NJC

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c9nj05124d

Efficient solvent- and temperature-tuned access to aldoxime ethers and phenolic functions by Pd-catalyzed C–O cross-coupling of aldoximes with aryl bromides and bromo-chalcones†

Reeta,[ab] T. M. Rangarajan,*[c] Kumar Kaushik,[a] Rishi Pal Singh,[c] Manjula Singh[d] and Raj Pal Singh*[a]

Received 11th October 2019,
Accepted 15th December 2019

DOI: 10.1039/c9nj05124d

rsc.li/njc

A single method with a functionality switching option was developed for the first time for the Pd-catalyzed C–O cross-coupling of aryl bromides and bromo-chalcones with aldoximes. The ligand *t*BuXPhos (**L2**) was found to be an effective supporting ligand for the Pd-catalyzed coupling of aldoximes with bromo coupling partners. The functionality switching from oxime ethers to a phenolic or hydroxy group was driven by solvent or temperature. This method offers the products in good to excellent yields in short reaction times.

Introduction

Oxime ethers are not only the fundamental constituents of pharmaceutical, bioactive (Fig. 1) and agricultural chemicals,[1] as the potent inhibitors of transthyretin amyloid fibril formation,[1a] antibiotic (cefmenoxime),[1b] antifungal[1c] (oxiconazole), antihistamine (**1a**),[1d] therapeutic agent for insomnia (eplivanserin (**1b**)),[1e,f] melanin-concentrating hormone 1 receptor antagonist (**1c**),[1g] antiplasmodial,[1h] monoamine oxidase, and acetyl cholinesterase inhibitor (**1d**),[1i] insecticidal,[1j] fungicidal,[1k] herbicidal agents,[1l] *etc.*, but also important and versatile precursors in the synthesis of various structural motifs.[2]

O-Aryl oxime ethers have received special attention due to their accessibility to numerous medicinally and synthetically important organic compounds[2] such as benzoxazole,[3a–c] dihydrobenzofuran,[3d,e] benzofurans,[3e–i] phenols,[3j] quinolines,[3k] 3-aminobenzisoxazoles,[3l] and pyrroles.[3m] Conventionally, the synthesis of *O*-aryl oxime ethers is achieved *via* (i) the condensation of *O*-aryloxyamines with carbonyl compounds[1a,3e,f,4] and (ii) *O*-arylation of oximes with activated nitro- or fluoroarene derivatives in the presence of a strong base *via* an S_NAr-type process.[1a,3e,4a,5] The former can be achieved *via* the amine exchange reaction of 2,4-dinitrophenoxyamine with phenols[3f,6] and *O*-arylation of ethyl acetohyroxamate,[1a,4d,7] or *N*-protected hydroxylamine[8] with electron-deficient aryl systems, in the presence of a strong base *via* an S_NAr-type process, and subsequent hydrolysis with acid. Recently, several other improved methods have been developed for the synthesis of aryloxyamines.[1g,3f,g,m,n,9,10]

Unfortunately, the synthesis of *O*-aryl oxime ethers by direct coupling of aryl halides and oximes is not well explored;[11a] however, several other methods are available for the coupling of ketoximes with arylboronic acids by copper catalysts[11b–f] and diaryliodonium salts,[3f,g,12] which are obtained from aryl halides, but commercially, these starting materials are relatively more expensive than aryl halides.

Moreover, similarly to oximes,[2c,14] *O*-arylaldoxime ethers are also important starting materials for the synthesis of biologically active nitriles,[2a] benzoxazoles,[3b,c] and phenols.[3i] Although aldoxime ethers have received considerable interest, no efficient methods have been reported thus far for their synthesis. Aldoxime ethers synthesized *via* the copper-mediated direct coupling of aryl coupling partners with aldoximes suffer from harsh reaction conditions and poor yields.[11a,b,d,e] T. Punniyamurthy *et al.* reported the efficient copper triflate-mediated synthesis of benzoxazoles from aldoxime ethers, which were synthesized from the condensation of aryloxyamines and benzaldehydes. The synthesis of aryloxyamines is slightly cumbersome, and hence has limited substrate scope (Scheme 1).[3b] Therefore, the synthesis of benzoxazoles through this method is likely to be less striking.

Therefore, efficient methods for the synthesis of aldoxime ethers from aryl bromides and aldoximes are in demand and need to be urgently developed.

Additionally, the introduction of phenolic function(s) in organic compounds is one of the essential synthetic tasks in organic chemistry since phenols are important synthetic intermediates of a myriad of useful compounds and constituents of

[a] *Centre for Fire, Explosive and Environment Safety, DRDO, Delhi, India. E-mail: rajcfees@gmail.com*
[b] *Department of Chemistry, University of Delhi, Delhi, India*
[c] *Department of Chemistry, Sri Venkateswara College, University of Delhi, New Delhi, India. E-mail: rangarajan93150@gmail.com*
[d] *Department of Chemistry, Shivaji College, University of Delhi, New Delhi, India*

† Electronic supplementary information (ESI) available: Detailed procedures, characterization data, and spectra. See DOI: 10.1039/c9nj05124d

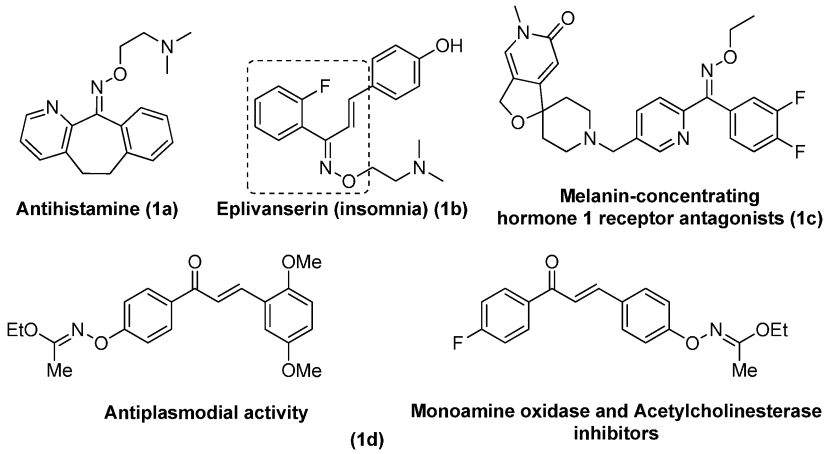
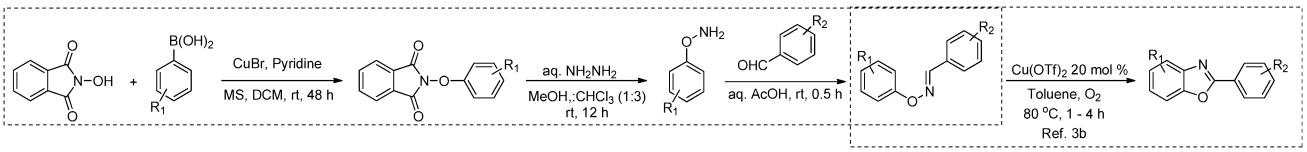


Fig. 1 Oxime ether-containing molecules with therapeutic properties.



Scheme 1 Synthesis of aldoxime ethers and subsequent cyclization.

