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Metal-free diaryl etherification of tertiary amines by *ortho*-C(sp^2)-H functionalization for synthesis of dibenzoxazepines and dibenzoxazepinones

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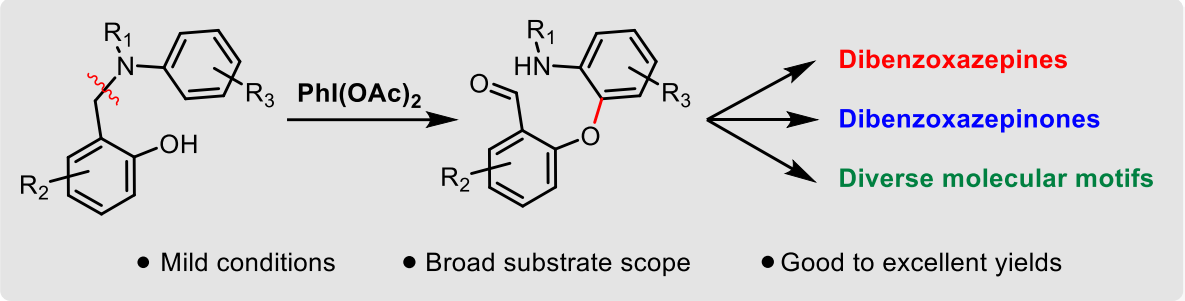

Abstract:

A phenyliodine(III) diacetate (PIDA) mediated umpolung reactivity of tertiary amines with suitably substituted *ortho*-hydroxybenzyl, phenyl units is exploited to facilitate *ortho*-C(sp^2)-H functionalization to afford diaryl ethers. Presence of an ortho-CHO and secondary amine functionalities in the resulting diaryl ether, generated *in situ*, were utilized for synthesis of dibenzoxazepines and dibenzoxazepinones. Mild conditions, broad substrate scope with good to excellent yields, and scope for further diversification of diaryl ether are highlights of this methodology.

Introduction:

Dibenzoxazepines and dibenzoxazepinones are pharmaceutically relevant molecules present in antidepressants and antipsychotics. These privileged structural motifs possess

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broad range of biological activities such as anti-HIV, antitumor, antioxidant, oral contraceptive, TRPA1 agonist, sodium channel blocker, CNS depressant, antinflammatory, and antinociceptive property. [1] As natural products, dibenzoxazepinones were reported as antioxidant metabolites isolated from the leaves of *Carex distachya*.[1c] Many approaches have been developed for the synthesis of dibenzoxazepine core skeleton. Traditionally, base-promoted nucleophilic aromatic substitution (S_NAr) reaction was employed to construct the seven-membered ring of dibenzoxazepinones via Smiles rearrangement of suitable electrophilic substrates by a domino C–O and C–N coupling reactions.[2] A base-promoted green protocol has been developed for synthesis of dibenz[*b*,*f*][1,4]oxazepin-11-amines by S_NAr with concomitant addition reaction.[3] Post-Ugi reaction, an intramolecular microwave-assisted Ullman diaryl etherification was used as an attractive strategy to synthesize highly substituted dibenz[*b*,*f*][1,4]oxazepine scaffold.[4] Key precursors generated from diaryl etherification methodology served as suitable substrates for various intramolecular seven-membered ring formation strategies such as reductive lactamization, Pd-catalyzed condensation, cyclocarbonylation, Smiles rearrangement, Cu-catalyzed Goldberg reaction to afford dibenzoxazepinones.[5] Alternatively, intramolecular diaryl etherification as the later annulation event under metal-catalyzed and base-promoted conditions from substrates with suitably tethered phenol and halo-substituted phenyl units was also developed.[6] Dibenzoxazepines have also been used as valuable synthetic intermediates in the development of more complex heterocyclic structures.[7]

Recently, dibenzoxazepinone synthesis was reported by hypervalent iodine (III) reagent (HIR) mediated intramolecular C-N bond formation from 2-(aryloxy)benzamides synthesized by Cu-mediated diaryl etherification,[8] but failed with substrates containing strong electron withdrawing and donating groups. Another example involving usage of HIR reagent such as phenyliodine(III) diacetate (PIDA) involved intramolecular cyclization of two aryl groups from 2-hydroxy-*N*-phenylbenzamides affording dibenz[*d*,*f*][1,3]oxazepin-6(7*H*)-ones.[9] HIR is considered as a mild and metal-free alternative for the construction C–C and C–heteroatom bonds.[10] HIR mediated oxidative dearomatizing transformations for ortho-substituted phenols were utilized in synthesis of complex natural products.[11] Similar to phenolic substrates, tertiary amines were also

