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Enhancing Reactivity and Selectivity of Aryl Bromides: A Complementary Approach to Dibenzo[*b,f*]azepine Derivatives

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Abstract: Dihydrodibenzo[*b,f*]azepines and dibenzo[*b,f*]azepines can be efficiently synthesized from aryl bromides, *o*-bromoanilines and norbornene or norbornadiene by means of palladium catalysis. This protocol gives access to dibenzo[*b,f*]azepine core containing a variety of electron-withdrawing substituents on both aromatic rings and complements the previously reported methodology where electron rich aryl iodides were preferentially used. The presence of KI, even in sub-stoichiometric amount, is crucial for this three-component reaction. The proper addition of iodide anions has a dramatic effect on reaction rate and selectivity. A formal three-step synthesis of the tricyclic antidepressant Clomipramine (Anafranil®) is also described.

Introduction

7-Membered nitrogen heterocycles represent an important class of molecules mainly because of their relevance in medicinal chemistry. In particular, 5*H*-dibenzo[*b*,*f*]azepines are attractive targets for synthetic chemists due to their remarkable biological activities.[1] In fact, the 5*H*-dibenzo[*b*,*f*]azepine scaffold can be found in pharmaceutically important structures such as carbamazepine, oxcarbazepine and clomipramine, widely used as antiepileptic and anti-anxiety drugs.[1] Molecules containing dibenz[*b*,*f*]azepine nucleus display also antioxidant,[2] antiviral,[3] antimicrobial,[4] antimalarial[5] and anticancer[6] activities. Moreover, the same tricyclic skeleton is present in chiral bidentate ligands,[7] electroluminescent[8] and photoelectric[9] materials. The 10,11-dihydrodibenzo[*b,f*]azepine framework has traditionally been synthesised through cyclization of *o*,*o'*-diaminobibenzyls, which can be dehydrogenated to iminostilbene, for many years considered to be the key intermediate for the production of oxcarbazepine and carbamazepine.[1a] Environmental and toxicological drawbacks prompted Novartis to develop a new protocol to specifically produce oxcarbazepine.[10] None of these methods are convenient for the synthesis of tailor-made functionalized structures with different steric and electronic properties. In this view, an interesting synthesis of fluorinated dibenzoazepines, based on a ring expansion reaction starting from isatine, indole and acridine derivatives, has been reported by Stachulski and coworkers.[11] The directed remote metalation (DreM) strategy was exploited by Snieckus et al. in the development of an efficient and regioselective route to dibenzo[*b*,*f*]azepinones.[12] In general, the use of transition-metal catalysts guarantees wide generality and high functional group tolerance even in the construction of seven-membered nitrogen heterocycles.[13] In this framework, Buchwald[13f] and Lautens[13a,b] reported versatile Pd- and Pd/Rh-catalyzed methods respectively, starting from *ortho*-vinyl haloaryls and *ortho*-substituted anilines. Moreover, transition-metal catalyzed C-H activation strategy can unlock novel and favorable synthetic methodology to access the dibenzoazepine scaffold.[13h] As an example, the synthesis of oxcarbazepine (Trileptal), was successfully accomplished by means of palladium-catalyzed intermolecular *α*-arylation of a ketone as the key step, from commercially available 2'-aminoacetophenone and 1,2-dibromobenzene. However, the very limited scope once more prevented the preparation of analogues.

In recent years, our research group has disclosed new routes to functionalized five, six and seven-membered fused N-heterocyclic compounds by means of the palladium/norbornene system, which allows sequential *ortho* C-H activation and double *ortho* and *ipso* functionalization of aryl halides.[14] This singular methodology, named Catellani reaction, has been widely studied

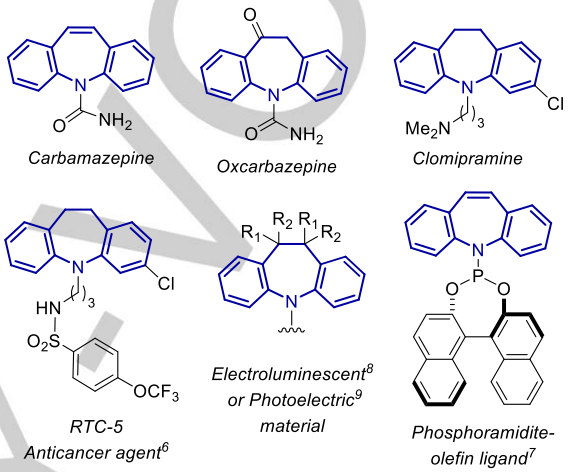

Figure 1. Dihydrodibenzo[*b,f*]azepine motif in therapeutic agents, advanced materials and metal ligands.