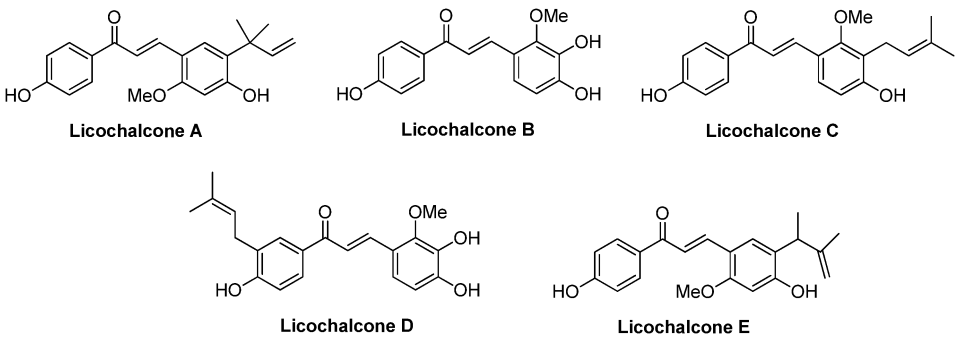


Fig. 2 Structure of natural chalcones containing hydroxyl groups.

over 200 approved drugs and 100 000 natural products.[3i] Chalcones are a group of natural products with widespread medicinal properties. Many natural and synthetic chalcones containing hydroxyl groups are biologically active[13] (Fig. 1 and 2). However, the synthesis of hydroxy chalcones through the classical Claisen–Schmidt condensation of benzaldehydes with acetophenones in the presence of aqueous alkaline bases is not effective due to the fact that the presence of hydroxyl substituents in the aromatic rings decreases the reactivity of the carbonyl compounds through delocalization of the negative charge on oxygen, which is generated by the action of a base. Therefore, the acid-catalyzed Aldol reaction is considered to be the preferred method of interest.[13a,b]

Recently, Fier and Maloney revealed aldoximes as hydroxide surrogates in the Pd- and Cu-catalyzed conversion of aryl bromides and aldoximes to phenols. The advantage of this method is the late stage hydroxylation of drug-like molecules.[3j] However, the Pd-catalyzed method requires expensive palladacycle catalysts and phosphine ligands, and the Cu-catalyzed method requires the multi-step synthesis of oxalamide ligands, which starts with the expensive starting material 3-methylisatoic anhydride ($55/1 g or $514/25 g)[15] and also a ligand that may not be commercially available.[3j]

Herein, we report the relatively inexpensive *t*BuXPhos ligand-supported Pd-catalyzed coupling of aldoximes with aryl bromides and bromo-chalcones as coupling partners under mild reaction conditions with solvent- and temperature-facilitated functionality switching from aldoxime ethers to phenolic functions.

Results and discussion

First, we examined different phosphine ligands (**L1–L12**) (Fig. 3) for the Pd-catalyzed coupling of 4′-bromoacetophenone **1**, with 4-methylbenzaldoxime **i**, under the conditions of [(π-allylPdCl)$_2$]

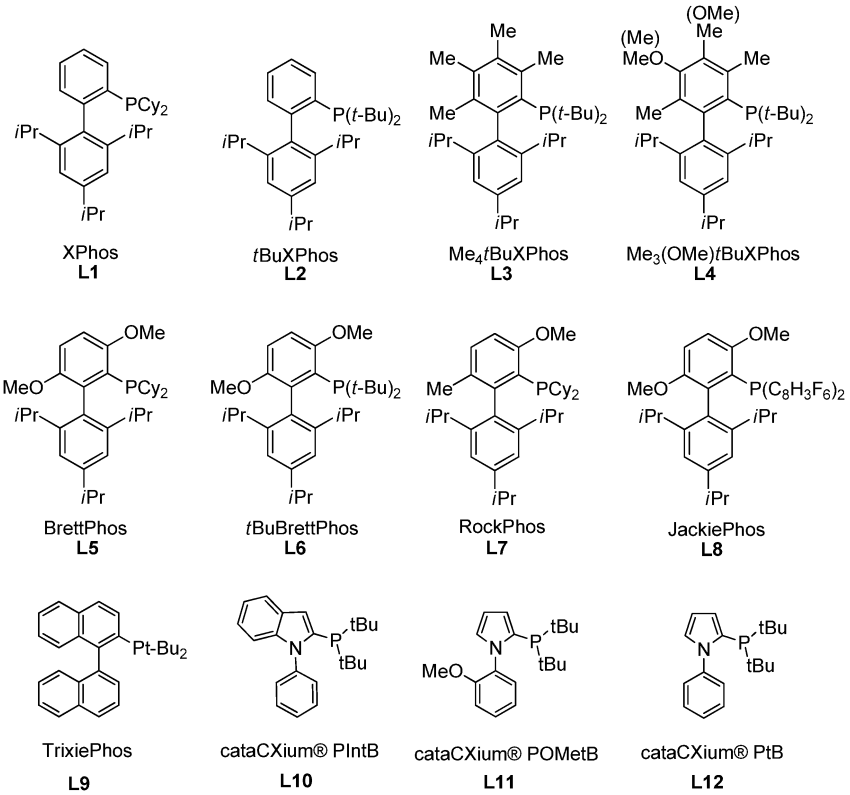


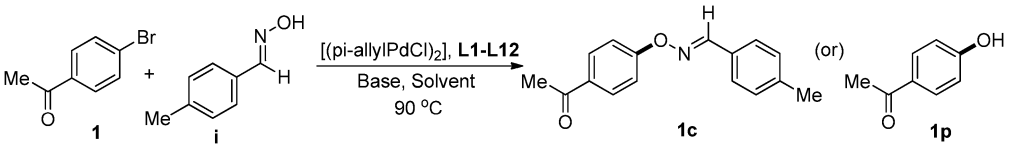
Fig. 3 Structure of the phosphine ligands used for screening.

(1.0 mol%), Cs_2CO_3 (1.5 eq.), in toluene at 90 °C (Table 1). Among the twelve ligands examined, only five ligands (**L2**, **L5–L7**, and **L9**) were found to be promising in the coupling reaction to afford the desired product **1c** in 83%, 75%, 83%, 78%, and 82% yield, respectively, with complete conversion (entries 1–12). Additionally, the ligand *t*BuXPhos (**L2**) facilitated the coupling in a shorter reaction time (1.5 h) compared to the others (entry 2).

Under the same conditions with **L2**, the base KOH was also found to be as effective as Cs_2CO_3 to give the desired product **1c** in the good yield of 81% (entry 13). Further, with a change in the reaction solvent from toluene (non-polar) to DMF (polar) under the conditions with **L2** at 90 °C, surprisingly, the reaction afforded the product phenol **1p** in 92% yield (entry 14),[3j] and the same at a lower temperature of 40 °C (entry 15) was unsuccessful and even no coupled product **1c** was formed, and therefore no phenol. With this interesting result, we further investigated the same phenolic product (**1p**) with ligands **L3–L7** in DMF solvent at 90 °C. Besides **L3** and **L4**, the other ligands **L5–L7** gave the desired product **1p** in good to excellent yields (entries 18–20, respectively). The effect of the base KOH was also checked for the formation of **1p** in DMF solvent, which was successful with a reduced yield of only 59% (entry 21). The moderately polar solvent THF was chosen to carry out the reaction using **L2** at 75 °C, and the phenolic product **1p** was obtained in excellent yield of 93% (entry 22), while the same using **L6** afforded the product **1p** in only 85% yield (entry 22). It was very surprising that the reaction in THF solvent at even 40 °C using **L2** afforded the oxime-coupled product **1c** in 90% yield (entry 24), which is quite good compared to the reaction yield in toluene. This result reveals that the solvent THF can promote the coupling at both low and high temperature; however, at high temperature THF also promoted the oxime–imine proton-abstraction, which led to the formation of phenol. This result and the reaction in DMF (entry 15) clearly imply that the formation of phenol occurs only after the formation of the coupled product, which immediately undergoes base-promoted imine proton abstraction,[3j] as shown in Scheme 2.

