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Metal Catalyzed Coupling/Carbonylative Cyclizations for Accessing Dibenzodiazepinones: An expedient route to Clozapine and other drugs

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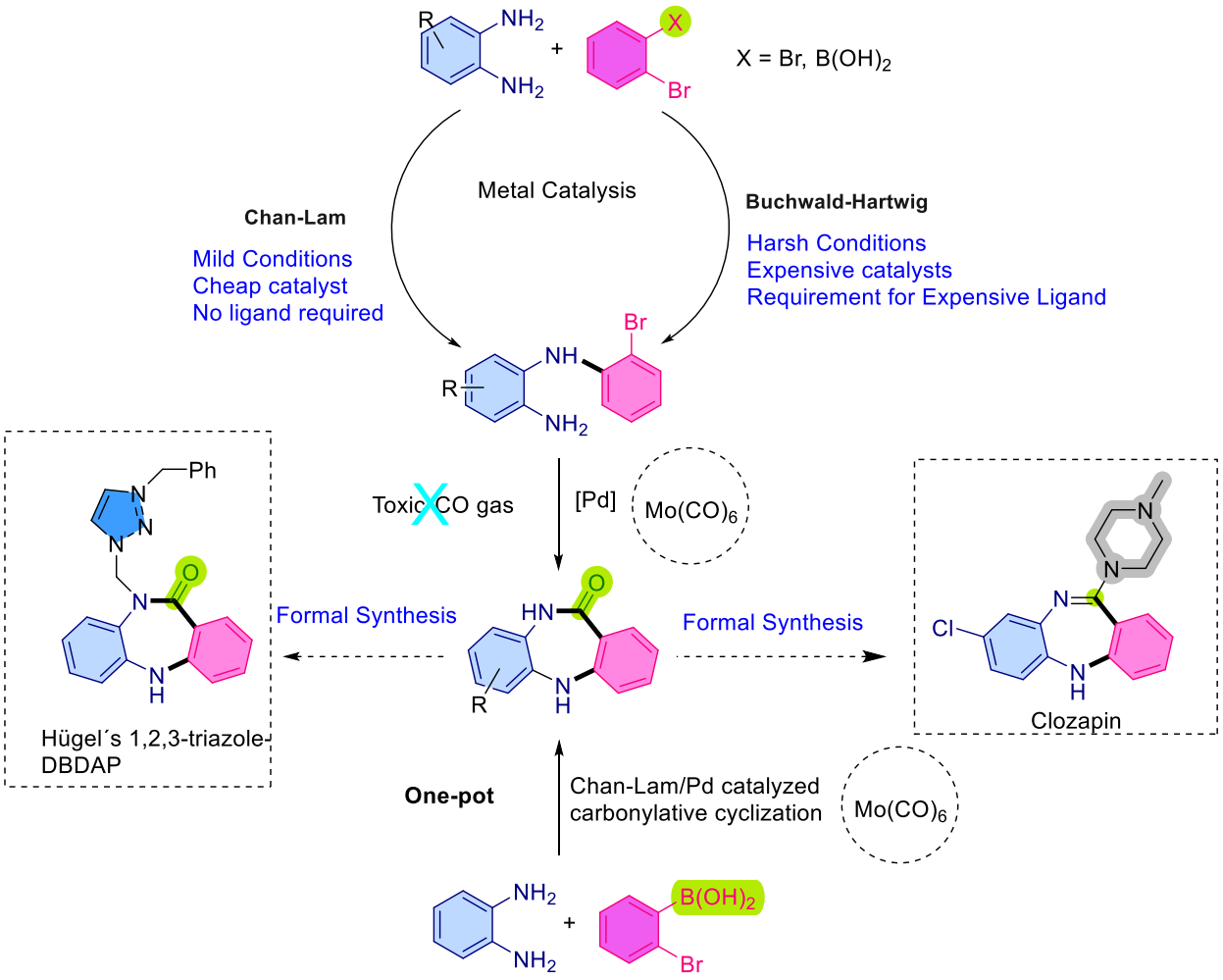
Abstract

A sequential strategy to access 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepinones (DBDAPs) is disclosed in this article through Palladium and Copper catalyzed amination (Buchwald-Hartwig (B-H) or Chan-Lam (C-L)) followed by palladium catalyzed carbonylative cyclization with $Mo(CO)_6$ as CO surrogate (to avoid toxic CO handling) of readily available *o*-pheneylenediamine and either 1,2-dibromobenzene or 2-bromobenzeneboronic acid. 10,11-Dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepinone could be synthezised in good yield using a sequential catalytic procedure, using both C-L and B-H approaches. Gratifingly, the use of the C-L reaction was more impressive, and afforded the dibenzodiazepinones in good yields (up to 45%; 2 steps) and much milder conditions

using copper as the catalyst. The synthetic utility of this novel strategy was showcased by demonstrating a formal synthesis for the anti-psychotic drug clozapine and to an anti-cancer triazole-DBDAP hybrid.



Introduction

Dibenzodiazepines units are without doubt highly privileged structures, endowed with numerous medicinally relevant properties, and notably include anti-anxiolytic and anti-

depressant activities. These scaffolds have received much interest from the medicinal chemist community, which led to the development of several anti-depressant agents such as dibenzepin, sintamil, as well as the well-known medication, clozapine, an FDA-approved atypical anti-psychotic drug, that has been adopted as a treatment of schizophrenia and schizoaffective disorders (**Figure 1**).[1-2] Dibenzodiazepinones were also found to exhibit significant anti-cancer properties,[3] as they were found to effectively inhibit tumor invasion *in vitro*,[4] and induce apoptosis among several cancer cell lines.[5] Additionally, several dibenzodiazepinone based structures were proven to act as p21-activated kinase (PAK) inhibitors,[6] and Chk1 inhibitors.[7] The above mentioned pharmaceutical properties of the dibenzodiazepinone class have driven the development of novel synthetic strategies leading to these scaffolds in a step-economical and greener manner. Our previous review in 2018 focuses on a variety of routes to these compounds.[8]

The well-known Buchwald-Hartwig (B-H) and Chan-Lam (C-L) reactions have proven to be highly useful procedures that allows the step-economical synthesis of diverse biologically relevant heterocycles through C-N bond formation.[9] These approaches resulted in shortening the synthetic routes that were widely employed to access these heterocyclic scaffolds. Over the last decades, the Chan-Lam coupling reaction has drawn great attention among the synthetic chemistry community which contributed to the development of various synthetic routes to relevant heterocycles in high efficiency.[10] The Chan-Lam coupling is considered a greener alternative to traditional C-N coupling, as it can be carried out under mild reaction conditions (room temperature and short reaction time etc,), plus it dosen´t require expensive metals like Pd, being carried out with Cu.

In 2011, Buchwald *et al*. introduced an efficient synthetic strategy to construct diverse dibenzodiazepinones through a sequential methodology consisting of a B-H coupling between *o*-carbonylanilines and 1,2-dihaloarene derivatives providing access to key precursors that undergo a tandem amination-intramolecular cyclization via a cross coupling reaction with NH_3.[11] The reaction was undertaken in the presence of a catalytic amount of palladium catalyst and afforded a library of dibenzodiazepinones structures in good to excellent yields (**Scheme 1a**).