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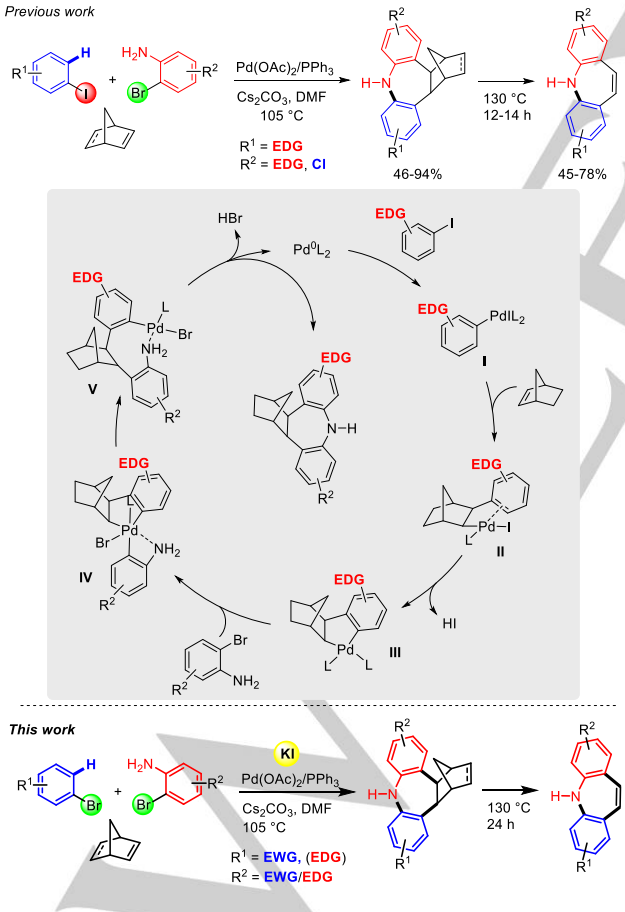
by us[15] and other research groups[16] who have significantly contributed to increasing its generality and applicability. In particular, we reported the one-pot synthesis of 10,11-dihydrodibenzo[*b,f*]azepine and dibenzo[*b,f*]azepine derivatives through palladium catalysis from aryl iodides, 2-bromoanilines and norbornene/norbornadiene.[14d] This process combines the advantage of a C-H activation-based synthesis of the hardly accessible dibenzo[*b,f*]azepine nucleus, with those deriving from the use of an inexpensive ligand, such as triphenylphosphine, available starting materials and mild reaction conditions (Scheme 1, *previous work*). The reaction pathway, proposed on the basis of previous experimental studies and DFT calculations,[14d, 17] is shown in Scheme 1. Oxidative addition of an aryl iodide to Pd^0L_2 affords the well-known complex **I** and is followed by norbornene insertion leading to *cis,exo*-arylnorbornylpalladium intermediate **II**.[18] For steric reasons this species is prevented from undergoing β-H elimination and in the presence of a base readily forms palladacycle **III** through activation of the C–H bond in *ortho* position. Subsequent oxidative addition of *o*-bromoaniline to **III** generates complex **IV** with the assistance of the chelating NH_2 group, which then favors the Csp^2–Csp^3 coupling delivering complex **V**. Intramolecular Buchwald-Hartwig reductive elimination to form the C-N bond from **V** provides dibenzoazepine product **3** and concomitantly regenerates the catalytically active Pd(0) species. This protocol is applicable to various substrates and leads to diversely functionalized dibenzoazepines in satisfactory to good yields. However, aryl iodides activated by electron-withdrawing substituents (EWG) are rather little tolerated, mainly because of their high reactivity, thereby preventing or limiting the formation of the products expected. Here we report a palladium-catalyzed complementary approach to EWG-substituted 5H-dibenzo[*b,f*]azepines from aryl bromides, *o*-bromoanilines and norbornene/norbornadiene (Scheme 1, *this work*). The presence of iodide anions is crucial to the enhancement of reactivity and selectivity of the reaction, allowing the synthesis of dibenzoazepines decorated with electron withdrawing groups on both aromatic rings, largely widening the previous reaction scope.



Scheme 1. Catellani-type complementary approaches to substituted dibenzo[*b,f*]azepines.