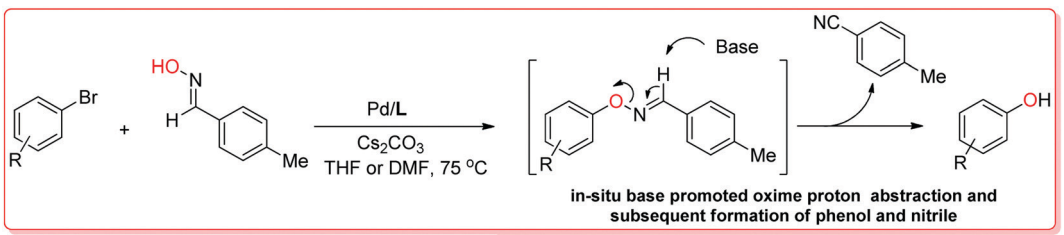
Further Pd source optimization (see ESI†) for the coupling reaction in toluene showed that $[(\pi\text{-allylPdCl})_2]$ is an excellent catalyst for the coupling of oxime. With these promising ligands and optimized reaction conditions, we again aimed to find the best conditions for the coupling of oxime with the neutral aryl bromide, 3′-bromoacetophenone (Table 2). Among the 5 ligands examined (entries 1–5) for the coupling of oxime in toluene, only two ligands *t*BuBrettPhos, **L6**, and RockPhos, **L7**, were effective towards the coupling reaction with 2.0 mol% Pd-catalyst loading, affording the coupling product **11c** in good yields (entries 3, and 4, respectively). The ligand *t*BuXPhos (**L2**) gave the coupled product **11c** with the conversion of 90% and yield of 70% over 4.0 h (entry 1). The promising ligands **L6** and **L7** in toluene were also checked for the coupling reaction in DMF, which gave the phenolic product **11p** in excellent yields (entries 6, and 7, respectively). The solvent THF was inefficient for substrate **7** with a different electronic nature using the promising ligand **L7** at 40 °C (entry 8). This result reveals that

Table 1 Optimization of the reaction conditions for the Pd-catalyzed cross-coupling of 4′-bromoacetophenone with 4-methylbenzaldoxime[a]



Entry	Ligand	Base	Solvent	Reaction time[b] (h)	Conv. (%)	Yield[c] (%) 1a	1b
1	**L1**	Cs_2CO_3	Toluene	12.0	ND	NR	—
2	**L2**	Cs_2CO_3	Toluene	1.5	100	**83**	—
3	**L3**	Cs_2CO_3	Toluene	16.0	ND	NR	—
4	**L4**	Cs_2CO_3	Toluene	16.0	ND	NR	—
5	**L5**	Cs_2CO_3	Toluene	2.0	100	75	—
6	**L6**	Cs_2CO_3	Toluene	2.0	100	**83**	—
7	**L7**	Cs_2CO_3	Toluene	2.0	100	78	—
8	**L8**	Cs_2CO_3	Toluene	12.0	ND	NR	—
9	**L9**	Cs_2CO_3	Toluene	2.0	100	**82**	—
10	**L10**	Cs_2CO_3	Toluene	15.0	ND	NR	—
11	**L11**	Cs_2CO_3	Toluene	12.0	ND	NR	—
12	**L12**	Cs_2CO_3	Toluene	12.0	ND	NR	—
13	**L2**	KOH	Toluene	1.0	100	**81**	—
14	**L2**	Cs_2CO_3	DMF	1.0	100	—	**92**
15	**L2**	Cs_2CO_3	DMF	23	ND	NR	NR[d]
16	**L3**	Cs_2CO_3	DMF	22	ND	NR	NR
17	**L4**	Cs_2CO_3	DMF	24	ND	NR	NR
18	**L5**	Cs_2CO_3	DMF	2.0	100	—	85
19	**L6**	Cs_2CO_3	DMF	1.0	100	—	**92**
20	**L7**	Cs_2CO_3	DMF	1.5	100	—	**91**
21	**L2**	KOH	DMF	3.0	100	—	59
22	**L2**	Cs_2CO_3	THF	2.0	100	6	**93**[e]
23	**L6**	Cs_2CO_3	THF	2.0	100	5	**85**[e]
24	**L2**	Cs_2CO_3	THF	5.0	100	**90**[d]	—

[a] Reaction conditions: 4′-bromoacetophenone (0.5 mmol, 1.0 eq.), 4-methylbenzaldoxime (0.55 mmol, 1.1 eq.), base (0.75 mmol, 1.5 eq.), [(π-allylPdCl)$_2$] (1.0 mol%), ligand, **L1–L12** (2.5 mol%), solvent (2.0 mL), 90 °C, Ar atm. [b] Reaction time optimized by TLC. [c] Isolated yield. [d] 40 °C. [e] 75 °C; NR = no reaction; ND = not determined.



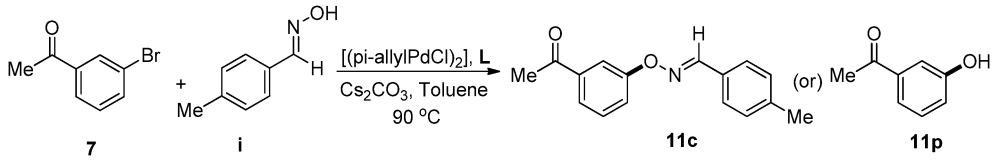
Scheme 2 Mechanism of the base-promoted *in situ* oxime imine proton abstraction and subsequent phenol formation.

the solvent, for a given catalyst system, also plays a key role in facilitating the coupling with product selectivity.

Moreover, the promising ligands were also examined again for their suitability for the coupling of oxime **i**, with the substrate (*E*)-3-(3-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one, **16** (Table 3). The reaction required 3.0 mol% Pd-catalyst loading for this substrate and was carried out in toluene at 75 °C. Only ligands **L2** and **L7** were found to be better supporting ligands in producing product **20c** in good yields (entries 1 and 4) while the reaction in DMF produced product **20p** in good yields (entries 6, and 7), respectively. The promising ligand **L6** (Table 2, entry 3) was unsuccessful for this substrate (Table 3, entry 3). In contrast to aryl bromides, the reaction in THF at 75 °C using ligands **L2** and **L7** gave the coupled product **20c** in good yields (entries 8, and 9, respectively) rather than **20p**. However, the reaction in THF at 40 °C was incomplete over a 20 h reaction time, although product **20c** was obtained in 72% yield (entry 10). This result reveals that the electronic nature of 3-substituted simple aryl bromides and bromo-chalcones is different and they react differently under the given conditions. The selectivity of the products for the 3-substituted bromo coupling partners was caused by the solvent rather than temperature. None of the ligands supported the Pd-catalyzed coupling of the electron-rich aryl bromides 4-bromotoluene and 4-bromoanisole with oxime under the reaction conditions. Therefore, the catalyst system and ligand did not facilitate the coupling of aldoxime with electron-rich aryl bromides.