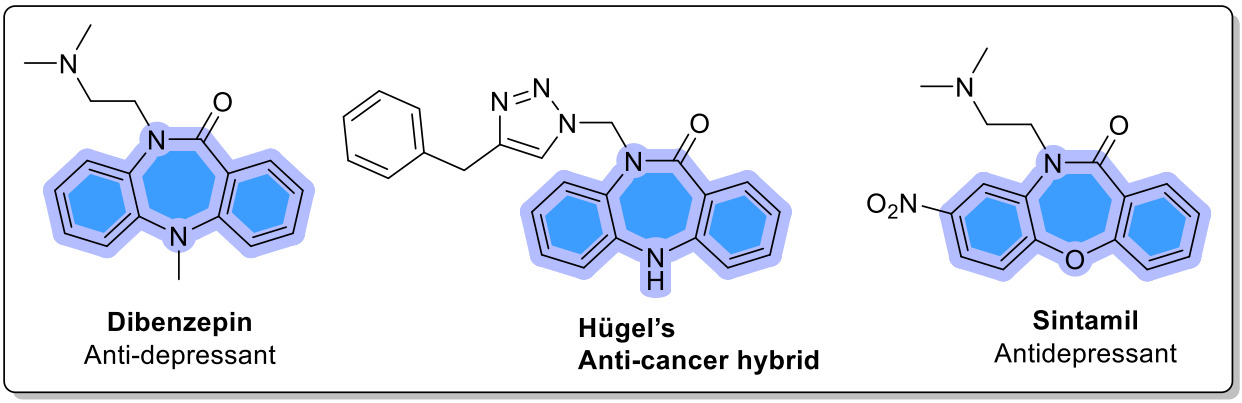
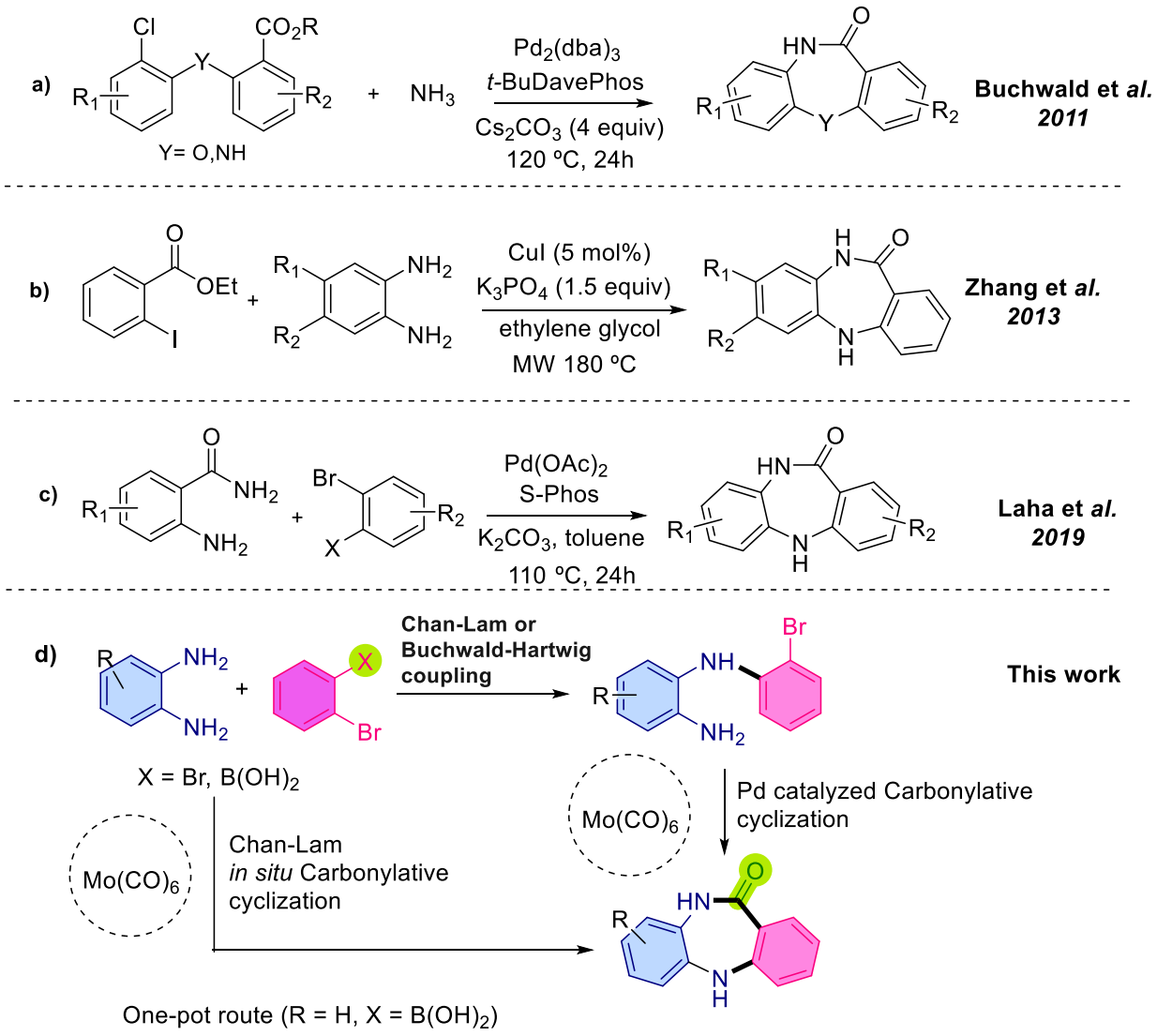


Figure 1 : Biologically active dibenzodiazepinones.

In 2013, Zhang *et al.* developed a synthetic route leading to structurally diverse dibenzodiazepinones via copper catalyzed C-N bond coupling between 2-halobenzoates and *O*-phenylenediamine leading to a key intermediate that will undergo an intramolecular *N*-acylation to afford the afford the corresponding dibenzodiazepinone structure in high yields (**Scheme 1b**).[12] Another innovative strategy was reported by Laha *et al.*, aiming to access dibenzodiazepinone structures via double *N*-arylation of 2-aminobenzamides with 1,2-dihaloarenes using a palladium based catalytic system.[13]

Mechanistic investigations supported the fact that the regioselective *N*-arylation of 2-aminobenzamide occurs first at the amide position. This approach enabled the successful synthesis of a broad spectrum of dibenzodiazepinone units in a one-pot fashion. The synthetic utility of Laha's approached was highlighted by preparing the corresponding dibenzodiazepinone which was further reacted with *N*-methyl piperazine in the presence of $TiCl_4$ to afford Clozapine, an antipsychotic drug.

We now disclose a different but facile approach to access several 10,11-dihydro-5*H*-dibenzo[b,e][1,4]diazepinones, using a sequential Chan-Lam and B-H carbonylative cyclization (d, **Scheme 1**). This approach has not been resported previously (the methods a-c indicated in Scheme 1 have a different route, and none involve either a Chan-Lam or carbonylative cyclization). For the sake of health and safety, and given that our infrastructures did not permit the use of molecular CO, we felt more secure with a suitable suitable surrogate.



Scheme 1: Different synthetic route to DBDAPs (a-c),including our novel approaches (d).

The present approaches enable the formation of two C-N bonds along with a C-C bond and provide a good alternative to previously reported strategies, as it enables the formation of these structures in a multicomponent fashion in the presence of a CO surrogate through the *in situ* formation of an *o*-(2-bromophenyl)aminoaniline intermediate (d **Scheme 1**). It should be noted these target compounds have been of great interest to our group and in 2015, we reported a proposed novel methodology for the synthesis of dibenzodiazepines[14], however, upon later careful review of the product structure it was revealed that the purported dibenzodiazepine products were, in fact, diarylimines, which

resulted from nucleophilic addition of the aniline reagents to the aldimine substrates, followed by elimination of an tosylamine product. This was one of the principle driving forces for the development of the work discussed in this report.