Results and Discussion

Preliminary studies began with the reaction involving 3-trifluoromethyliodobenzene, *o*-bromoaniline and norbornene as the reactants, carried out under the previous standard conditions (Table 1, entry 1).[14d] After 24 h, the dibenzoazepine **3a** expected was obtained in 4% yield only (NMR yield), together with a large amount of methanotriphenylene-type isomers **4a** and **4a'** in 4:1 molar ratio (73% total yield). This result is representative of the high reactivity of EWG-substituted aryl iodides compared with 2-bromoanilines under these reaction conditions (see Supporting Information for details). To prevent this reactivity mismatch, we then resorted to aryl bromides in place of the corresponding iodides. However, the same reaction carried out using 3-trifluoromethylbromobenzene led to a very poor yield of the desired dibenzoazepine **3a** (Table 1, entry 2). Higher temperatures or longer reaction times gave worse results. Conversion of the starting materials was quite limited (less than 10%), so several palladium precursors were then tested. PdI_2 was the most active one among them (27%, Table 1, entry 3), and more importantly, only traces of compounds **4a**/**4a'** were detected. Dibenzoazepine **3a** was produced in 36% yield by adding an extra source of iodide anions (Table 1, entry 4). As the amount of KI was doubled (0.5 equiv), the yield of **3a** reached 42% (Table 1, entry 5). Unexpectedly, when we carried out the reaction using $Pd(OAc)_2$ in conjunction with KI (0.5 equiv), yield of the desired compound **3a** further increased to 60% at 70% 2-bromoaniline conversion (Table 1, entry 6). Prolonging the reaction time to 64 h allowed total conversion of the starting materials, achieving 83% yield of **3a** (Table 1, entry 7). A significant reduction in the reaction rate was observed when the concentration of iodide anions was raised (Table 1, entry 8), suggesting that an optimal compromise needs to be found for each substrate. Other iodide salts were found to affect the reaction rate. In particular, NaI, used in the same concentration, was slightly less effective (Table 1, entry 9), while NBu_4I proved to be almost completely inactive (Table 1, entry 10), as well as inorganic bromides (Table 1, entries 11 and 12).

Having identified the optimal conditions above (Table 1, entry 7), we examined the scope of the reaction by

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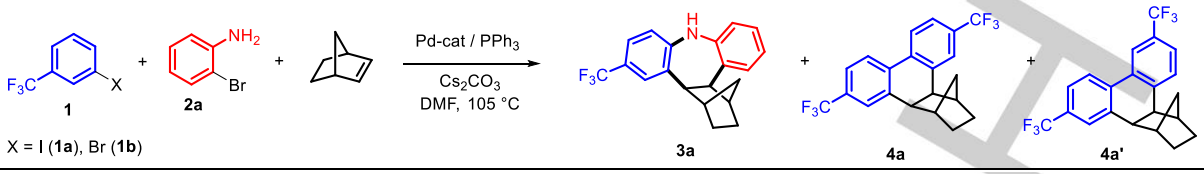
Table 1. Pd-catalyzed synthesis of dibenzoazepine **3a** from 3-trifluoromethylhalobenzenes, 2-bromoaniline and norbornene.[a]



Entry	1	Pd source	Halide salt (equiv)	Time (h)	Conv.[b] (%) 1a	Conv.[b] (%) 2a	Yield[c] (%) 3a	Yield[c] (%) 4a/4a'
1	**1a**	$Pd(OAc)_2$	-	24	100	13	4	73(67)[d]
2	**1b**	$Pd(OAc)_2$	-	40	10	10	5	-
3	**1b**	PdI_2	-	40	33	31	27	traces
4	**1b**	PdI_2	KI (0.25)	40	42	40	36	traces
5	**1b**	PdI_2	KI (0.50)	40	52	49	42	2
6	**1b**	$Pd(OAc)_2$	KI (0.50)	40	73	70	60	3
7	**1b**	**$Pd(OAc)_2$**	**KI (0.50)**	**64**	**100**	**95**	**83(80)[d]**	**4**
8	**1b**	$Pd(OAc)_2$	KI (1.00)	64	63	58	46	2
9	**1b**	$Pd(OAc)_2$	NaI (0.50)	64	81	76	62	3
10	**1b**	$Pd(OAc)_2$	NBu_4I (0.50)	64	32	29	14	-
11	**1b**	$Pd(OAc)_2$	KBr (0.50)	64	20	18	11	-
12	**1b**	$Pd(OAc)_2$	NaBr (0.50)	64	16	14	8	-