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efficient substrates in HIR mediated transformations involving functionalization of C(sp^3)-H bond adjacent to nitrogen.[12] Herein, we report *ortho*-C(sp^2)-H bond functionalization of tertiary amines in presence of PIDA to afford diaryl ether (Figure 1). Diaryl etherification is an important synthetic strategy achieved mostly by Cu- and Pd-catalyzed cross-coupling reactions.[13] The metal-free alternative for diaryl etherification with HIR involving diaryliodonium salts is an attractive strategy,[14] applied towards synthesis of ortho-CHO diaryl ethers.[15] In the present study, PIDA induced umpolung reactivity of tertiary amines affords diaryl ether with an *ortho*-CHO and secondary amine substituents that upon subsequent treatment with $NaBH(OAc)_3$ and PCC provided dibenzoxazepines and dibenzoxazepinones, respectively (Figure 1). The present method serves as a metal-free alternative to the existing methods *vide supra* with a broad substrate scope. Further synthetic applications of this methodology from diaryl ether were demonstrated with an array of transformations to access other bioactive skeletons.

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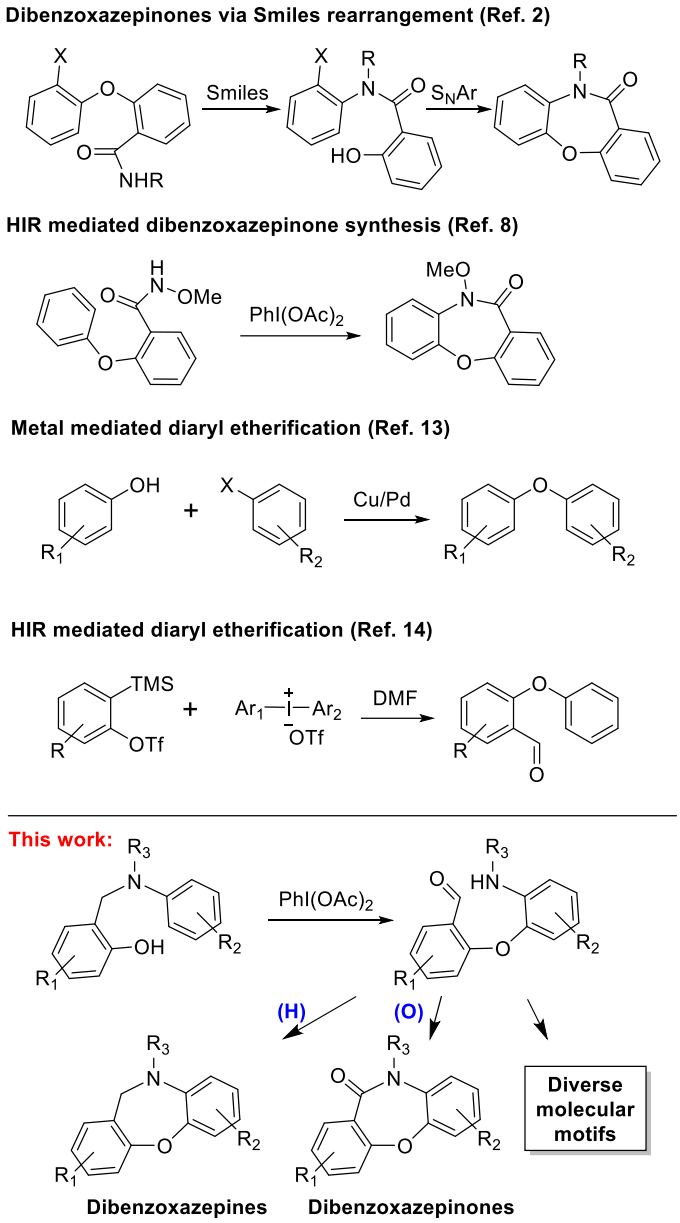

Figure 1. Strategies for dibenzoxazepinone, diaryl ether synthesis and present work

Results and Discussion:

A novel intramolecular diaryl etherification strategy for the key seven-membered ring formation to afford dibenzoxazepines was envisaged using tertiary amines with suitably substituted *ortho*-hydroxybenzyl, phenyl units under metal-free conditions by using HIRs. In an initial attempt (Table 1), tertiary amine **1a** treated with one equivalent of PIDA at