Results and Discussion

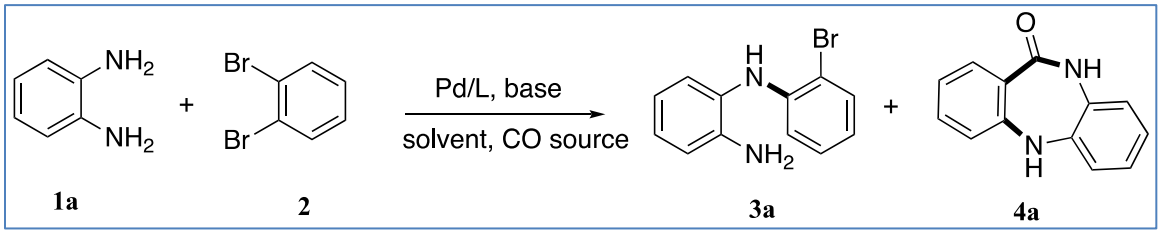
I – Synthesis of *o*-(2-bromophenyl)aminoaniline via Buchwald-Hartwig C-N coupling.

I.1 – *One-Pot* Synthesis of Dibenzodiazepinones

Our preliminary attempt to synthesize DBDAPs via B-H amination and/carbonylation was carried out in the presence of *O*-phenylenediamine (**1**) and 1,2-dibromobenzene (**2**) as model reactant using $Pd(OAc)_2$ in combination with *t*-BuXPhos (2-Di-*t*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl) (5 mol%), and Et_3N (2.5 equiv.) as base in DMF. In this case, the DMF served as the CO surrogate, as it was disclosed that DMF, the reaction solvent, could act as a potential carbon monoxide surrogate under certain circumstances, notably, in metal catalyzed amino carbonylation procedures.[15-16] Unfortunately, no DBDAP was obtained, we only observed the formation of intermediate (**3**) in 25% yield (**entry 1, Table 1**). Next, the same procedure was carried out in the presence of molybdenum hexacarbonyl ($Mo(CO)_6$) (2 equiv.) as CO surrogate, under the previous conditions, but again we only observed the formation of intermediate (**3**) in 21% yield (**entry 2, Table 1**). Changing the ligand to triphenyphosphine, didn't provide any improvement of the reaction outcome as only traces of the intermediate (**3**) were obtained (**entry 3, Table 1**). Switching to DBU as base under these conditions, gave intermediate (**3**) in 35% yield (**entry 4, Table 1**). The reaction was then screened using two different bidentate ligands; XPhos and XantPhos and, using the previous reaction conditions, however, we only obtained traces of intermediate (**3**) (**entries 5 and 6, Table 1**). A slight improvement of the yield of the intermediate (**3**) was obtained when using DBU in dioxane, which was obtained in 42%, but only traces of the target DBDAP was observed (**entry 7, Table 1**). The difficulty encountered in the formation of DBDAP, prompted us to test alternative CO surrogates. The reaction was then performed using $Co_2(CO)_8$ (0.3 eq) in the presence of DBU, the intermediate (**3**) was obtained 35% yield, in the absence of the DBDAP (**4)** (**entry 8, Table 1**). Formic acid an effective CO surrogate[16-17], was also

screened. The reaction was carried out in the presence of acetic anhydride (Ac_2O) as an activator, unfortunately, no DBDAP was obtained (**entry 9, Table 1**).

Table 1 : Exolorative study of the sequential Buchwald-Hartwig amination/Pd-Catalyzed carbonylative cyclization leading to DBDAPs.



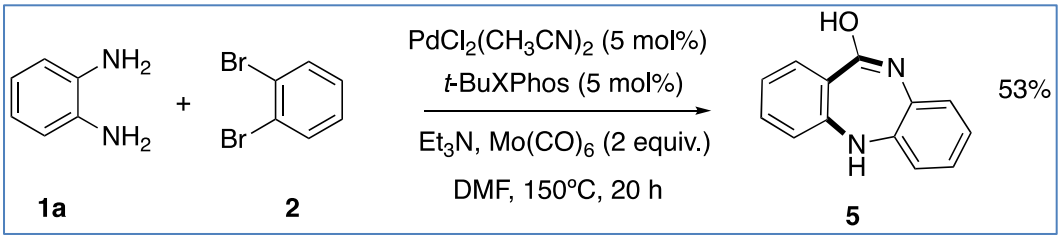
1a 2 3a 4a

Entry	Cat (%mol)	Ligand	CO	Base	Solvent	3[a]	4[a]
1	$Pd(OAc)_2$ (5)	*t*BuXPhos	-	Et_3N	DMF	25%	0
2	$Pd(OAc)_2$ (5)	*t*BuXPhos	$Mo(CO)_6$	Et_3N	DMF	21 %	0
3	$Pd(OAc)_2$ (5)	PPh_3	$Mo(CO)_6$	Et_3N	DMF	Trace	0
4	$Pd(OAc)_2$ (5)	*t*BuXPhos	$Mo(CO)_6$	DBU	DMF	35%	0
5	$Pd(OAc)_2$ (5)	XPhos	$Mo(CO)_6$	Et_3N	DMF	Traces	0
6	$Pd(OAc)_2$ (5)	XantPhos	$Mo(CO)_6$	Et_3N	DMF	Traces	0
7[b]	$Pd(OAc)_2$ (5)	*t*BuXPhos	$Mo(CO)_6$	DBU	Dioxane	42%	Traces

8[b]	$Pd(OAc)_2$ (5)	*t*BuXPhos	$Co_2(CO)_8$	DBU	DMF	35%	-
9[b]	$Pd(OAc)_2$ (5)	*t*BuXPhos	HCOOH/Ac_2O	Et_3N	DMF	-	-

Reaction conditions: o-Phenylenediamine **(1)** (0.46 mmol), dibromobenzene **(2)** (0.46 mmol), Base (2.5 equiv.), CO surrogate ($Mo(CO)_6$ and other CO surrogate (2 equiv.) or $Co_2(CO)_8$ (0.3 equiv.)), solvent (5 mL), 130 ºC, 20h. [a] Isolated yields. [b] the reaction was carried out during 24h [c] The reaction was carried out at 100 ºC.

When we undertook the B-H amination/carbonylative cyclization of *o*-phenylenediamine (**1a**) with 1,2-dibromobenzene (**2**) in the presence of 5 mol% of $PdCl_2(CH_3CN)_2$ and 5 mol% of *t*-BuXPhos in the presence of Et_3N (2.5 equiv.) and $Mo(CO)_6$ in DMF at 150ºC, surprisingly this afforded the 5*H*-dibenzo[b,e][1,4]diazepin-11-ol (**5**), the tautomer of DBDAP (**4a**) in 54% (**Scheme 2**). We attempted to convert this to the keto form (**4a**) using TFA to shift the equilibrium towards the dibenzodiazepinone (**4a**) but this proved to be futile under these conditions, as only the iminol (**5**) structure was observed.