[a] Reaction conditions: **1** (0.48 mmol, 1.1 equiv), **2a** (0.44 mmol, 1.0 equiv), norbornene (0.53 mmol, 1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), Cs_2CO_3 (1 mmol, 2.25 equiv), in DMF (10 mL) under N_2 at 105 °C. [b] Determined by GC analysis. [c] Yields were determined via ^1H NMR analysis with the internal standard method. [d] Isolated yield in brackets.

reacting electron-poor aryl bromides with 2-bromoanilines and norbornene (Table 2). Aryl bromides bearing electron-withdrawing substituents in *ortho*, *meta* or *para* position in combination with 2-bromoaniline and norbornene gave the corresponding dibenzoazepines **3** in good to excellent yields. The effect of KI was marked in all the examples examined. Various functional groups were tolerated, including CF_3 (products **3a**, **3b** and **3c**), Cl (products **3d**, **3e** and **3f**), CO_2Me (products **3g** and **3h**), Br (products **3i** and **3j**) and F (product **3k**), providing handles for further product diversification. Noteworthily, substituents in *meta* position on the starting aryl bromide led to better yields of **3** (**3a**, **3d** and **3g**). 2-Bromoanilines bearing an electron-donating or an electron-withdrawing group were found to be suitable substrates, providing the desired products **3l** and **3m** in good to excellent yields (Table 2).

The 5H-dibenzoazepine scaffold can be more interesting from a synthetic point of view,[1-9] so we proceeded to examine the reaction using norbornadiene in place of norbornene, with the aim of accessing the valuable 5H-dibenzo[*b,f*]azepines by triggering a sequential *retro*-Diels-Alder. Norbornadiene is more reactive than norbornene and the reaction conditions found for the latter are not often suitable for the former.[14d] Indeed, further optimization work was carried out (see Supporting Information for details) and this allowed us to develop a specific protocol for the synthesis of 5*H*-dibenzo*[b,f]*azepine derivatives. The optimal amount of KI was the same used for the norbornene procedure (0.5 equiv), while 2 equiv of norbornadiene were necessary to ensure satisfactory to good yields. As previously demonstrated,[14d] the final *retro*-Diels Alder step generally occur when smoothly increasing the reaction temperature to 130 °C (see Experimental section). The reaction scope was then examined and the results are reported in Table 3. Gratifyingly, aryl bromides bearing electron-withdrawing groups readily react with electron-rich and electron-poor 2-bromoanilines and norbornadiene, providing satisfactory to good yields of the 7-membered ring derivatives. A wide variety of functional groups can be successfully employed on both aromatic rings, such as Cl, F, NO_2, CF_3 and CN. Substituents *ortho* to NH group (located at the C(8)- and C(10)-positions) are normally not allowed, probably for steric reasons. Notably, this one-pot transformation gives access to symmetrical compounds, such as **5g**, useful for enantioselective applications.[7] Halogenated dibenzoazepines with reduced ADRs (Adverse Drug Reactions), can be readily prepared in a one-pot fashion (products **5c-h**).[19] Other electron-withdrawing functional groups, such as CO_2R (R = Me, Et, *t*Bu), can be effectively employed on starting arylbromides **1** and **2**. It is worth noting that in the absence of KI, compounds **5i–5k** and **5n** with an ester group on the aniline moiety, were not obtained at all. In particular, compounds **5j** and **5n**, precursor of promising imipramine analogous with increased bioselectivity properties,[20] can now be obtained in 56 and 35% yield, respectively, through a one-pot reaction from commercially available and readily prepared starting materials.

The methodology described can also be applied to electron-rich aryl bromides **1** with satisfactory results (Table 4). 10,11-Dihydrodibenzo[*b,f*]azepines **3o-s**[14d], previously prepared from aryl iodides (red yields), are now accessible from the corresponding bromides, sometimes with improved yields (**3n** and **3p**). Noteworthily, yields of compounds **3n** and **3o** remained

