 h	ND	NR[g]

[a]Reaction Conditions: Aryl halides (0.5 mmol, 1.0 eq.), ketoxime (0.525 mmol, 1.05 eq.), Cs_2CO_3 (1.5 mmol, 1.5 eq.), [(π-allyl)PdCl]$_2$ (1.0 mol %), *t*BuXPhos (**L7**) (2.5 mol %), toluene (2.0 mL), temperature 90 °C, Ar atm. [b]Isolated yield. [c][(π-allyl)PdCl]$_2$ (2.0 mol %), *t*BuXPhos (**L7**) (5.0 mol %); [d]$[Pd_2(dba)_3]$ (1.0 mol %), *t*BuXPhos (**L7**) (2.5 mol %).

smoothly coupled with activated aryl bromides to afford the

desired products (**9**-**20**) in good to excellent yields. The catalyst system comprised of $[Pd_2(dba)_3]$/*t*BuXPhos (**L7**) was also checked for the coupling of 1-bromo-4-nitrobenzene and 4-bromobenzophenone with acetophenone oxime to afford the desired products **2** and **5** in 75% and 85% respectively.

Table 3 Pd-catalyzed *O*-arylation of ketoximes with aryl bromides.[a,b]



Reaction conditions: Bromo-chalcones (0.5 mmol, 1.0 eq.), ketoximes (0.5 mmol, 1..0 eq.), Cs_2CO_3 (1 mmol, 2 eq.), $(\pi\text{-allyl})PdCl]_2$ (3.0 mol %), *t*BuXPhos (**L7**) (7.5 mol %), toluene (3.0 mL), temperature 75 °C, Ar atm; [b]Isolated yield.

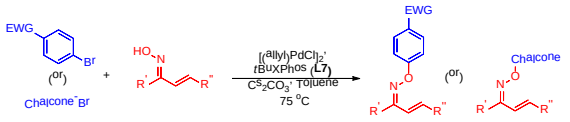
Owing to widespread applications of chalcones in medicinal,[1j,k,m,17] synthetic,[18] and material chemistries,[19] we extend the generality of the catalyst system to bromo-chalcones as coupling partner in the C–O cross-coupling reaction with ketoximes. These novel chalcone products may open the door to find several therapeutic properties (Scheme 1).[1m,n] The coupling of various ketoximes with different bromo-chalcones by $[(\pi\text{-allyl})PdCl]_2$/*t*BuXPhos (L7) system was required to carry out with 3.0 mol % Pd-catalyst loading and a bit lower temperature, 75 °C (Table 4). The chalcones bearing the bromine substitution on the 3-phenyl ring, (*E*)-3-(4-bromophenyl)-1-(substitutedphenyl)prop-2-en-1-ones, were coupled smoothly with different ketoximes to afford the desired products **21**-**29** in moderate to excellent yields (60-90%).

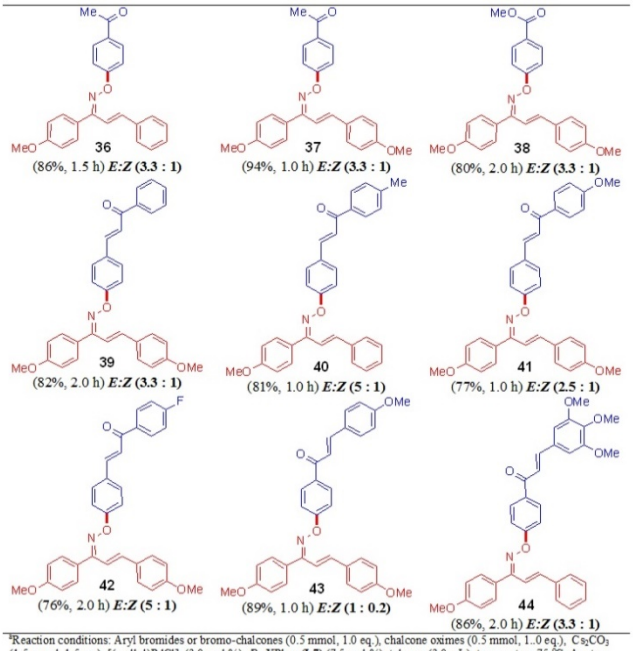
Table 4 Pd-catalyzed C–O cross-coupling of bromo-chalcones with ketoximes[a,b]

Similarly, the chalcones bearing the bromine substitution on the 1-phenyl ring, (*E*)-1-(4-bromophenyl)-3-(substitutedphenyl)prop-2-en-1-ones, were also coupled smoothly with different ketoximes to afford the desired coupled products 30-35 in good to excellent yields (73-98%). The yield range shows that (*E*)-1-(4-bromophenyl)-3-(substituted-phenyl)prop-2-en-1-ones, tolerate well under reaction conditions than (*E*)-3-(4-bromophenyl)-1-(substituted-phenyl)prop-2-en-1-ones. Interestingly, many reactions were complete in short reaction times.

Finally, we turned our attention, with eager, to explore the coupling of chalcone oximes with activated aryl bromides and bromo-chalcones as the chalcone oximes interestingly underwent *N*-arylation rather than *O*-arylation product under the reported conditions. [15] Moreover, no efficient methodology is available for *O*-arylation of chalcone oximes except an example reported by Mo and coworkers.[15c] Chalcone oximes were obtained by reaction of corresponding chalcones with hydroxylamine hydrochloride in the presence of pyridine as base in methanol to afford the product with a mixture of isomers *E*:*Z* (about 3:0.3). The coupling was carried out with 3.0 mol % catalyst loading at 75 °C (Table 5).