With the optimized reaction conditions in hand, we then explored the applicability of the method in the coupling of

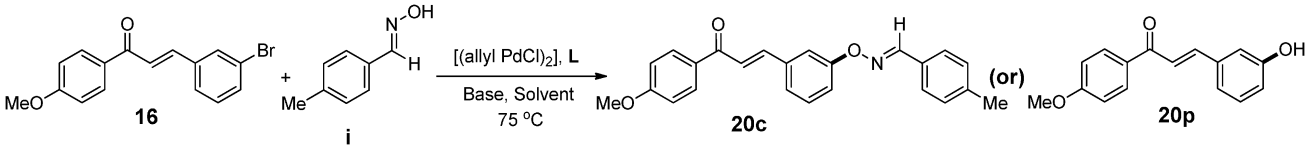
Table 2 Optimization of the reaction conditions for the Pd-catalyzed cross-coupling of 3′-bromoacetophenone with 4-methylbenzaldoxime[a]



Entry	Ligand	Base	Solvent	Reaction time (h)	Conv. (%)	Yield[b] (%) 2a	2b
1	**L2**	Cs_2CO_3	Toluene	4.0	90	70	—
2	**L5**	Cs_2CO_3	Toluene	23.0	ND	NR	—
3	**L6**	Cs_2CO_3	Toluene	3.0	100	**88**	—
4	**L7**	Cs_2CO_3	Toluene	2.0	100	**87**	—
5	**L9**	Cs_2CO_3	Toluene	7.0	60	42	—
6	**L6**	Cs_2CO_3	DMF	6.0	98	—	**92**
7	**L7**	Cs_2CO_3	DMF	5.0	98	—	**90**
8	**L7**	Cs_2CO_3	THF	9.0	60	53[c]	—

[a] Reaction conditions: 3′-bromoacetophenone (0.5 mmol, 1.0 eq.), 4-methylbenzaldoxime (0.55 mmol, 1.1 eq.), Cs_2CO_3 (0.75 mmol, 1.5 eq.), [(π-allylPdCl)$_2$] (2.0 mol%), ligand, (5.0 mol%), solvent (2.0 mL), Ar atm. 90 °C. [b] Isolated yield. [c] 40 °C, NR = no reaction. ND = not determined.

Table 3 Optimization of the reaction conditions for the Pd-catalyzed cross-coupling of (*E*)-3-(3-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one with 4-methylbenzaldoxime[a]

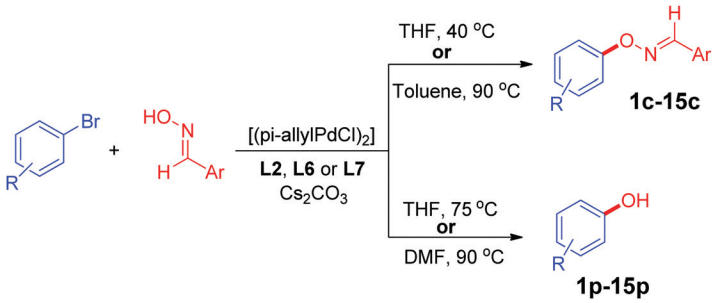


Entry	Ligand	Base	Solvent	Reaction time (h)	Conv. (%)	Yield[b] (%) 3a	3b
1	**L2**	Cs_2CO_3	Toluene	3.0	97	**78**	—
2	**L5**	Cs_2CO_3	Toluene	22.0	ND	NR	—
3	**L6**	Cs_2CO_3	Toluene	22.0	60	42	—
4	**L7**	Cs_2CO_3	Toluene	6.0	97	**78**	—
5	**L9**	Cs_2CO_3	Toluene	22.0	ND	NR	—
6[c]	**L2**	Cs_2CO_3	DMF	2.0	100	—	**80**
7[c]	**L7**	Cs_2CO_3	DMF	2.0	100	—	**79**
8	**L2**	Cs_2CO_3	THF	3.0	100	**81**	—
9	**L7**	Cs_2CO_3	THF	6.0	98	79	—
10[d]	**L2**	Cs_2CO_3	THF	20.0	80	72	—

[a] Reaction conditions: (*E*)-3-(3-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (0.5 mmol, 1.0 eq.), 4-methylbenzaldoxime (0.55 mmol, 1.1 eq.), Cs_2CO_3 (0.75 mmol, 1.5 eq.), [(π-allylPdCl)$_2$] (3.0 mol%), ligand (7.5 mol%), solvent (2.0 mL), 75 °C, Ar atm. [b] Isolated yield. [c] 90 °C. [d] 40 °C, NR = no reaction. ND = not determined.

various aryl bromides and bromo-chalcones with benzaldoximes. The aryl bromide substrates required 1.0 or 2.0 mol% catalyst loading for the coupling reaction to be effective, and those bearing an electron-withdrawing group at *p*-position seemed to be more labile with temperature in THF solvent (Table 4). The catalyst system Pd/*t*BuXPhos (**L2**) was effective towards the coupling of activated aryl bromides with 4-methylbenzaldoxime in THF solvent, interestingly, even at 40 °C and afforded the coupled products **1c–6c** in good to excellent yields (entries 1–6). On the contrary, when the same reaction was carried out at 75 °C, the phenolic products, **1p–6p**, were obtained in good to excellent yields (entries 1–6) except **4p**. Unfortunately, 1-bromo-4-nitrobenzene **4** failed to give the phenolic product **4p** at 75 °C, whereas it gave the coupled product **4c** successfully at 40 °C in 97% yield. Thus, the THF solvent promotes the functionality switching at different temperature extremes and more precisely, the oxime proton was not labile to be abstracted by base at 40 °C, whereas it was promoted at 75 °C. The catalyst system could also effectively couple the activated aryl bromides with various oximes at 40 °C to afford the coupled products **7c–10c** in good to excellent yields (entries 7–10). The ligands *t*BuBrettPhos (**L6**) and RockPhos (**L7**) were found to be good supporting ligands for the [(π-allyl)PdCl]$_2$ catalyst in the coupling of aryl bromides bearing an electron-withdrawing group at the *m*-position with various oximes (Table 2). The reaction for these substrates required relatively higher catalyst loadings (2.0 mol%) and the product selectivity towards oxime ethers and phenols was achieved using the solvents toluene and DMF, respectively, rather than temperature.

Table 4 Pd-Catalyzed C–O cross-coupling of aryl bromides with aldoximes with functionality switching by temperature and solvent