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room temperature using conventional HFIP as the solvent did not lead to complete consumption of the starting material. However, tertiary amine **1a** underwent a complete transformation within 10 min with two equivalents of PIDA forming a new C-O bond with concomitant C-N bond cleavage affording compound **2a** in 34% yield (entry 1). The structure of compound **2a** was unambiguously confirmed by single crystal X-ray analysis (see Supporting Information). Further variation of the solvents, other HIRs, oxidants and mode of additions examined were not effective for the formation of **2a** which led to the choice of PIDA and HFIP as the optimal combination. The reaction conducted in presence of K_2CO_3, to scavenge the generated acetic acid by-product from PIDA, did not significantly improve the yield of compound **2a** (entry 2). Compound **2** with appropriately substituted aldehyde and secondary amine is prone to undergo reductive amination to afford the desired dibenzoxazepine. Accordingly, a simple tertiary amine **1b** substrate was initially subjected to PIDA mediated oxidation to afford compound **2b** which without purification was treated with excess $NaBH_4$ in methanol for reductive amination. This reaction in an overall two steps produced the desired dibenzoxazepine **3b** in 67% yield (entry 3). Conducting the reductive amination step on the crude aldehyde in presence of additives (entries 4-5) and other reductants (entries 6-7) could not improve the yield of dibenzoxazepine formation considerably. Interestingly, addition of three equivalents of $NaBH(OAc)_3$ in the same pot after complete consumption of tertiary amine afforded dibenzoxazepine **3b** with an enhanced yield of 77% (entry 8), and presence of an additive could not further improve the yield (entry 9). Changing the reductant to an oxidant in the second step should produce dibenzoxazepinone **4**. An initial attempt with tertiary amine **1a** with an addition of one equivalent of PCC in dichloromethane in the same pot led to a sluggish outcome. However, treatment of one equivalent of PCC on the isolated intermediate **2c** in an overnight reaction afforded dibenzoxazepinone **4c** in 70% yield (entry 10) and an increase of PCC to two equivalents led to reaction completion within one hour with 73% yield (entry 11). The choice of tertiary amine **1c** is pertinent in the context of optimization of this methodology due to the high relevance of nitro-substitution in dibenzoxazepinone based anti-depressant drug Sintamil. Even though other oxidants (entries 12-17) failed to afford the desired product, sodium hypochlorite in acetic acid

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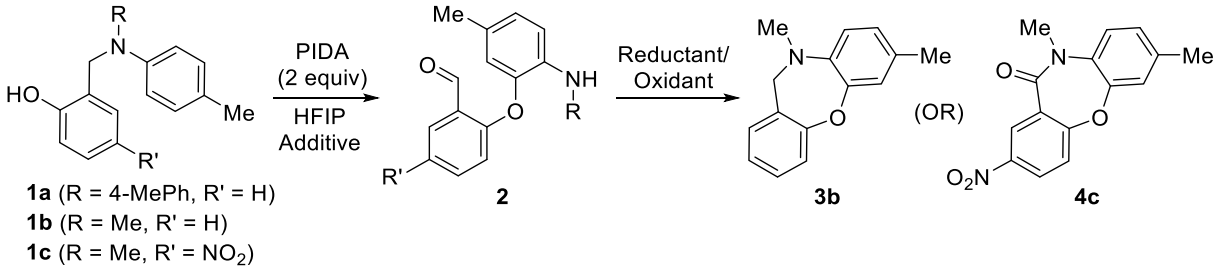
produced dibenzoxazepinone **4c** in 57% yield (entry 18) but failed while using acetonitrile (entry 19).