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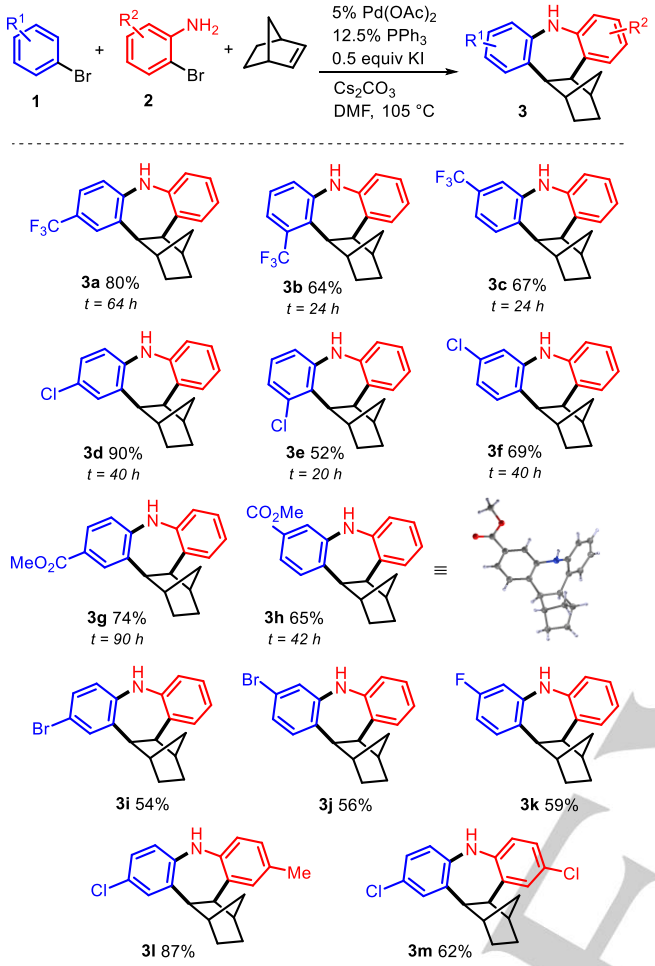
Table 2. Scope of the Pd-catalyzed synthesis of dihydrodibenzoazepines **3** from electron-poor aryl bromides, 2-bromoanilines and norbornene.[a,b]



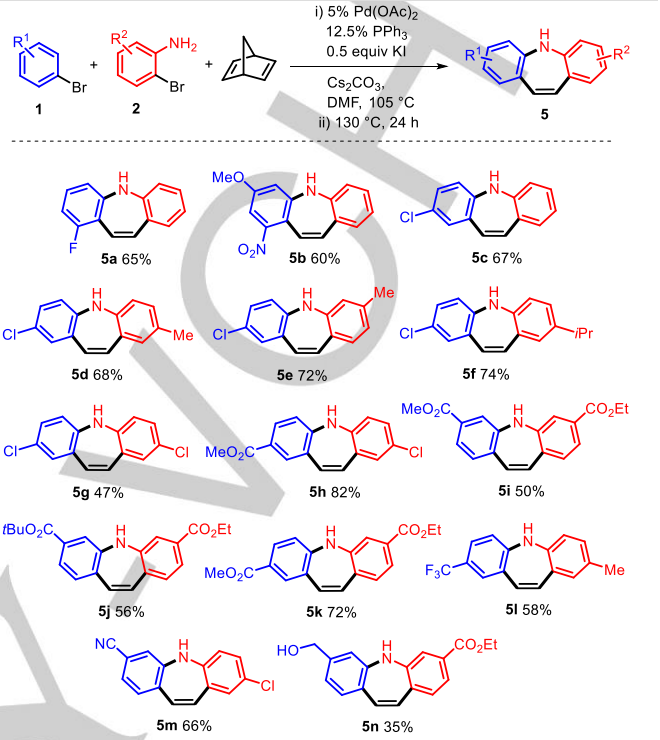
[a] Reaction conditions: **1** (1.1 equiv), **2** (0.44 mmol, 1.0 equiv), norbornene (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), KI (0.5 equiv), Cs_2CO_3 (2.25 equiv), in DMF (10 mL) under N_2 at 105 °C. [b] Isolated yield.

unchanged in the presence of KI (80/78% for **3n** and 51/51% for **3o**), while the reaction time was remarkably reduced (18 vs 48 h for **3n** and 18 vs 42 h for **3o**).