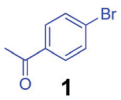
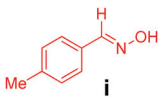
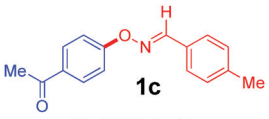
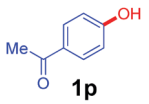
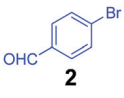
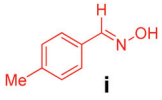
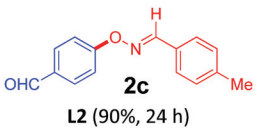
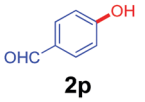
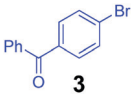
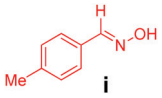
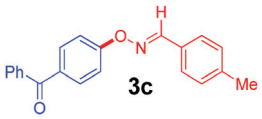
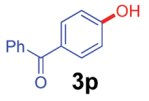
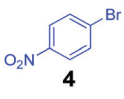
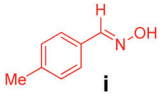
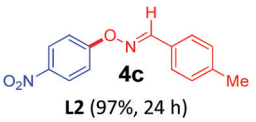
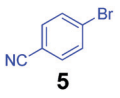
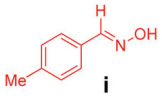
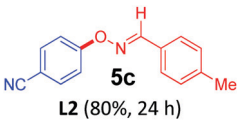
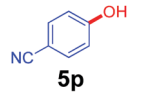
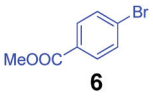
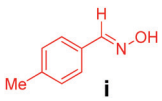
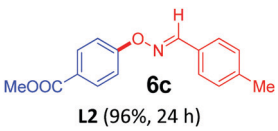
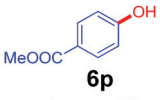
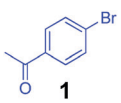
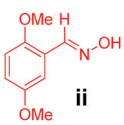
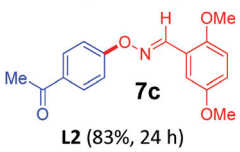
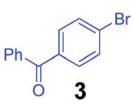
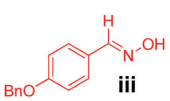
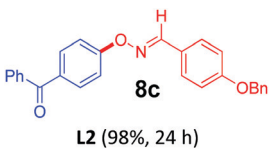
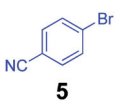
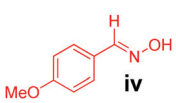
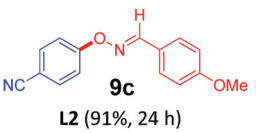
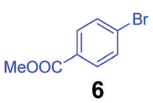
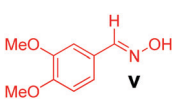
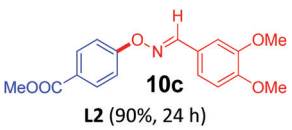
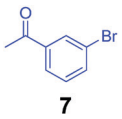
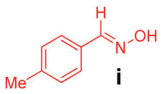
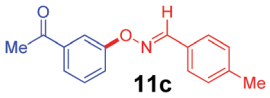
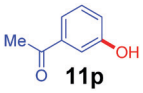
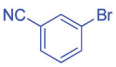
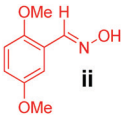
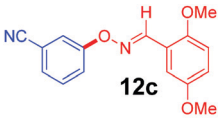
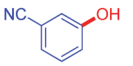
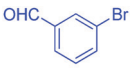
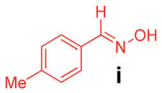
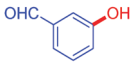
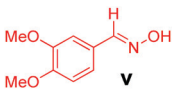
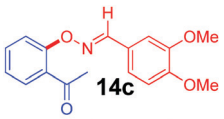
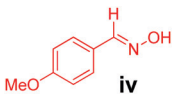
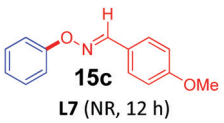
Entry	Ar–Br	Oxime	Product, L (yield[a] % & time) THF[b] (40 °C)	THF[b] (75 °C)
1	 1	 i	 1c L2 (85%, 24 h)	 1p L2 (92%, 1 h)
2	 2	 i	 2c L2 (90%, 24 h)	 2p L2 (98%, 3 h)
3	 3	 i	 3c L2 (98%, 24 h)	 3p L2 (82%, 3 h)
4	 4	 i	 4c L2 (97%, 24 h)	 4p L2 (NR, 17 h)
5	 5	 i	 5c L2 (80%, 24 h)	 5p L2 (98%, 2 h)
6	 6	 i	 6c L2 (96%, 24 h)	 6p L2 (79%, 4 h)
7	 1	 ii	 7c L2 (83%, 24 h)	NC
8	 3	 iii	 8c L2 (98%, 24 h)	NC
9	 5	 iv	 9c L2 (91%, 24 h)	NC
10	 6	 v	 10c L2 (90%, 24 h)	NC

Table 4 *(continued)*

			Product, **L** (yield[a] % & time)	
			Toluene[c] (90 °C)	DMF[d] (90 °C)
11	 **7**	 **i**	 **11c** **L6** (88%, 3 h) **L7** (87%, 2 h)	 **11p** **L6** (92%, 2 h) **L7** (90%, 5 h)
12	 **8**	 **ii**	 **12c** **L7** (85%, 3 h)	 **12p** **L6** (95%, 3 h)
13	 **9**	 **i**	 **13c** **L7** (98%, 1 h)	 **13p** **L6** (92%, 2 h)
14	 **10**	 **v**	 **14c** **L7** (NR, 10 h)	 **14p** **L6** (NR%, 13 h)
15	 **11**	 **iv**	 **15c** **L7** (NR, 12 h)	 **15p** **L6** (NR, 16 h)

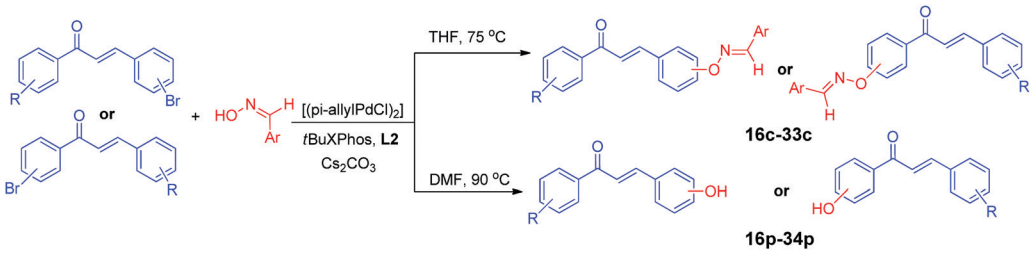
Reaction conditions: [a] Isolated yield. [b] Aryl bromides (1.0 mmol, 1.0 eq.), aldoximes (1.05 mmol, 1.05 eq.), Cs_2CO_3 (1.5 mmol, 1.5 eq.), [(π-allyl)PdCl]$_2$ (1.0 mol%), *t*BuXPhos (**L2**) (2.5 mol%), Ar atm. [c] Aryl bromides (1.0 mmol, 1.0 eq.), aldoximes (1.05 mmol, 1.05 eq.), Cs_2CO_3 (1.5 mmol, 1.5 eq.), [(π-allyl)PdCl]$_2$ (2.0 mol%), *t*BuBrettPhos (**L6**) (or) RockPhos (**L7**) (5.0 mol%), toluene (3.0 mL), 90 °C, Ar atm. [d] Aryl bromides (1.0 mmol, 1.0 eq.), aldoximes (1.05 mmol, 1.05 eq.), Cs_2CO_3 (1.5 mmol, 1.5 eq.), [(π-allyl)PdCl]$_2$ (2.0 mol%), *t*BuBrettPhos (**L6**) (or) RockPhos (**L7**) (5.0 mol%), DMF (2.5 mL), 90 °C, Ar atm.

The product oxime ethers **11c–13c** and phenols **11p–13p** were obtained in good to excellent yields in toluene and DMF (entries 11–13), respectively. However, the catalyst system did not facilitate the coupling of oximes with substrates such as 2′-bromoacetophenone and bromobenzene.

Next, we turned out our attention to bromo-chalcones as a coupling partner to access novel chalcones. The oximes could successfully couple with either of the phenyl rings of bromo-chalcones. The *t*BuXPhos ligand was promising to support the Pd-catalyzed coupling of oximes, unlike with 3-bromo-1-substituted benzene, and with 3-bromo-chalcones as well. The reaction of bromo-chalcones, (*E*)-3-(4-bromophenyl)-1-(substituted phenyl)-prop-2-en-1-ones, with 4-methylbenzaldoxime was driven by the Pd/*t*BuXPhos system in THF solvent at 75 °C to give the C–O coupled products **16c–19c** in good yields (Table 5). The 3-bromo-chalcone, (*E*)-3-(3-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one, **16**, was also effectively coupled by the catalyst system to afford the coupled product **20c** in 81% yield. The other oximes, such as 4-methoxybenzaldoxime **iv**, and 4-benzyloxybenzaldoxime **iii**, were also successfully coupled with bromo-chalcones **13** and **15** to afford the desired products **21c–23c**, respectively, in good yields and the reactions were completed within 3–4 h. Similarly, the other bromo-chalcones, (*E*)-1-(4-bromophenyl)-3-(substituted phenyl)prop-2-en-1-ones, nicely coupled using the catalyst system with 4-methylbenzaldoxime **i** to afford the coupled products **24c–29c** in good to excellent yields. The other oximes such as 4-methoxybenzaldoxime, **iv**, and 3,4-dimethoxybenzaldoxime, **v**, and 4-benzyloxybenzaldoxime, **iii**, were coupled with bromo-chalcones to give the coupled products **30c–33c** in good to excellent yields, respectively.