Table 1. Optimization of reaction conditions[a]



1a (R = 4-MePh, R' = H)
1b (R = Me, R' = H)
1c (R = Me, R' = NO_2)

Entry	Additive	Reductant/ Oxidant	**2a**	Yield[h] **3b** (2 steps)	**4c** (2 steps)
1	-	-	34	-	-
2	K_2CO_3	-	46	-	-
3[b]	-	$NaBH_4$	-	67	-
4[b]	K_2CO_3	$NaBH_4$	-	50	-
5[b]	$BF_3.Et_2O$	$NaBH_4$	-	70	-
6[b]	-	$NaBH(OAc)_3$	-	71	-
7[b]	-	$NaCNBH_3$	-	65	-
8[c]	-	$NaBH(OAc)_3$	-	77	-
9[c]	$BF_3.Et_2O$	$NaBH(OAc)_3$	-	69	-
10[d]	-	PCC	-	-	70
11[e]	-	PCC	-	-	73
12[d]	-	DMP	-	-	n.d.
13[d]	$NaHCO_3$	DMP	-	-	n.d.
14[d]	-	NBS	-	-	n.d.
15[d]	-	NIS	-	-	n.d.
16[d]	-	*m*-CPBA	-	-	n.d.
17[d]	-	DDQ	-	-	n.d.

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18[f]	-	NaClO	-	-	57
19[g]	-	NaClO	-	-	n.d.

[a]Reaction conditions: All reactions were conducted at room temperature without using distilled solvents. Compound **1a/1b/1c** (0.18 mmol) in HFIP (1 mL) was the scale of the reactions for the first step. [b]To the crude mixture of compound **2**, after quenching, reductant (3 equiv) in MeOH (1 mL) was added. [c]$NaBH(OAc)_3$ (3 equiv) was added to the same pot. [d]To the isolated compound **2c** by column chromatography, oxidant (1 equiv) in DCM (1 mL) was added. [e]PCC (2 equiv) was used. [f]Solvent used in second step was AcOH. [g]Solvent used in second step was CH_3CN. [h]Isolated yields. n.d. = not detected.The optimization studies revealed the broad scope of this methodology involving varied substitutions in benzyl (A ring), phenyl (B ring) and N-alkyl groups of the tertiary amines as shown in Scheme 1. Under the optimized conditions (entry 8, Table 1), tertiary amines bearing activating as well as deactivating groups in either of the mono- or di-substituted A ring and para-substituted B ring conveniently converted to dibenzoxazepines **3b**–**3ab** in moderate to good yields. In general, tertiary amines with deactivating groups (halo, nitro) in A ring and ones with activating groups (alkyl, methoxy) in B ring afforded dibenzoxazepines in good yields. For instance, substrate **1c** with nitro substitution in A ring and **1i** with tert-butyl substitution in B ring afforded dibenzoxazepines **3c** and **3i** in 83 and 92% yields, respectively. Accordingly, substrate **1v** with both nitro and tert-butyl substitutions in A and B rings, respectively, afforded dibenzoxazepine **3v** in 87% yield. Meta-substituted B rings afforded a mixture of separable regioisomers **3ac**, **3ac′**–**3ae**, **3ae′** since the nucelophilic attack by OH group is feasible in either of the ortho-positions of the B ring. Dimethoxy substituted B ring offered a single regioisomer **3af**–**3ah**, arising due to electronic reasons. Substrates with N-benzyl substitution afforded dibenzoxazepines **3ai** and **3aj** which serves as a third variable group in the tertiary amine for diversification. However, when the substrate bears an ortho-substitution in the B ring the cyclization did not occur. Presence of a 3,4-(methylenedioxy) group in the B ring produced the desired dibenzoxazepine **3ak** in 40% yield similar to substrates, *vide supra*, with dimethoxy substituted B ring. Compound **3ak** with a tetracyclic framework could be a novel entry in

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the class of tetracyclic antidepressants. Tertiary amine with two benzylic alcohols where one of them containing nitro-substitution did not undergo ring formation and the other with no substitution participated in dibenzoxazepine **3al** formation in 52% yield, confirmed by HMBC analysis of its methylated analog (see Supporting Information). An attempt involving further cyclization using dibenzoxazepine **3al** under the optimized conditions led to seven-membered ring opening to afford the corresponding aldehyde **2al** which upon subsequent reduction reformed dibenzoxazepine **3al**. A successful dibenzoxazepinone **4c** formation by successive PIDA and PCC oxidations from the optimization studies prompted us to further demonstrate the substrate scope of this reaction (Scheme 2). Accordingly, tertiary amines with different substitutions in the A and B rings afforded dibenzoxazepinones **4** in moderate yields.