Table 5 Pd-catalyzed C–O cross-coupling of chalcones oximes[a,b]





[a]Reaction conditions: Aryl bromides or bromo-chalcones (0.5 mmol, 1.0 eq.), chalcone oximes (0.5 mmol, 1..0 eq.), Cs_2CO_3 (1.5 mmol, 1.5 eq.), [(π-allyl)PdCl]$_2$ (3.0 mol %), *t*Bu-XPhos (**L7**) (7.5 mol %), toluene (3.0 mL), temperature 75 °C, Ar atm; [b]Isolated yield – a mixture of E and Z isomers and the ratio given based on H-NMR signal integration.

First, (2*E*)-1-(4-methoxyphenyl)-3-phenyl prop-2-en-1-one oxime was coupled with 4-bromoacetophenone; interestingly, the reaction was complete in 1.5 h, and gave the expected *O*-coupled product 36 in 86% yield. The *O*-arylation product was confirmed

by ^{13}C NMR with characteristic =N–O–C(Ar) carbon signal which appeared about 160 p.m., while it would not appear in the *N*-arylation product.[15] The *O*-arylated product was also obtained as a mixture of *E*:*Z* isomers (3.3:1) determined from ^{1}H NMR spectrum. ^{13}C NMR signals of *E*- isomers were identified from signals of *Z*-isomers in the mixture by their intensity and DEPT-90, and only few ^{13}C NMR signals were seen for *Z*- isomers due to their low concentration in the mixture. Next, (2*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-one oxime was also smoothly coupled with with 4-bromoacetophenone and methyl 4-bromobenzoateto afford the desired *O*-coupled products **37** and **38** in 94 and 80% yields respectively with same *E*:*Z* isomers ratio. The catalyst system was also successfully used for the coupling of bromo-chalcones with chalcone oximes for the first time. The chalcone oxime, (2*E*)-1,3bis-(4-methoxyphenyl)prop-2-en-1-one oxime was coupled with (*E*)-3-(bromophenyl)-1-phenyl prop-2-en-1-one to afford the desired product **39** in good yield, 82%. The other chalcone oximes were also effectively coupled with various bromo-chalcones to afford the products **40**, **41**, and **42** in 81, 77, and 76% yields respectively. The (*E*)-1-(bromophenyl)-3-(substitutedphenyl)prop-2-en-1-ones were also coupled to afford the desired products **43**, and **44** in 89, and 86% respectively. All the reactions were complete in short reaction times. The aldoximes could also be effectively coupled with activated aryl bromides by this catalyst system has recently been published.[21]

Conclusions

In summary, a Pd-catalyzed methodology for C–O cross-coupling of ketoximes with activated aryl bromides and bromo-chalcones is described. Chalcone oximes, for the first time, coupled with activated aryl bromides and bromo-chalcones in good yields and short reaction times. Only two ligands *t*BuXPhos (**L7**) and TrixiePhos (**L11**) were found to be shown the coupling and the former was more effective than the latter in the coupling of ketoximes with a Bromo coupling partner. The mild reaction conditions and substrate tolerance make this method potentially helpful for medicinal chemists to access a wide array of novel chalcones for the biological screening process to find the novel therapeutic agents. Moreover, most of these chalcone oxime ethers have selective MAO-B inhibitory effect and two of these compounds have a dual-targeting inhibitory effect towards MAOs and AChE to treat neurodegenerative related diseases.[15d]

Experimental

General Procedure for the Palladium-Catalysed C–O Cross-Coupling Reaction of Aryl bromides and Bromochalcones with Ketoximes

An oven dried 10 mL two-neck round bottomed flask was equipped with a magnetic stir bar, a rubber septum, a condenser and an argon balloon on the top of the condenser with the aid of an adaptor. The flask was charged with Cs_2CO_3 and dried with hot air gun under vacuum. The R.B. flask was allowed to cool under argon atmosphere. Bromo coupling partner, ketoximes, Pd-source and ligands were added in quick succession. The flask was then evacuated and refilled with argon for three times. To this, 2.0 mL of anhydrous toluene was added via syringe and again the flask evacuated and refilled with argon for three times. The flask was placed in a pre-heated oil bath at a temperature 75 °C or 90 °C. The reaction mixture was stirred vigorously until completion of the reaction as indicated by TLC analysis. The reaction mixture was allowed to cool to room temperature and the crude product was purified by column chromatography on silica gel (60-120 mesh size) using ethyl acetate-hexane solvent mixture as eluent. The solvent removal under reduced pressure afforded the desired compounds as a solid.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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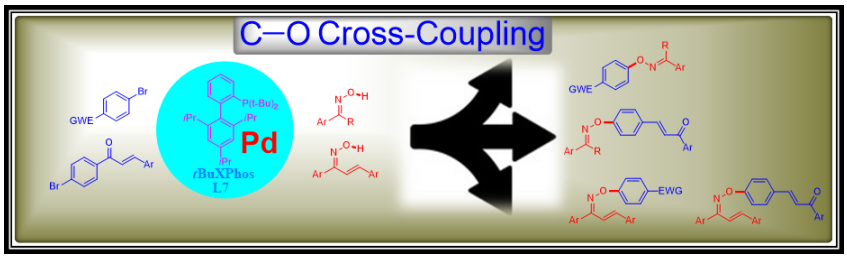
An Easy Access to Oxime ethers by Pd-Catalyzed C–O Cross-Coupling of Activated Aryl bromides with Ketoximes and Chalcone oximes

Max. Table height 6 cm



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