Since synthetic and natural chalcones with hydroxyl groups have received considerable interest due to their significant biological activity, we were interested in the incorporation of a hydroxyl group[3j] in chalcones using 4-methylbenzaldoxime as a hydroxide surrogate. Switching the reaction solvent from THF to DMF under the optimized reaction conditions led to switching of the functionality from oxime ethers to phenolic compounds (Table 5). With 3.0 mol% Pd catalyst loading and *t*BuXPhos (**L2**), both types of bromo-chalcones smoothly reacted with 4-methylbenzaldoxime, **i**, in DMF solvent to afford the hydroxyl chalcones in short reaction times. The bromo-chalcones (*E*)-3-(4-bromophenyl)-1-(substituted phenyl)prop-2-en-1-ones were reacted with the hydroxide surrogate 4-methyl-benzaldoxime to form hydroxychalcones **16p–20p** in good to excellent yields. Similarly, (*E*)-1-(4-bromophenyl)-3-(substituted phenyl)prop-2-en-1-ones were well tolerant under the reaction conditions to afford the hydroxylated products **24p–34p** in more than 95% yield.

Table 5 Pd-Catalyzed C–O cross-coupling of bromo-chalcones with aldoximes in different solvents



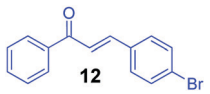
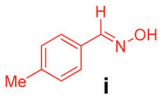
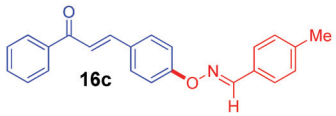
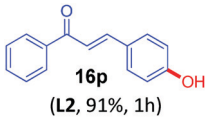
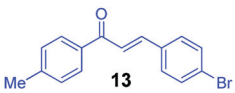
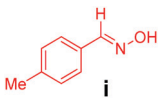
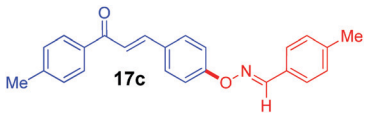
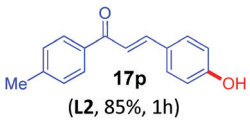
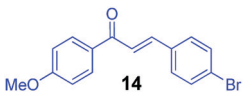
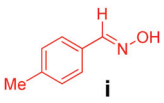
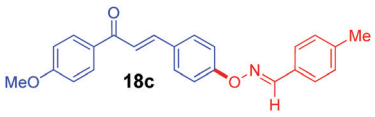
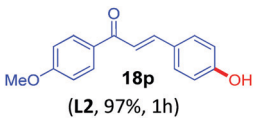
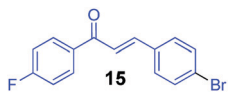
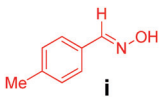
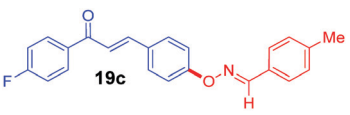
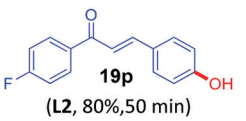
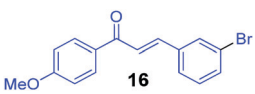
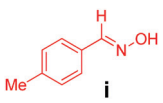
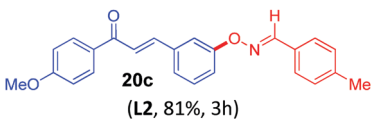
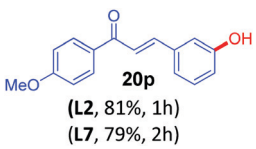
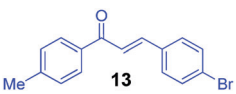
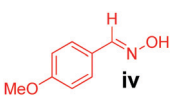
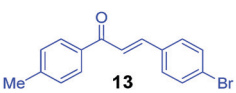
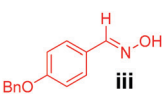
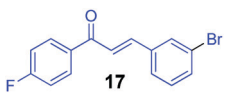
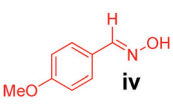
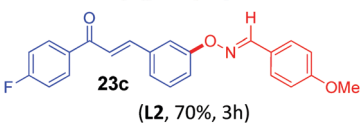
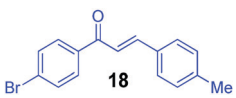
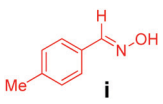
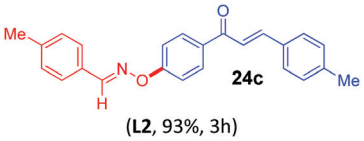
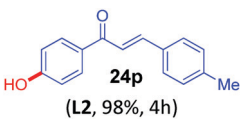
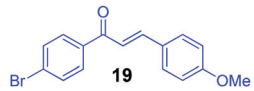
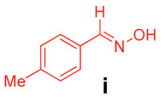
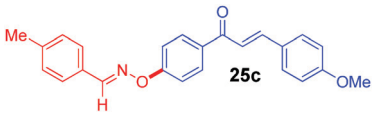
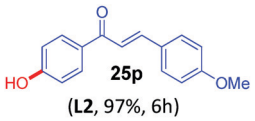
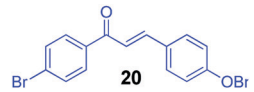
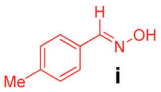
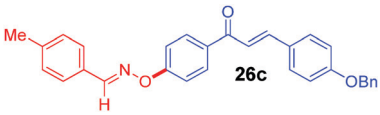
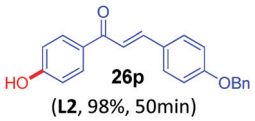
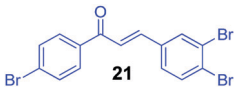
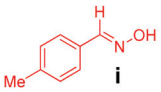
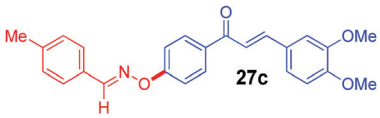
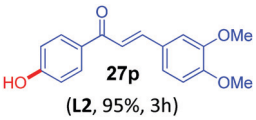
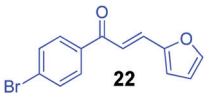
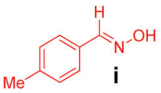
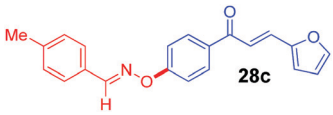
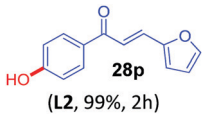
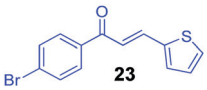
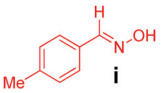
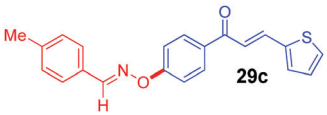
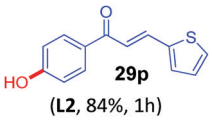
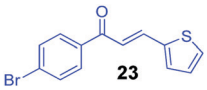
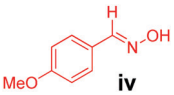
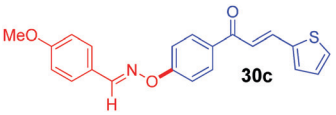
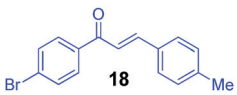
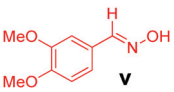
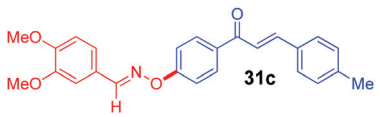
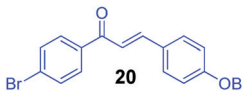
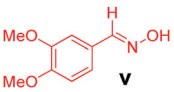
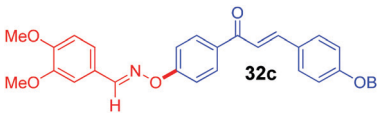
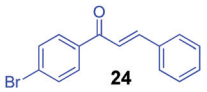
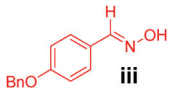
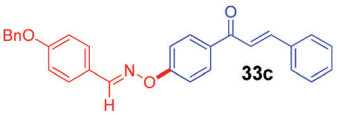
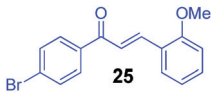
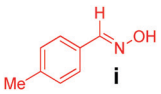
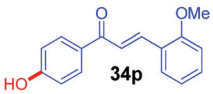
Entry	Ar–Br	Oxime	Product, L (yield[a] % & time) THF[b] (75 °C)	DMF[b] (90 °C)
1			 (L2, 79%, 4h)	 (L2, 91%, 1h)
2			 (L2, 73%, 3h)	 (L2, 85%, 1h) (L7, 82%, 1h)
3			 (L2, 78%, 2h)	 (L2, 97%, 1h)
4			 (L2, 75%, 4h)	 (L2, 80%,50 min)
5			 (L2, 81%, 3h)	 (L2, 81%, 1h) (L7, 79%, 2h)
6			 (L2, 81%, 4h)	NC
7			 (L2, 73%, 4h)	NC
8			 (L2, 70%, 3h)	NC
9			 (L2, 93%, 3h)	 (L2, 98%, 4h)