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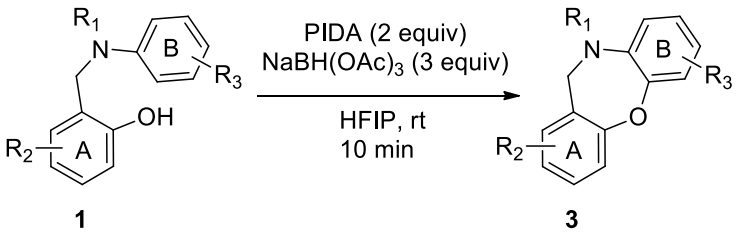
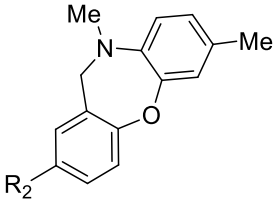
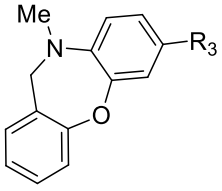
Scheme 1. Substrate scope of dibenzoxazepines



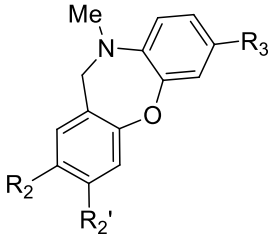
1 **3**



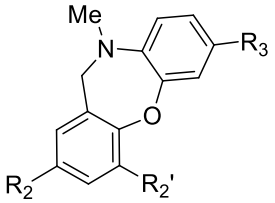
3b (R_2 = H, 77%)
3c (R_2 = NO_2, 83%)
3d (R_2 = Br, 70%)
3e (R_2 = OMe, 24%)



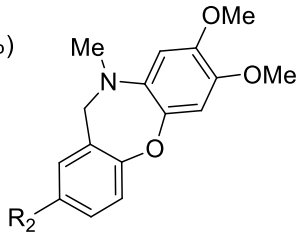
3f (R_3 = H, 59%)
3g (R_3 = OMe, 76%)
3h (R_3 = Et, 80%)
3i (R_3 = *t*-Bu, 92%)
3j (R_3 = Cl, 51%)
3k (R_3 = Br, 64%)



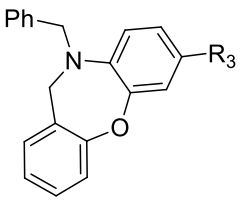
3l (R_2 = Br, R_2' = H, R_3 = Et, 63%)
3m (R_2 = Br, R_2' = H, R_3 = *t*-Bu, 73%)
3n (R_2 = Br, R_2' = H, R_3 = Br, 43%)
3o (R_2 = Cl, R_2' = H, R_3 = Et, 81%)
3p (R_2 = Cl, R_2' = H, R_3 = OMe, 66%)
3q (R_2 = OMe, R_2' = H, R_3 = OMe, 31%)
3r (R_2 = OMe, R_2' = H, R_3 = Et, 39%)
3s (R_2 = H, R_2' = Me, R_3 = Me, 54%)
3t (R_2 = H, R_2' = Me, R_3 = *t*-Bu, 64%)
3u (R_2 = NO_2, R_2' = H, R_3 = Et, 81%)
3v (R_2 = NO_2, R_2' = H, R_3 = *t*-Bu, 87%)
3w (R_2 = NO_2, R_2' = H, R_3 = OMe, 40%)
3x (R_2 = NO_2, R_2' = H, R_3 = Br, 40%)



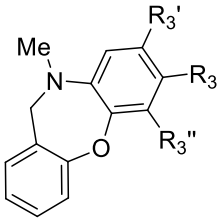
3y (R_2 = Br, R_2' = OMe, R_3 = *t*-Bu, 54%)
3z (R_2 = R_2' = Cl, R_3 = Me, 52%)
3aa (R_2 = R_2' = Cl, R_3 = *t*-Bu, 79%)
3ab (R_2 = R_2' = R_3 = Cl, 47%)



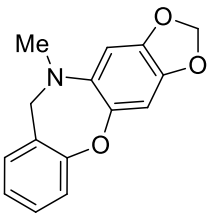
3af (R_2 = H, 43%)
3ag (R_2 = Br, 54%)
3ah (R_2 = NO_2, 44%)



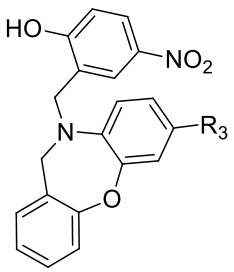
3ai (R_3 = Me, 61%)
3aj (R_3 = OMe, 40%)