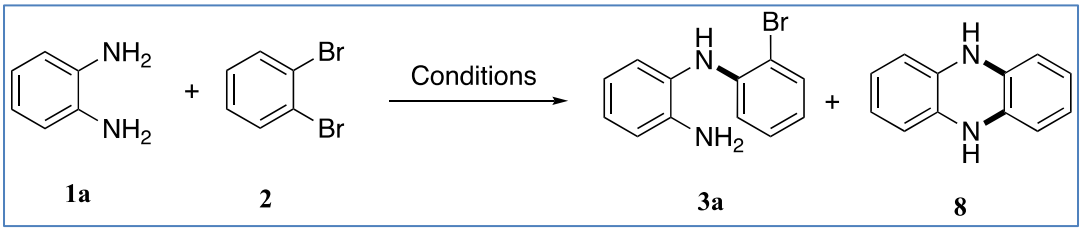
Scheme 2 : One-pot synthesis of 5*H*-dibenzo[b,e][1,4]diazepin-11-ol (**5**).

I.2 – Attempt at accessing dibenzodiazepinone via step-wise synthesis

Due to the difficulty encountered in the one-step synthesis of DBDAPs, we embarked on an in-depth study of the B-H coupling/carbonylative cyclization in a step-wise fashion. Our first attempt was conducted using the previous conditions, which led to the desired compound **(3)** in 15% yield **(entry 1, Table 2**). Changing the ligand to PPh_3 under the same conditions (**entry 2, table 2**) resulted in pooer results, as only traces of the desired compound **(3)** were observed. Then, we considered XPhos (**entry 3, Table 2**), and the

bidendate ligands XantPhos and DPEPhos (**entries 4 and 5**, **Table 2**), but no improvements were observed. Then, we considered testing an alternative palladium source, namely Pd_2dba_3, but again only traces of the compound **(3)** were observed **(entry 6, Table 2**). Next, we considered increasing the $Pd(OAc)_2$ catalyst loading to 10 mol% and the *t*-BuXphos ligand to 15 mol% in the presence of DBU and DMF, under these conditions, the intermediate **(3)** was obtained in 15 % yield along with the undesired phenazine **(8)** side product in 5% yield, produced by a further C-N bond coupling (**entry 7, Table 2**). We decided to decrease the amount of base and time, but little improvement was observed (**entry 8, Table 2**). Given the well-established role of the base on the B-H coupling, we considered exploring alternative bases. We conducted the reaction in the presence of the previously disclosed catalytic system, upon using *t*-BuOK **(3)** was obtained in 22% yield (**entry 9, Table 2**). Conducting the reaction in the presence of Cs_2CO_3 in DMF, failed to provide any improvement (**entry 10, Table 2**). Replacing the DMF by dioxane as solvent in the presence of DBU led to a significant improvement in the yield of the reaction, as the intermediate **(3)** could be obtained in 40% yield, along with the phenazine **(8)** in 48% (**entry 11, Table 2**). Next, we considered other ligands such as XPhos and DPEPhos, in the presence of Cs_2CO_3 as base in dioxane, however the undesired phenazine product **(8)** could still be obtained in moderate yield under these conditions (**entries 12 and 13, Table 2**). In the presence of SPhos ligand, Cs_2CO_3 and toluene as solvent, the desired intermediate **(3)** was obtained in 20% along with the phenazine **(8)** in a yield of 55% (**entries 14, Table 2**). Although, toluene was also shown to be a good solvent for this B-H coupling reaction, we were unable to prevent the double B-H reaction from occurring leading to the phenazine **(8)**, even when shortening the reaction time to 1h.

Table 2 : Influence of the catalytic system, base, and solvent combination on the outcome of the Buchwald-Hartwig reaction.



Entry	Cat (mol%)	Ligand	Base	Solvent	Time	3[a]	8[a]
1	$Pd(OAc)_2$ (5)	*t*BuXPhos	Et_3N	DMF	10h	15	-
2	$Pd(OAc)_2$ (5)	PPh_3	Et_3N	DMF	10h	-	-
3	$Pd(OAc)_2$ (5)	XPhos	Et_3N	DMF	10h	-	-
4	$Pd(OAc)_2$ (5)	XantPhos	Et_3N	DMF	10h	-	-
5	$Pd(OAc)_2$ (5)	DPEPhos	Et_3N	DMF	10h	-	-
6	Pd_2dba_3 (5)	*t*BuXPhos	DBU	DMF	24h	Traces	-
7	$Pd(OAc)_2$ (10)	*t*BuXPhos	DBU	DMF	24h	15	5
8[b]	$Pd(OAc)_2$ (10)	*t*BuXPhos	DBU	DMF	10h	10	-
9[b]	$Pd(OAc)_2$ (10)	*t*BuXPhos	*t*-BuOK	DMF	24h	22	-
10[b]	$Pd(OAc)_2$ (10)	*t*BuXPhos	Cs_2CO_3	DMF	24h	Traces	-
11[b]	$Pd(OAc)_2$ (10)	*t*BuXPhos	DBU	Dioxane	24h	40	48
12[b]	$Pd(OAc)_2$ (10)	XPhos	Cs_2CO_3	Dioxane	10h	45	39
13[c]	$Pd(OAc)_2$ (10)	DPEPhos	Cs_2CO_3	Dioxane	10h	35	30
14[c]	$Pd(OAc)_2$ (10)	SPhos	Cs_2CO_3	Toluene	10h	20	55

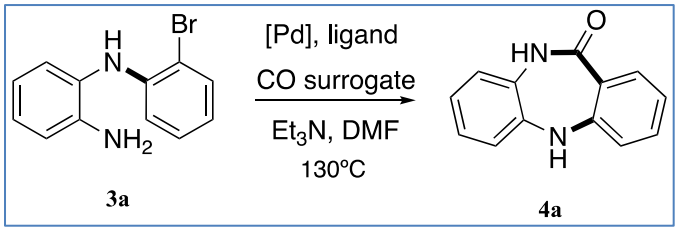
Reaction conditions: o-Phenylene diamine (**1**) (0.46 mmol), dibromobenzene (**2**) (0.05 mmol), base (2.5 equiv.), DMF (5 mL), 110ºC, 24h. *o*-(2-bromophenyl)aminoaniline (**3**) and 5,10-dihydrophenazine (**8**) products were detected by TLC and ^{1}H-NMR, yields determined after product isolation. [a] Isolated yields [b] 1.5 equivalents of base were used. [c]1.2 equivalents of base were used.

Interestingly we noticed that in the initial one-pot reactions indicated in Table 1, the yields of the diarylamine **(3)** were better when $Mo(CO)_6$, was present (**Entry 4, Table 1**) as when it was absent (**Entry 7, table 3**). This might be due to: (a) the CO surrogate inhibiting the formation of the unwanted phenazine **(8)** side-product, and/or (b) the $Mo(CO)_6$, acts as a cocatalyst. An investigative study was thus undertaken to elucidate the effect of the

molybdenum reagent on the reaction using a simple model system consisting of aniline and bromobenzene (See: Figure S.I, and Table s.I, Supporting information). In this study the model system that consisted of aniline and *o*-bromobezene were used. The reaction was monitored over a 90 min period and contrary to what what was originally believed the reaction without the Mo reagent gave better results during the first 90 mins. Some of the reasons for this result are given in the supporting information.