The synthetic utility of this protocol was further demonstrated with the formal synthesis of Clomipramine®, prepared in three steps starting from commercial reagents (Scheme 2). Readily available 4-bromochlorobenzene, 2-bromoaniline and norbornadiene were subjected to the standard reaction conditions to afford the desired 3-chloro-5*H*-dibenzo[b,f]azepine **5o** in 65% yield, which was readily converted to the corresponding 10,11-dihydrocompound **6o** in 95% yield *via* a facile reduction of the conjugated double bond through the versatile Mg/MeOH procedure.[21] The desired Clomipramine can be finally obtained by a conventional alkylation procedure employing 3-chloro-N,N-dimethylpropan-1-amine.[22]

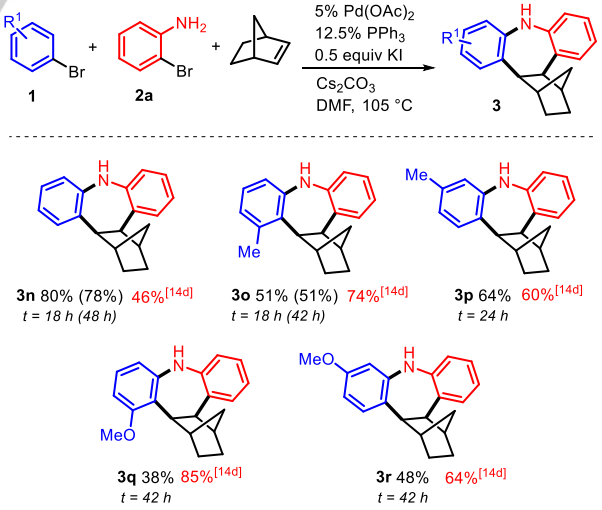
The present cascade sequence leads to several intriguing questions, for example, the singular inertia of this reaction system and the remarkable accelerating effect exerted by iodide anions.

Table 3. Scope of the Pd-catalyzed synthesis of 5H-dibenzoazepines **5** from electron-poor aryl bromides, 2-bromoanilines and norbornadiene.[a,b]



[a] Reaction conditions: **1** (1.1 equiv), **2** (0.44 mmol, 1.0 equiv), norbornadiene (2.0 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), KI (0.5 equiv), Cs_2CO_3 (2.25 equiv), in DMF (10 mL) under N_2 at 105 °C for 46-90 h and at 130 °C for 24 h. [b] Isolated yield.

Table 4. Pd-catalyzed synthesis of 5H-dibenzoazepines **3** from electron-rich aryl bromides, 2-bromoanilines and norbornene.[a,b]



[a] Reaction conditions: **1** (1.1 equiv), **2** (0.44 mmol, 1.0 equiv), norbornene (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), KI (0.5 equiv), Cs_2CO_3 (2.25 equiv), in DMF (10 mL) under N_2 at 105 °C. [b] Isolated yield.

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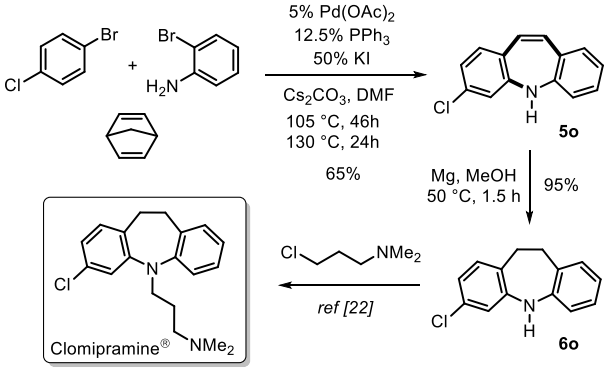
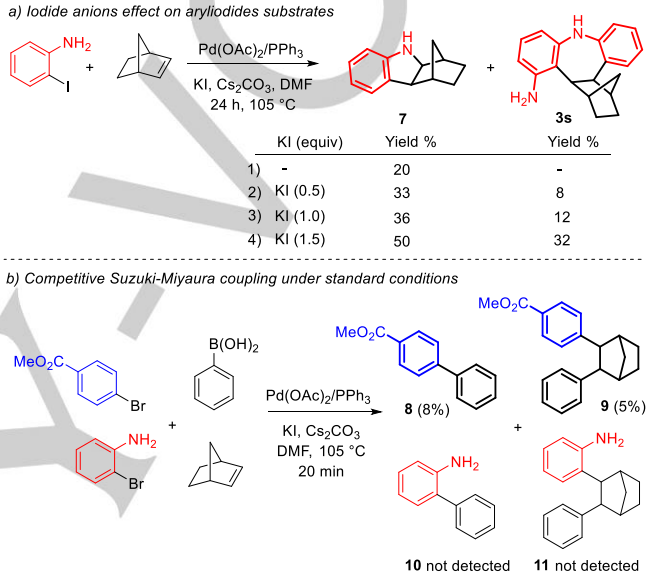


Scheme 2. A 3-step formal synthesis of Clomipramine®.