3ac (R_3' = Cl, R_3 = F, R_3'' = H, 41%)
3ac' (R_3' = H, R_3 = F, R_3'' = Cl, 23%)
3ad (R_3' = Cl, R_3 = R_3'' = H, 12%)
3ad' (R_3' = R_3 = H, R_3'' = Cl, 33%)
3ae (R_3' = CF_3, R_3 = R_3'' = H, 28%)
3ae' (R_3' = R_3 = H, R_3'' = CF_3, 41%)



3ak (40%)



3al (52%)

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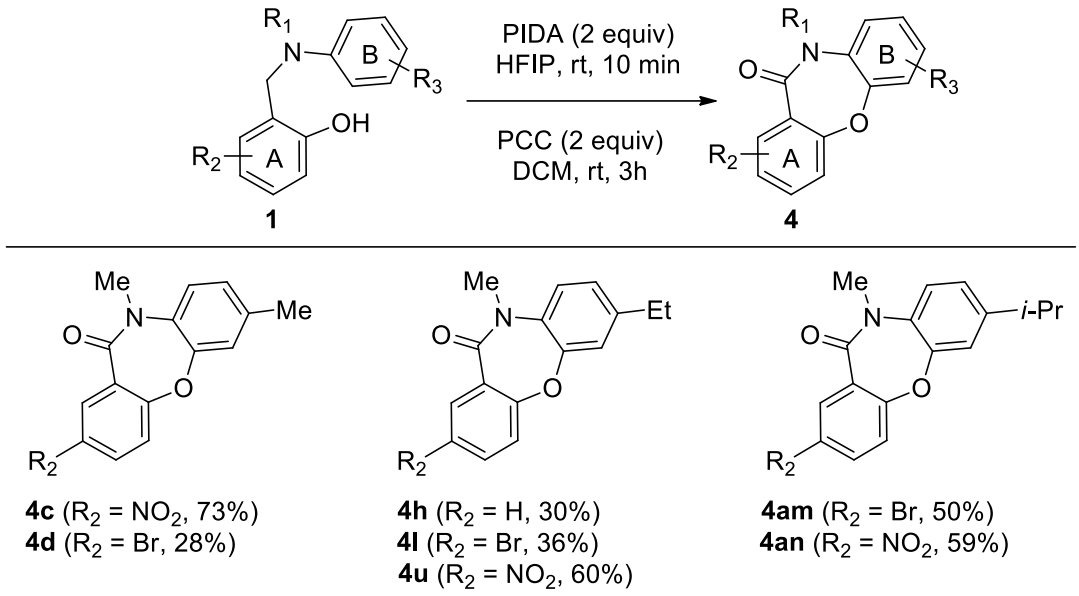
Scheme 2. Substrate scope of dibenzoxazepinones



A plausible mechanism has been proposed similar to activation of tertiary amines in presence of PIDA.[12] Oxidative dearomatization of phenols in presence of PIDA are well documented,[16] however, tertiary amine will be more reactive for the initial ligand exchange with PIDA. Accordingly, reaction of tertiary amine **1** with PIDA affords intermediate **I** (Scheme 3). Nucleophilic attack of the phenoxide on the electro-deficient ortho-carbon of the aniline ring in intermediate **I** is proposed analogous to a nucleophilic attack of the aniline ring on the electron-deficient aromatic carbon atom of the anthranilic ring after PIDA activation.[9] This key seven-membered ring formation accompanied by elimination of phenyl iodide affords intermediate **II** that rearomatizes to provide dibenzoxazepine **3**. It is worth mentioning that stabilization of intermediate **I** by the presence of deactivating groups in A ring and activating groups in B ring promotes formation of dibenzoxazepines in good yields, observed in substrate scope. Usage of one equivalent of PIDA produced a mixture of dibenzoxazepine **3** and diaryl ether **2** along with unreacted tertiary amine **1** as observed over TLC (see Supporting Information). Dibenzoxazepine **3** is further reactive with PIDA due to the presence of tertiary amine. Therefore, a second equivalent of PIDA affords intermediate iminium ion **IV** which is