After uncovering the optimum conditions to access *o*-(2-bromophenyl)aminoaniline via the B-H coupling reaction, it was decided to explore the carbonylative intramolecular cyclization of the intermediate (**3)** using different catalytic systems. To elucidate the role of the palladium catalyst in this process, we carried out the initial attempt under metal free-conditions using molybdemum hexacarbonyl $Mo(CO)_6$ as CO surrogate, in the presence of Et_3N in DMF. The reaction was performed at 130 ºC, as we believe that high temperature will promote the cyclization of the sterically hindered intermediate **(3)**, but no DBDAP was achieved under these conditions (**entry 1, Table 4**). Next, $Pd(OAc)_2$ was employed under ligand free conditions, but again the desired DBDAP product **(4)** could not be attained (**entry 2, Table 3**). Then, we performed the reaction in the presence of *t*-BuXPhos as ligand, in this case, only traces of the DBDAP (4) was obtained (**entry 3, Table 3**). When the reaction was carried out in the presence of DPEPhos (**entry 4, Table 3**), we were delighted to obtain the final dibenzodiazepine in 80% yield. Then, we considered screening another bidentate ligand XantPhos, which led to the obtention of the desired product **(4)** in an excellent yield of 90% (**entry 5, Table 3**). This result implied that diphosphine ligands were essential for the success of this reaction. The reactivity of Co_2CO_8 as CO surrogate was also explored, in this case the reaction afforded the DBDAP product in 55% yield (**entry 6, Table 3**). The molybdenum hexacarbonyl $Mo(CO)_6$, has shown to be powerful CO surrogate in this carbonylative intramolecular cyclization. The efficacy of $Mo(CO)_6$ is due to the energetically favorable dissociation of $Mo(CO)_n$ into $Mo(CO)_{n-1}$ which was proven to be a highly exothermic reaction in the presence of metal catalysts especially after the dissociation of the first CO group. Considering these aspects, we proposed a mechanism for this palladium catalyzed intramolecular cyclization.

Table 3 : The intramolecular catalytic carbonylative cyclization conditions for *o*-(2-bromophenyl)aminoaniline.



Entry	Catalytic system	CO surrogate	Yield (4a)[a] (Overall 2-steps)
1	None	$Mo(CO)_6$	-
2	$Pd(OAc)_2$	$Mo(CO)_6$	-
3	$Pd(OAc)_2$/tBuXPhos	$Mo(CO)_6$	Traces
4	$Pd(OAc)_2$/DPEPhos	$Mo(CO)_6$	80% (44%)
5	$Pd(OAc)_2$/XantPhos	$Mo(CO)_6$	90% (50%)
6	$Pd(OAc)_2$/XantPhos	Co_2CO_8	55% (30%)

Reaction conditions: o-(2-bromophenyl)aminoaniline **(3)** (0.46 mmol), $Pd(OAc)_2$ (10 mol%), ligand (30 mol%, $Mo(CO)_6$ (1 equiv.), Et_3N (1 equiv.) DMF (5 mL), 130 ºC, 20h. The reaction was monitored by TLC. [a] Isolated yields.

It should be noted that the best oveall yield for the synthesis of **(4a)** using the step-wise approach was 50% (Table 3).

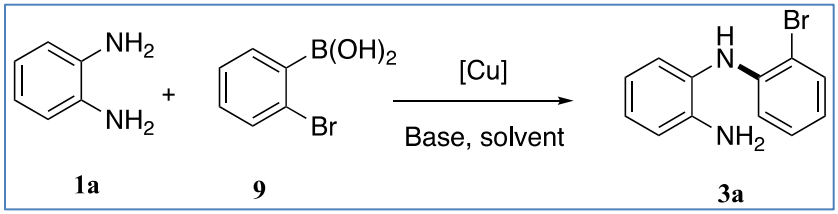
II – Synthesis of dibenzodiazepinones via Chan-Lam amination/carbonylative coupling

II.1– Synthesis of *O*-(2-bromophenyl)aminoaniline via Chan-Lam C-N coupling

Inspired by the previously independently reported work by Chan[18] and Lam[19] and co-workers, we considered performing the reaction of *o*-phenylene diamine (**1**) with 2-bromobenzene boronic acid (**9**) in the presence of $Cu(OAc)_2$, Et_3N as base in DCM at 50 ºC (**entry 1, Table 4**), and gratifingly under these conditions, the reaction afforded

compound **(3**) in 48% yield. These Chan-Lam couplings were undertaken under an aerobic atmosphere which is an environmentally benign oxidant. Further screening using dioxane as solvent resulted in an increase in the yield to 55%, whilst DMF gave access to **(3)** in a lower yield (30%) (**entry 2 and 3, Table 4**). Next, we considered testing the performance of copper iodide (CuI) (20 mol%) as catalyst, in the presence of Et_3N both in dioxane and DMF, these conditions resulted in the obtainment of the desired compound **(3)** in 59% and 35% yields, respectively (**entries 4 and 5, Table 4**). Increasing the reaction temperature to 100 ºC resulted in a reduction of the reaction yield due to degradations (**entry 6, Table 4**). Then, we considered decreasing the amount of CuI to 10 mol% which led to a decrease of the reaction yield to 31% (**entry 7, Table 4**). Other bases; dimethylaminopyridine (DMAP) and diisopropylethyl amine (DIPEA) were tested under the previous reaction conditions but failed to improve the yield. In the presence of DMAP, no sign of the compound was detected, while with DIPEA, **(3)** was obtained in 19% yield (**entries 8 and 9, table 4**). Then, we tested $CuSO_4.5H_2O$, in the presence of Et_3N as a base in two different solvents DCM and dioxane, both gave the desired compounds in good yields of 60% and 50%, resepectively (**entries 10 and 11, Table 4**).

Table 4 : Optimisation of the Cham-Lam coupling conditions between *o*-phenylenediamine and 2-bromophenylboronic acid.



Entry	Copper source	Base	Solvent	3[a]
1	$Cu(OAc)_2$	Et_3N	DCM	48%
2	$Cu(OAc)_2$	Et_3N	Dioxane	55%
3	$Cu(OAc)_2$	Et_3N	DMF	30%

4	CuI	Et_3N	Dioxane	59%
5	CuI	Et_3N	DMF	35%
6[b]	CuI	Et_3N	DMF	23%
7[c]	CuI	Et_3N	DMF	31%
8	CuI	DMAP	DMF	ND
9	CuI	DIPEA	DMF	19%
10	$CuSO_4.5H_2O$	Et_3N	Dioxane	60%
11	$CuSO_4.5H_2O$	Et_3N	DCM	50%

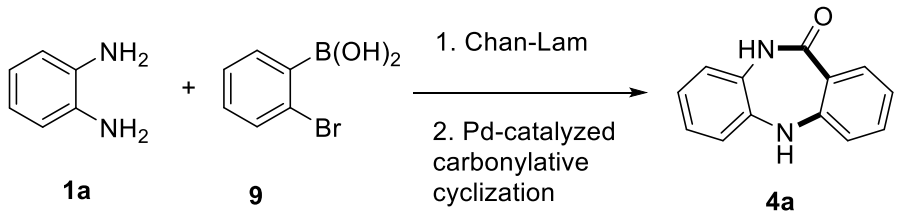
Reaction conditions: o-phenylene diamine **(1)** (0.46 mmol), 2-bromobenzene boronic acid (0.46 mmol) **(9)** (1 equiv.), copper catalyst (20 mol%), base (1.5 equiv.), (5 mL) solvent 50 ºC 1-2 hours. The reaction was monitored by TLC. [a] Isolated yield [b] Reaction performed at 100ºC. [c] 10 mol% CuI were used. ND Not detected.