Table 5 *(continued)*

10	 19	 i	 25c (L2, 67%, 2h)	 25p (L2, 97%, 6h)
11	 20	 i	 26c (L2, 92%, 2h)	 26p (L2, 98%, 50min)
12	 21	 i	 27c (L2, 70%, 3h)	 27p (L2, 95%, 3h)
13	 22	 i	 28c (L2, 97%, 2h)	 28p (L2, 99%, 2h)
14	 23	 i	 29c (L2, 84%, 1h)	 29p (L2, 84%, 1h)
15	 23	 iv	 30c (L2, 82%, 1h)	NC
16	 18	 v	 31c (L2, 95%, 2h)	NC
17	 20	 v	 32c (L2, 73%, 3h)	NC
18	 24	 iii	 33c (L2, 71%, 1h)	NC
19	 25	 i	NC	 34p (L2, 87%, 4h)

Reaction conditions: [a] Bromo-chalcones (0.5 mmol, 1.0 eq.), aldoximes (0.525 mmol, 1.05 eq.), Cs_2CO_3 (0.75 mmol, 1.5 eq.), $[(\pi\text{-allyl})PdCl]_2$ (3.0 mol%), *t*BuXPhos (**L2**) (7.5 mol%), Ar atm. [b] Isolated yield.

Conclusions

In conclusion, we developed a convenient methodology for the coupling of aldoximes with aryl bromides and bromo-chalcones using an inexpensive *t*BuXPhos ligand (**L2**)-supported Pd-catalyzed C–O cross-coupling reaction. We demonstrated the role of solvent and temperature towards the selectivity of the products, oxime or phenols, in the Pd-catalyzed C–O cross-coupling reaction for the first time. The catalyst system was highly efficient for activated aryl bromides in THF solvent and gave the coupled products

even at 40 °C, whereas the hydroxylated products at 75 °C. The catalyst system Pd/**L2** could effectively facilitate the coupling of bromo-chalcones with aldoximes in THF to give the coupled products in good to excellent yields, whereas in DMF the hydroxylated products were obtained in good to excellent yields. For bromo-chalcones, and the temperature did not result in selectivity for phenols. The catalyst system Pd/**L2** could not facilitate the reaction with less activated (*m*-substituted) aryl bromides, while the other ligands *t*BuBrettPhos (**L6**) or RockPhos (**L7**) could facilitate the coupling in toluene at 90 °C to afford the coupled products, whereas in DMF at 90 °C afforded the hydroxylated products. None of the catalyst systems resulted in the coupling of neutral and deactivated aryl bromides with aldoxime. This method offers the functionality switching option, and consequently direct access to a wide range of aldoxime ethers of synthetic importance and novel chalcones for various biological screening studies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Authors are grateful to Defence R & D Organization (DRDO) for financial assistance. Authors also acknowledge Director, CFEES, DRDO and Principal, Sri Venkateswara College, University of Delhi, for their encouraging support throughout this work. We thank Head, Department of Chemistry and USIC, University of Delhi for providing analytical and other technical supports.

Notes and references

1 (*a*) S. M. Johnson, H. M. Petrassi, S. K. Palaninathan, N. N. Mohamedmohaideen, H. E. Purkey, C. Nichols, K. P. Chiang, T. Walkup, J. C. Sacchettini, K. B. Sharpless and J. W. Kelly, *J. Med. Chem.*, 2005, **48**, 1576–1587; (*b*) K. Tsuchiya, M. Kondo, M. Kida, M. Nakao, T. Iwahi, T. Nishi, Y. Noji, M. Takeuchi and Y. Nozaki, *Antimicrob. Agents Chemother.*, 1981, **19**, 56–65; (*c*) E. J. van Hoogdalem, W. E. van den Hoven, I. J. Terpstra, J. van Zijtveld, J. S. C. Verschoor and J. N. Visser, *Eur. J. Pharm. Sci.*, 1997, **5**, 119–127; (*d*) I. H. Bhatt, T. R. Chitturi, R. K. Pal, B. Samanta and R. Thennati, WO2003087059, 2003; (*e*) A. Prieur, W. Rein, P. Verpillat and E. Weinling, WO2010055461, 2010; (*f*) C. Garcia and C. Hoff, WO2010055255, 2010; (*g*) T. Suzuki, M. Kameda, M. Ando, H. Miyazoe, E. Sekino, S. Ito, K. Masutani, K. Kamijo, A. Takezawa, M. Moriya, M. Ito, J. Ito, K. Nakase, H. Matsushita, A. Ishihara, N. Takenaga, S. Tokita, A. Kanatani, N. Sato and T. Fukami, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5339–5345; (*h*) Reeta, R. Vinoth, T. M. Rangarajan, Ayushee, R. P. Singh and M. Singh, *Bioorg. Chem.*, 2019, **86**, 631–640; (*i*) Reeta, S. C. Baek, J. P. Lee, T. M. Rangarajan, Ayushee, R. P. Singh, M. Singh, G. F. Mangiatordi, O. Nicolotti, H. Kim and B. Mathew, *CNS Neurol. Disord. Drug Targets*, 2019, **18**, 643–650; (*j*) D. Hong, Y. Wei, S. Siyu, L. Ling, S. Lei, Q. Hongwei, L. Chunjian, S. Jian and S. Yujun, *Chin. J. Org. Chem.*, 2017, **37**, 3155–3162; (*k*) J. X. Huang, Y. M. Jia, X. M. Liang, W. J. Zhu, J. J. Zhang, Y. H. Dong, H. Z. Yuan, S. H. Qi, J. P. Wu, F. H. Chen and D. Q. Wang, *J. Agric. Food Chem.*, 2007, **55**, 10857–10863; (*l*) J. Ma, M. Ma, L. Sun, Z. Zeng and H. Jiang, *J. Chem.*, 2015, 8, DOI: 10.1155/2015/435219.

2 (*a*) Z. Mirjafary, M. Abdoli, H. Saeidian, S. Boroon and A. Kakanejadifard, *RSC Adv.*, 2015, **5**, 79361–79384; (*b*) K. Narasaka and M. Kitamura, *ARKIVOC*, 2006, **vii**, 245–260; (*c*) D. S. Bolotin, N. A. Bokach, M. Y. Demakova and V. Y. Kukushkin, *Chem. Rev.*, 2017, **117**, 13039–13122; (*d*) Z. Mirjafary, M. Abdoli, H. Saeidian, A. Kakanejadifard and S. M. F. Farnia, *RSC Adv.*, 2016, **6**, 17740–17758; (*e*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *Chem. Commun.*, 2007, 4041–4043; (*f*) Y. Jiang, W. C. Chan and C. M. Park, *J. Am. Chem. Soc.*, 2012, **134**, 4104–4107; (*g*) F. P. Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem.*, 2009, **74**, 4934–4942; (*h*) T. Zhang, R. Xie, T. Zhang, X. Mei, J. Yang and J. Ning, *J. Pestic. Sci.*, 2013, **38**, 88–90.