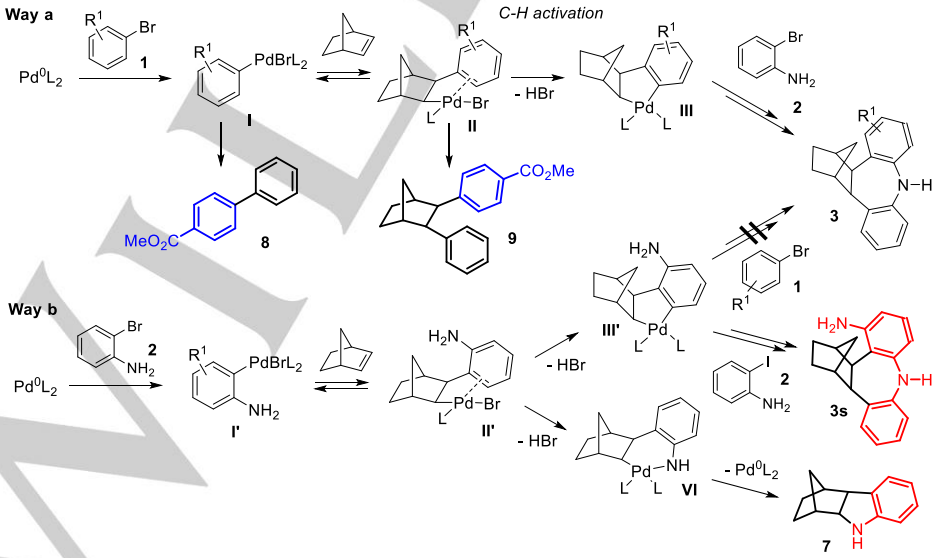
Furthermore, from a mechanistic point of view, since both bromides **1** and **2** might start the catalytic cycle, two possible reaction pathways could be proposed.

Firstly, the general passivity of the reaction system in the absence of KI might be explained by the inherent presence of aniline derivatives. These NH_2-containing substrates contribute to decreasing the overall reaction rate of the process, probably owing to an easy interaction with palladium, even in the presence of phosphine ligand.[14d, 23] Thus, the effect of KI would be crucial to increasing the overall reaction rate, probably by competing with the NH_2 group for the metal coordination.[14d]

Secondly, the accelerating effect exerted by iodide anions in this transformation can be explained by the *in situ* formation of highly nucleophilic palladium species able to increase the oxidative addition rate of aryl bromides.[24] Otherwise I^- anions can also promote the so called „*halogen exchange*“[25] and we currently cannot exclude this possibility. However, in order to support the „*ligand effect*“ idea for iodide anions, we set up a bromide-free system to prevent any halogen-exchange pathway. We then caused 2-iodoaniline and norbornene to react under standard conditions (Scheme 3a). In the absence of KI, only 20% of the 5-membered ring **7** was obtained (Scheme 3a, entry 1). When 0.5 equiv of KI were used, yield of **7** raised to 33% and, notably, dibenzoazepine **3s** was also formed with 8% yield (Scheme 3a, entry 2). These values further increased at higher [I^-] concentrations, reaching 50 and 32% yield of **7** and **3s** respectively, when 1.5 equiv of KI was



Scheme 3. Experimental findings.



Scheme 4. Possible reaction pathways: aryl bromide/2-bromoaniline sequence (*way a*) and 2-bromoaniline/aryl bromide sequence (*way b*).

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employed (Scheme 3a, entries 3 and 4). These results suggest that iodide anions play the role of active ligand in this transformation.[26]

Finally, from the mechanistic point of view, two possible reaction pathways can be proposed (Scheme 4, *way a* and *b*). Indeed, both bromides **1** and **2** might start the catalytic cycle since both could provide oxidative addition to palladium(0) species. If **1** begins the sequence (Scheme 4, *way a*), the oxidative addition to palladium (0) leads to complex **I**, which, after stereoselective norbornene insertion, affords intermediate **II**. After intramolecular C-H bond activation, an aryl-norbornyl palladacycle **III** is generated and its reaction with 2-bromoaniline **2** provides dibenzoazepine **3** and palladium(0). However, product **3** can also be obtained from *way b* (Scheme 4). Thank to their NH_2 group in *ortho* position, bromoanilines can compete with **1** for the oxidative addition on Pd(0), leading to complex **I'**. Norbornene insertion would lead to intermediate **II'**, which in turn could undergo C-H activation to palladacycle **III'**. Finally, reaction of **III'** with **1** would provide compound **3**.