II.2 – Accessing the scope of the *one-pot* Chan-Lam/Pd catalyzed carbonylative cyclization

Once the above mentioned conditions were obtained, we undertook a screening of the Chan-Lam/carbonylative synthesis of the DBDA in a one-pot manner. In the first reaction, *o*-phenylene diamine **(1)** and bromobenzene boronic acid **(9)** were reacted in a pressure flask under an inert atmosphere using copper iodide (CuI) as copper catalyst, Et_3N and $Mo(CO)_6$ as CO surrogate in the presence of $Pd(OAc)_2$/XantPhos as catalytic system for the carbonylative intramolecular cyclization, these conditions led to the obtainment of the compound **(4a)** in 45% yield (**entry 1, Table 5**). Using dioxane as solvent, in the presence of the same catalytic system, afforded the desired structure **(4a)** in moderate yield (37%) (**entry 2, Table 5**). Changing the ligand to DPEPhos resulted in a slight increase of the yield of **(4a)**, which was obtained in 40% (**entry 3, Table 5**). When the catalytic system $PdCl_2(NCCH_3)$/DPEPhos was employed, **(4a)** was accessed in a lower yield of 18% (**entry 4, table 5**). Under these reaction conditions, copper bromide was shown to be a good catalyst for this transformation, as it allowed the production of **(4a)** in 40% yield (**entry 5, table 5**). Then, we considered testing the performance of a different copper

source $Cu(OAc)_2$ under these reaction conditions using DMF and dioxane as solvents, in these cases, the final compound **(4a)** was obtained in 38% and 41% yield, respectively (**entries 6 and 7, table 5**). Next, we evaluated the performance of $CuSO_4.5H_2O$ in dioxane and DMF but lower yields were obtained (**entries 8 and 9, table 5**). With the optimized conditions in hand, we tested the one pot Chan-Lam intramolecular cyclization with several other *o*-phenyldiamine derivatives, however, several impurities were obtained. In the hope of obtaining better yields (best obtained with the one pot method = 41%) we looked at the step-wise synthesis.

Table 5: Substrate scope of the one-pot synthesis of dibenzodiazepine using via Chan-Lam coupling/Carbonylative intramolecular cyclization.



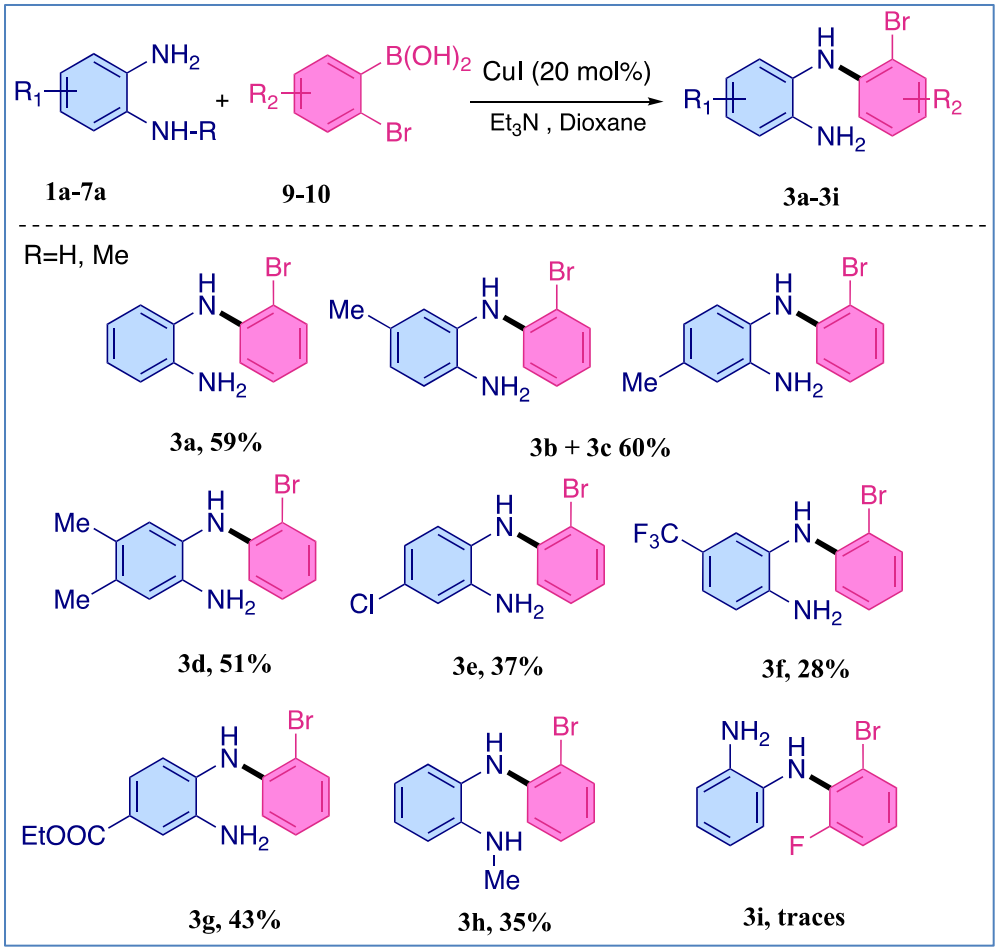
1a **9** **4a**

Entry	Copper source	Base	Solvent	Pd/ligand	4a[a]
1	CuI	Et_3N	DMF	$Pd(OAc)_2$/XantPhos	45%
2	CuI	Et_3N	Dioxane	$Pd(OAc)_2$/XantPhos	37%
3	CuI	Et_3N	DMF	$Pd(OAc)_2$/DPEPhos	40%
4	CuI	Et_3N	DMF	$PdCl_2(NCCH_3)_2$ / *XantPhos*	18%
5	CuBr	Et_3N	DMF	$Pd(OAc)_2$/Xantphos	40%
6	$Cu(OAc)_2$	Et_3N	DMF	$Pd(OAc)_2$/DPEPhos	38%
7	$Cu(OAc)_2$	Et_3N	Dioxane	$Pd(OAc)_2$/DPEPhos	41%
8	$CuSO_4.5H_2O$	Et_3N	Dioxane	$Pd(OAc)_2$/DPEPhos	18%
9	$CuSO_4.5H_2O$	Et_3N	DMF	$Pd(OAc)_2$/DPEPhos	Traces

Reaction conditions: o-Phenylene diamine (**1**) (0.5 mmol) (**9**) (0.5 mmol), Cu-catalyst (20 mol %), base (0.6 mmol), solvent (5 mL), 50 ºC, 1 h. Pd-catalytic system (5 mol%), $Mo(CO)_6$ (0.5 mmol) and base (0.5 mmol), 130 °C. [a] Isolated yields.