3 (*a*) G. M. Shutske, *J. Org. Chem.*, 1984, **49**, 180–183; (*b*) M. M. Guru, M. A. Ali and T. Punniyamurthy, *J. Org. Chem.*, 2011, **76**, 5295–5308; (*c*) M. M. Guru, M. A. Ali and T. Punniyamurthy, *Org. Lett.*, 2011, **13**, 1194–1197; (*d*) N. Takeda, M. Ueda, S. Kagehira, H. Komei, N. Tohnai, M. Miyata, T. Naito and O. Miyata, *Org. Lett.*, 2013, **15**, 4382–4385; (*e*) N. Takeda, O. Miyata and T. Naito, *Eur. J. Org. Chem.*, 2007, 1491–1509; (*f*) A. J. Castellino and H. Rapoport, *J. Org. Chem.*, 1984, **49**, 4399–4404; (*g*) O. Miyata, N. Takeda and T. Naito, *Org. Lett.*, 2004, **6**, 1761–1763; H. Gao, Q. L. Xu, C. Keene and L. Kurti, *Chem. – Eur. J.*, 2014, **20**, 8883–8887; (*h*) R. Ghosh, E. Stridfeldt and B. Olofsson, *Chem. – Eur. J.*, 2014, **20**, 8888–8892; (*i*) F. Contiero, K. M. Jones, E. A. Matts, A. Porzelle and N. C. O. Tomkinson, *Synlett*, 2009, 3003–3006; (*j*) P. S. Fier and K. M. Maloney, *Angew. Chem., Int. Ed.*, 2017, **56**, 4478–4482; (*k*) K. Uchiyama, Y. Hayashi and K. Narasaka, *Synlett*, 1997, 445–446; (*l*) S. D. Lepore and M. R. Wiley, *J. Org. Chem.*, 2000, **65**, 2924–2932; (*m*) Y. Cai, A. Jalan, A. R. Kubosumi and S. L. Castle, *Org. Lett.*, 2015, **17**, 488–491; (*n*) T. J. Maimone and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 9990–9991.

4 (*a*) E. Abele and E. Lukevics, *Org. Prep. Proced. Int.*, 2000, **32**, 235–264; (*b*) T. Sheradsky, *Tetrahedron Lett.*, 1966, **43**, 5225–5227; (*c*) T. Sheradsky, *J. Heterocycl. Chem.*, 1967, **4**, 413–414; (*d*) S. Kumar, R. Sharma, M. Garcia, J. Kamel, C. McCarthy, A. Muth and O. Phanstiel, *J. Org. Chem.*, 2012, **77**, 10835–10845; (*e*) S. K. Nimmagadda, S. C. Mallojjala, L. Woztas, S. E. Wheeler and J. C. Antilla, *Angew. Chem.*, 2017, **56**, 2454–2458.

5 (*a*) J. B. Baumann, *Synthesis*, 1975, 782; (*b*) A. Mooradian and P. E. Dupont, *J. Heterocycl. Chem.*, 1967, **4**, 441–444; (*c*) P. R. Guzzo, R. N. Buckle, M. Chou, S. R. Dinn, M. E. Flaugh, A. D. Kiefer, K. T. Ryter, A. J. Sampognaro, S. W. Tregay and Y. C. Xu, *J. Org. Chem.*, 2003, **68**, 770–778; (*d*) S. D. Lepore and M. R. Wiley, *J. Org. Chem.*, 2000, **65**, 2924–2932; (*e*) S. D. Lepore and M. R. Wiley, *Org. Lett.*, 2003, **5**, 7–10.

6 A. J. Castellino and H. Rapoport, *J. Org. Chem.*, 1984, **49**, 1348–1352.
7 (*a*) G. Zinner, G. Nebel and M. Hitze, *Arch. Pharm.*, 1970, **303**, 317–320; (*b*) Y. Tamura, J. Minamikawa and M. Ikeda, *Synthesis*, 1977, 1–18; (*c*) E. Miyazawa, T. Sakamoto and Y. Kikugawa, *Org. Prep. Proced. Int.*, 1997, **29**, 594–600.
8 (*a*) C. Baldoli, P. D. Buttero, E. Licandro and S. Maiorana, *Synthesis*, 1988, 344–355; (*b*) C. Legault and A. B. Charette, *J. Org. Chem.*, 2003, **68**, 7119–7122; (*c*) N. Nazarpack-Kandlousy, I. V. Chernushevich, L. J. Meng, Y. Yang and A. V. Eliseev, *J. Am. Chem. Soc.*, 2000, **122**, 3358–3366.
9 (*a*) H. M. Petrassi, K. B. Sharpless and J. W. Kelly, *Org. Lett.*, 2001, **3**, 139–142; (*b*) F. S. G. Wieczorek, L. T. Maillard, B. Badet and P. Durand, *J. Comb. Chem.*, 2010, **12**, 655–658.
10 (*a*) J. I. G. Cadogan and A. G. Rowley, *Synth. Commun.*, 1977, **7**, 365–366; (*b*) R. Ghosh and B. Olofsson, *Org. Lett.*, 2014, **16**, 1830–1832.
11 (*a*) P. De, Nonappa, K. Pandurangan, U. Maitra and S. Wailes, *Org. Lett.*, 2007, **9**, 2767–2770; (*b*) X. H. Feng, G. Z. Zhang, C. Q. Chen, M. Y. Yang, X. Y. Xu and G. S. Huang, *Synth. Commun.*, 2009, **39**, 1768–1780; (*c*) M. Mondal, G. Sarmah, K. Gogoi and U. Bora, *Tetrahedron Lett.*, 2012, **53**, 6219–6222; (*d*) A. Ali, A. G. Meyer and K. L. Tuck, *Synlett*, 2009, 0955–0959; (*e*) L. Wang, C. Huang and C. Cai, *Catal. Commun.*, 2010, **11**, 532–536; (*f*) S. A. R. Mulla, S. S. Chavan, S. M. Inamdar, M. Y. Pathan and T. M. Y. Shaikh, *Tetrahedron Lett.*, 2014, **55**, 5327–5332.
12 (*a*) L. C. M. Castro and N. Chatani, *Synthesis*, 2014, 2312–2316; (*b*) Y. Yang, X. Wu, J. Han, S. Mao, X. Qian and L. Wang, *Eur. J. Org. Chem.*, 2014, 6854–6857.
13 (*a*) O. Petrov, Y. Ivanova and M. Gerova, *Catal. Commun.*, 2008, **9**, 315–316; (*b*) Y. Pan, Y. Chen, Q. Li, X. Yu, J. Wang and J. Zheng, *Molecules*, 2013, **18**, 1693–1703.
14 (*a*) X. Deng, H. Cao, C. Chen, H. Zhou and L. Yu, *Sci. Bull.*, 2019, **64**, 1280–1284; (*b*) X. Jing, D. Yuan and L. Yu, *Adv. Synth. Catal.*, 2017, **359**, 1194–1201; (*c*) X. Zhang, J. Sun, Y. Ding and L. Yu, *Org. Lett.*, 2015, **17**, 5840–5842; (*d*) S. Chu, H. Cao, T. Chen, Y. Shi and L. Yu, *Catal. Commun.*, 2019, **129**, 105730.
15 Price of 3-methylisatoic anhydride, http://synquestlabs.com/product/id/67108.html.