Pathway *b* would be more plausible for 2-iodoaniline, which is able to start the catalytic cycle providing palladacycle **III'**. The subsequent reaction of **III'** with a second molecule of 2-iodoaniline leads to compound **3s** (Scheme 3a and 4). Analogously, hexahydro-1*H*-1,4-methanocarbazole **7**,[27] detected in small amounts when 2-bromoaniline was employed, can arise following *way b* (Scheme 4).

In order to ascertain the most probable reaction sequence, we attempted to trap some organometallic intermediates through the fast Suzuki-Miyaura coupling, whose conditions are compatible with those of dibenzoazepine formation.[15h] We then caused 4-carbomethoxybromobenzene, 2-bromoaniline and norbornene to react in the presence of phenylboronic acid (Scheme 3b). Upon just 20 min, non-negligible amounts of **8** and **9** were detected, arising from intermediates **I** and **II** with phenylboronic acid respectively, thereby supporting proposed pathway *a* (Scheme 3b and 4, *way a*). Homologous **10** and **11**, resulting from the corresponding **I'** and **II'** intermediates, were not observed. Further studies are currently in progress in our laboratories to shed light on this quite complex reactivity that involves different types of ligands (PPh_3, I^- anions and N containing substrates).

Conclusions

In summary, we have disclosed a complementary protocol to 10,11-dihydrodibenzo[*b,f*]azepine and dibenzo[*b,f*]azepine scaffolds from aryl bromides, 2-bromoanilines and norbornene/norbornadiene based on the crucial role of iodide anions. The reaction can tolerate an array of useful functional groups including electron withdrawing ones on the aromatic rings. The methodology described can be exploited in the preparation of Clomipramine and other useful intermediates. Specifically designed experiments allowed us to prove that KI can increase yields and selectivity by acting as competing ligand, and to propose the most plausible reaction pathway by trapping some key organometallic intermediates. Efforts to elucidate the accelerating effect obtained by adding inorganic iodide salts is currently underway in our laboratories. We believe this work will stimulate the use of iodide anion sources in other transformations, not only in Catellani-type reactions.

Experimental Section

General procedure for the palladium-catalyzed synthesis of cis,exo-1,2,3,4,4a,13b-hexahydro-1,4-methano-9H-tribenzo[b,f]azepines (**3**)

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with Cs_2CO_3, dried at 110 °C for 2 h (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes' stirring, a DMF solution (5 mL) of aryl bromide **1** (0.48 mmol), 2-bromoaniline **2** (0.44 mmol) and norbornene (50 mg, 0.53 mmol) was added; KI was then introduced (36 mg, 0.22 mmol). The resulting mixture was stirred in an oil bath at 105 °C for 20-90 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with a saturated solution of NaCl (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

*General procedure for the palladium-catalyzed synthesis of 5H-dibenz[b,f]azepine (**5**)*

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged under nitrogen with Cs_2CO_3 dried at 110 °C for 2 h (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes under stirring, a DMF solution (5 mL) of the aryl bromide **1** (0.48 mmol), 2-bromoaniline **2** (0.44 mmol) and norbornadiene (81 mg, 0.88 mmol) was added, and then KI was introduced (36 mg, 0.22 mmol). The resulting mixture was stirred in an oil bath at 105 °C for 24–72 h and then at 130 °C for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and extracted three times with a saturated solution of NaCl (25 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

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Keywords: palladium • C–H bond activation • 7-membered ring • azepine • iodide anions

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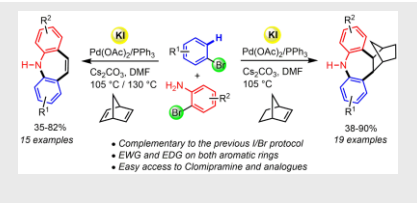
Layout 2:

FULL PAPER

Dibenzo[*b,f*]azepine derivatives can be efficiently synthesized from aryl bromides, *o*-bromoanilines and norbornene or norbornadiene by means of palladium catalysis. The presence of KI, even in sub-stoichiometric amount, is crucial for this three-component reaction, as it promotes reaction rate and selectivity. A formal three-step synthesis of the tricyclic antidepressant Clomipramine (Anafranil®) is also described.



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Enhancing Reactivity and Selectivity of Aryl Bromides: A Complementary Approach to Dibenzo[*b,f*]azepine Derivatives

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