II.3. Synthesis of 5,10-dihydro-11*H*-dibenzo[b,e][1,4] diazepin-11-ones via a stepwise Chan-Lam/ carbonylative cyclization

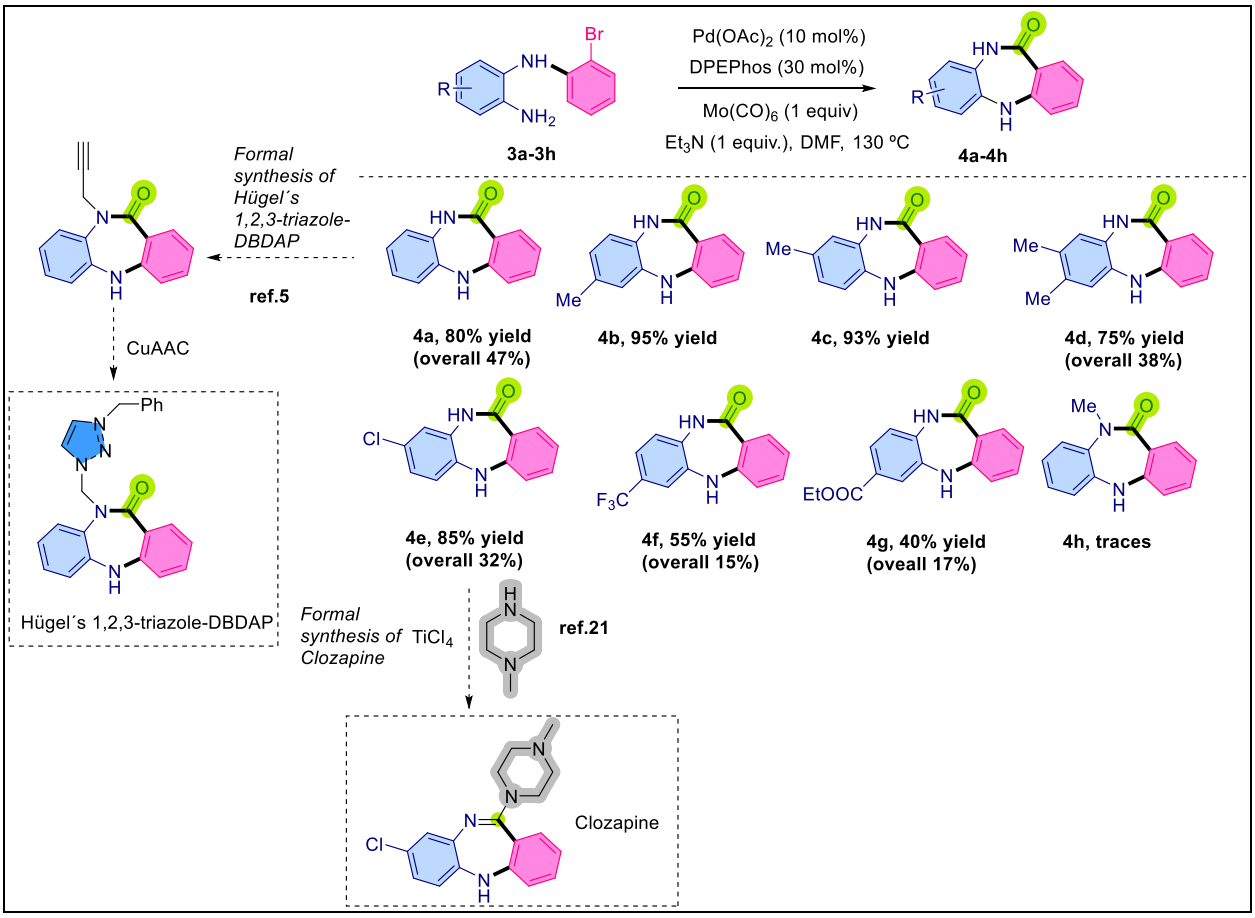
After disclosing the optimal conditions for the Chan-Lam coupling, we screened different varieties of *o*-phenylene diamine derivatives. Overall, the *o*-phenynelene substrates bearing electron-donating substituent on the benzene ring proceeded smoothly under these conditions and led to the desired structures in moderate to good yields (**Scheme 3**). The reactions were generally regioselective, except in the case of 4-methyl-*o*-phenylenediamine **(2a)** and *o*-bromophenyl boronic acid which gave a mixture of **(3b)** and **(3c)** in 60% yield (the ratio could not be determined). These were eventually separated and used in the cyclization step discussed below. The dimethyl *o*-phenylene amine **(3a)**, gave the desired compound **(3d)** in 51% yield. A slight decrease in yield was observed in the presence of the ester (COOEt) substituent, which furnished compound **(3g)** in 43% yield. Lower yields were observed in the case of electron-withdrawing substituents such as Cl and CF_3 group, which afforded the compounds **(3e)** and **(3f)** in 37% and 28% yields, respectively. The *N*-methylated precursor **(3h)** was also tolerated by this system and afforded the desired compound **(3h)** in 35% yield. The 2-bromo-6-fluorophenylboronic acid **(10)** only afforded the corresponding product **(3i)** in trace amounts.



Scheme 3 : Scope of the Chan-Lam coupling between *o*-phenylene diamines and 2-bromobenzene boronic acids.

With the *o*-(2-bromophenyl)aminoaniline derivatives in hand, we conducted the carbonylative intramolecular cyclization according to the previously disclosed conditions, in order to access the DBDAP structures. The unsubstituted DBDAP structure **(4a)** was obtained in 80% under these conditions (**Scheme 4**). The methyl substituted *o*-(2-bromophenyl)aminoanilines **(3)** obtained via Chan-Lam coupling could be efficiently separated and was subjected to the intramolecular carbonylative cyclization to yield the DBDAPs **(4b)** and **(4c)** in excellent yields of 93% and 95%, respectively. The dimethyl DBDAP **(4d)** could also be efficiently obtained under these conditions in 75% yield. The chloro substituted DBDAP **(4e)**, which is intermediate to the antipsychotic drug, clozapine, could also be obtained in good yield (this represented a formal synthesis to clozapine[20], if the procedure of Rao[21] is used, which entails heating **(4e)** with 1-methylpiperizine and

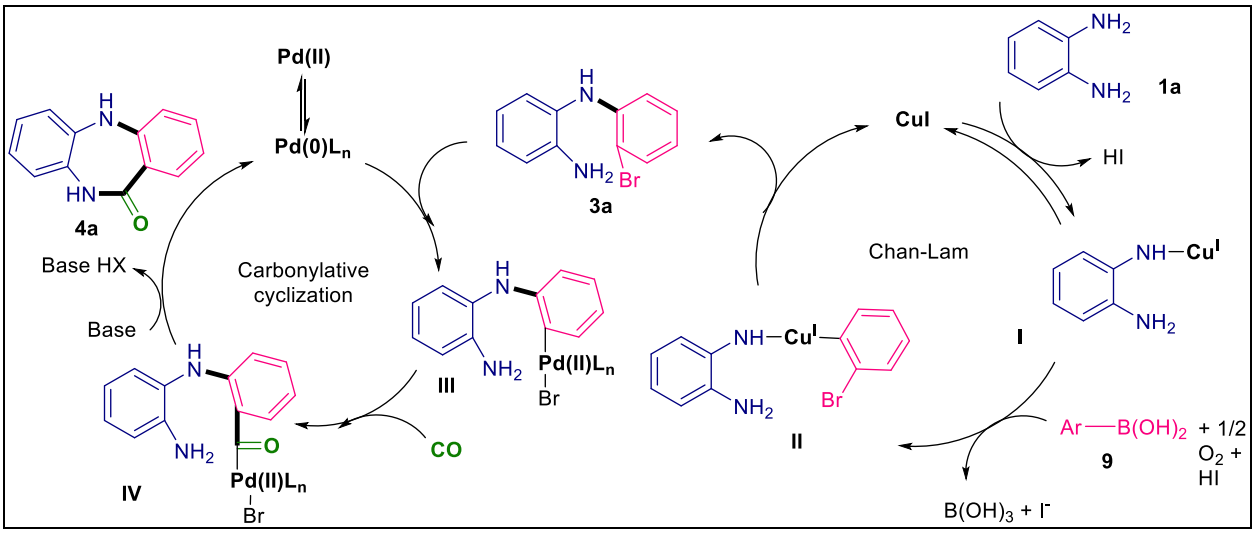
Ti(IV)Cl_4, Scheme 4). Also (**4a**) can be transformed to Hügel´s 1,2,3-triazole-DBDAP using the methodology described in their report (Scheme 5).[5] The CF_3 and COOEt substituted DBDA **(4f)** and **(4g)** were obtained with a slightly decreased yield of 55% and 40%, respectively. The *N*-methyl dibenzodiazepine **(4h)** could be accessed, but only in trace quantity. It should be noted that both the stepwise approach was slightly better than the one-pot approach in the case of the synthesis **(4a)** (47% Vs 41%).