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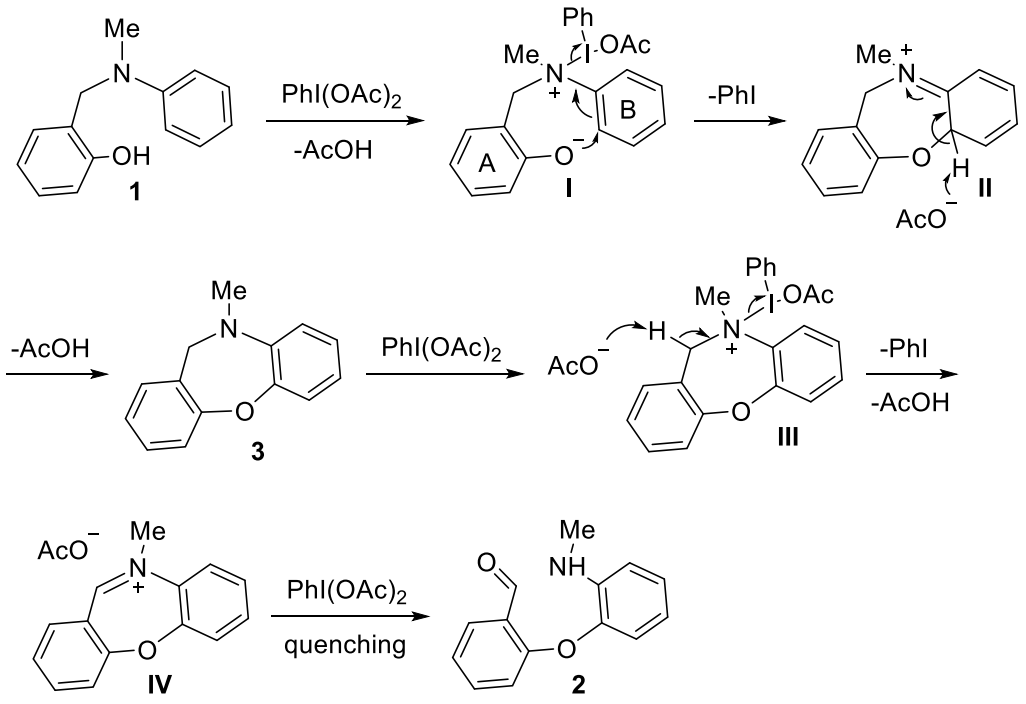
formed by abstraction of benzylic proton from the activated tertiary amine **III**. The reaction mixture was quenched upon complete consumption of the dibenzoxazepine **3** which ensue ring opening of iminium intermediate **IV** to afford diaryl ether **2**. This was again confirmed by the reaction of the dibenzoxazepine **3g** with 1 equiv of PIDA which led to the formation of diaryl ether **2g** in 87% yield (see Supporting Information). In absence of nucleophilic hydroxyl group, the competing benzylic proton abstraction to facilitate iminium ion formation takes place which upon hydrolysis produces benzaldehyde. Indeed formation of 2-methoxy-5-nitrobenzaldehyde was observed from tertiary amine **1c** with methyl protected hydroxyl group (see Supporting Information).

Scheme 3. Plausible mechanistic pathway



In order to further demonstrate the broad applicability of this methodology, an array of synthetic transformations were carried out on diaryl ether **2c** (Scheme 4). Treatment of compound **2c** with *tert*-butylisocyanide afforded a pharmaceutically relevant dibenzoxazepine-11-carboxamide **5**. A facile DDQ mediated oxidation of benzylic carbon afforded diaryl ether **6** flanked by three reactive functionalities. Presence of para-nitro substitution in ether facilitates an intramolecular *ipso*-substiution with secondary amine by

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Smiles rearrangement, interestingly, undertaken in presence of bleach to afford tertiary amine **7** in 85% yield. During this rearrangement, events that take place such as hopping of the hydroxyl group of tertiary amine **1c** from A ring to B ring and benzylic amine transformation to diphenyl amine are otherwise conceived by multi-step synthesis. Furthermore, tertiary amine **7** in presence of Dess-Martin periodinane and *p*-TsOH afforded *para*-benzoquinone **8** and dihydroacridine **9** in 40 and 55% yields, respectively. Structural confirmation of all the products was carried out by extensive 2D NMR analysis (see Supporting Information). A further extension of this methodology to afford dibenzodiazepine **11**, categorized as privileged structure by Evans et al.,[17] was obtained from tertiary amine **10** with an appropriate NHTs substitution.