Scheme 4 : Scope of the synthesis of DBDAPs.

Our mechanistic proposal is based on the information in previous reports by the groups of Bose[22], Watson[23] and Stahl[24]. Mechanistically, under basic condition, the reaction is triggered by copper catalyzed activation of *o*-phenylene diamine **(1a)**, followed by the oxygen promoted insertion of the phenylboronic acid coupling partner **(9)** to deliver intermediate **(II)** that undergoes reductive elimination to give diarylamine **(3a)** along with

regeneration of the copper catalyst (**Scheme 6**). Then, a palladium promoted oxidative addition of the C-Br bond takes places to deliver palladium species **(III)**. Then insertion of CO that is released by $Mo(CO)_6$, should afford intermediate **(IV)** that undergoes a base promoted intramolecular cyclization via nucleophilic attack of the amine.[25] Finally, the dibenzodiazepinone **(4a)** would be obtained through reduction elimination of the palladium catalyst.



Scheme 6 : Proposed mechanism.

Conclusions

In summary, we have reported two one-pot pathways and two step-wise pathways to access dibenzodiazepinone (DBDAP) derivatives via copper catalyzed Chan-Lam amination/carbonylative cyclization and Buchwald-Hartwig amination/carbonylative cyclization and their step-wise counterparts. Although the one-pot method worked for one example in both cases (but in one case it gave the DBDAP enol form), it failed to work for other substrates, and for that reason we had to rely on the step-wise approach. The more efficient method to access the diamine intermediate **(3)** was via the Chan-Lam amination (milder conditions, cheaper, earth-abundant catalyst, no expensive ligand requirement) as the Buchwald-Hartwig amination required harsher conditions and an expensive metal catalyst, and also gave an unwanted phenazine side product. The sequential stepwise

Chan-Lam amination/carbonylative cyclization afforded a number of DBDAP products, showing good functional group tolerance and giving the final products in good yields. In terms of overall best efficiency, it also would appear that the step-wise Chan-Lam/Pd catalyzed carbonylative cyclization was slightly better than the one-pot method. The most important of which was the cloro containing DBDAP (**4e**) that can be used to synthesize the antipsychotic drug clozapine (see above), a triazole-hybrid with anti-cancer properties, and can easily be used as the key part in the synthesis of other drugs like dibenzepine and biologically active natural products such as BU-4664L. We are currently looking at this methodology to access some of these targets, including the agrochemical boscalid.

Experimental

Synthesis of *o*-(2-bromophenyl)aminoaniline (3a)

Via Buchwald-Hartwig coupling: *o*-phenylene diamine (1) (0.05g, 1 equiv., 0.46 mmol) was added to a Radleys reaction tube (a Radleys® 12 position carousel reactor station was used) under N_2 and dissolved in dry Dioxane (5 mL). Next, (0.055 mL, 0.46 mmol) of 1,2- dibromobenzene (2) was added to the reaction mixture, followed by the addition of $Pd(OAc)_2$ (0.01g, 0.046 mmol), XPhos (0.032g, 0.069 mmol), and Cs_2CO_3 (0.18 g, 0.05 mol). The resulting reaction mixture was allowed to stir at 100ºC. The reaction was left stirring for several hours, followed by TLC. After consumption of the starting material (verified through TLC). The reaction was allowed to cool down, and was filtered through a celite pad to remove the residual catalyst and base. The solvent was then evaportated under reduced pressure and the crude was purified by flash chromatography (Hexane/AcOEt) (9/1), to yield the *O*-(2-bromophenyl)aminoaniline (3) compound as a purple oil (0.057g, 47% yield).

Via Chan-Lam coupling: *o*-Phenylene diamine (1) (0.05g, 1 equiv., 0.46 mmol) was added to a round bottom flask and dissolved in dry Dioxane (5 mL). Next, (0.092g, 1 equiv.,0.46 mmol) of 2-bromophenyl)boronic acid (9) was added, followed by the addition of Et_3N (0.07 mL, 0.055 mmol), and molecular sieves 3Å. The reaction was left

stirring at room temperature for several hours, and monitored by TLC. After consumption of the starting material (verified through TLC). The reaction mixture was filtered through a celite pad to remove the residual catalyst and base. The solvent was then evaporated under reduced pressure and the crude was purified by flash chromatography (Hexane/AcOEt) (9/1), to yield the *O*-(2-bromophenyl)aminoaniline (3a) compound as a purple oil (0.07g, 59% yield).^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.00 (s, NH_2, 2H), 5.76 (s, NH, 1H), 6.59-6.61 (d, *J*= 8Hz,Ar, 1H), 6.65-6.69 (t, *J*= 8Hz, Ar, 1H), 6.79-6-83 (t, *J*= 8Hz, Ar, 1H), 6.85-6.87 (d, *J*= 8Hz,Ar, 1H), 7.09-7.13 (m, Ar, 3H), 7.49-7.51 (d, *J*= 8Hz, Ar, 1H).^{13}C NMR ($CDCl_3$, 100 MHz) δ: 110.42, 114.41, 116.47, 119.48, 119.70, 127.00, 127.04, 128.39, 132.62, 142.45, 143.03. HRMS (ESI): m/z [M + H^+] calculated for $C_{12}H_{11}BrN_2$: 263,0184; Found: 263.0178.

Synthesis of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one (4a)

o-(2-Bromophenyl)aminoaniline (3a) (0.05g, 0.19 mmol) was added to a Radley's® 12 position carousel reactor tube to which DMF, then $Pd(OAc)_2$ (4.26 mg, 0.019 mmol), DPEPhos (30 mg, 0.057 mmol), $Mo(CO)_6$ (50 mg, 1 equiv., 0.19 mmol), and Et_3N (0.026 mL, 0.19 mmol) were added. The reaction mixture was then stirred at 130 ºC under a nitrogen atmosphere. After completion of the reaction, as determined by TLC, the reaction mixture was allowed to cool to room temperature. The mixture was filtered through a pad of celite and washed with DCM, then the solvent was evaporated under reduced pressure to give a crude mixture. Further purification by flash chromatography (Hexane/AcOEt) (1/1), gave the desired compound 5,10-dihydro-11*H*-dibenzo[b,e][1,4]diazepin-11-one (4a) as a yellow solid yield (0.032 g, 80 %). M.p.: 249-251 ºC 1H NMR (DMSO-d6, 400 MHz) δ: 6.87-7.00 (m, Ar, 6H), 7.31-7.35 (t, J=8Hz, Ar, 1H),7.66-7.68 (d, J=8Hz, Ar,1H), 7.81 (s, Ar, 1H), 9.85 (s, Ar, 1H).13C NMR (CDCl3, 100 MHz) δ:119.52, 120.23, 121.17, 121.73, 123.24, 123.40, 124.95,130.29, 132.56, 133.67, 140.43, 150.92, 168.40. MS (ESI) m/z: 221.12 [M+H+].

Supporting Information

All experimental procedures and spectral data (NMR, mass spectra) are included in this file, including key kinetic studies.

Acknowledgements

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