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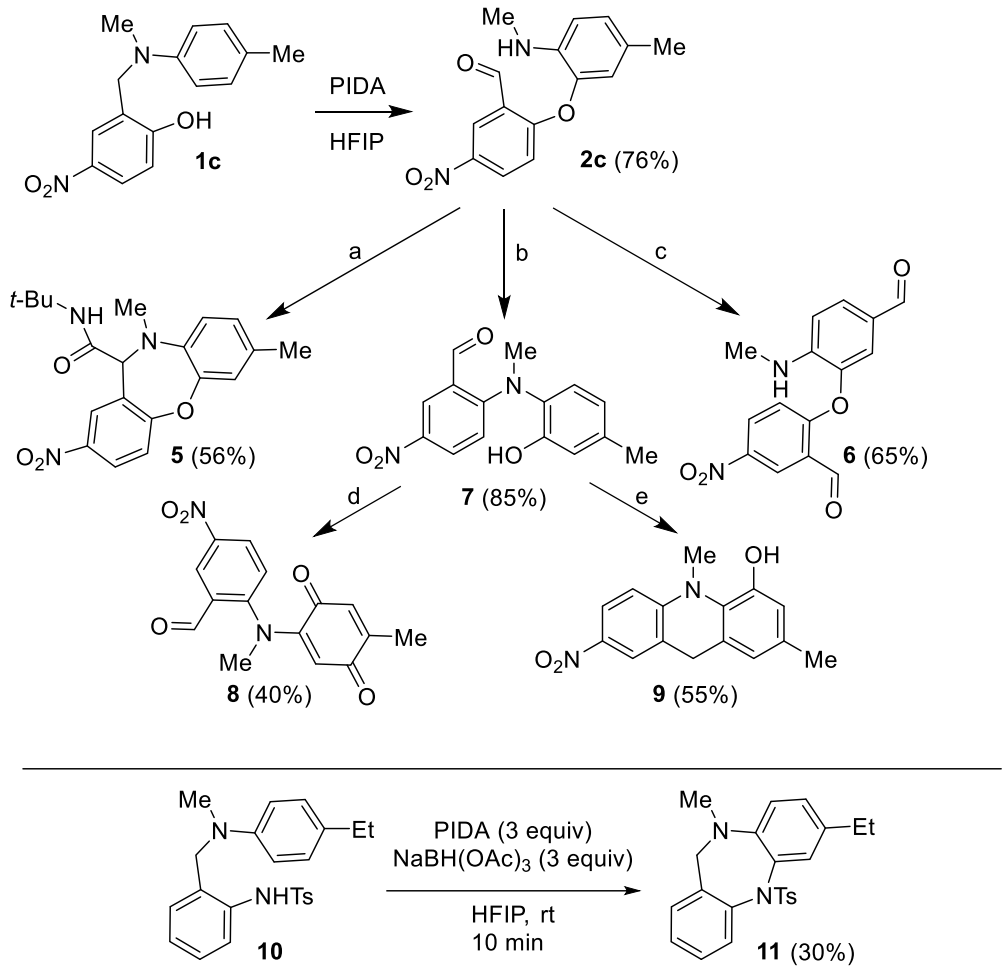
Scheme 4. Demonstration of applicability of methodology



Reaction conditions: (a) **2c** (1 equiv), *t*-BuNC (1 equiv), $InCl_3$ (cat.), MeOH, 60 °C; (b) **2c** (1 equiv), NaClO (2 equiv), 1M NaOH (cat), Bu_4NI (1.5 equiv), DCM, rt; (c) **2c** (1 equiv), AcOH (cat.), DDQ (3 equiv), DCM, rt; (d) **7** (1 equiv), DMP (1.5 equiv), DCM, rt; (e) **7** (1 equiv), *p*-TsOH (cat.), EtOH, 60 °C.

In conclusion, tertiary amines with suitably substituted *ortho*-hydroxybenzyl, phenyl units with varied substituents underwent diaryl ether formation endowed with *ortho*-CHO and secondary amine functionalities in presence of PIDA by *ortho*-C(sp^2)-H functionalization under mild conditions. An intramolecular seven-membered ring formation facilitated by $NaBH(OAc)_3$ and PCC provided dibenzoxazepines and dibenzoxazepinones, respectively. A broad substrate scope for dibenzoxazepine has been demonstrated, in particular,

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substrates with deactivating groups in A ring and activating groups in B ring offered good yields in a one-pot reaction. Furthermore, an array of synthetic transformations to further demonstrate the broad applicability of this methodology was carried out which afforded diverse molecular motifs.

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Keywords: Diaryl etherification • Hypervalent iodine reagent • Dibenzoxazepine • Dibenzoxazepinone • Metal-free • C(sp^2)-H activation/functionalization

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