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One-step three-component coupling of aromatic organozinc reagents, secondary amines, and aromatic aldehydes into functionalized diarylmethylamines

Erwan Le Gall,* Michel Troupel and Jean-Yves Nédélec

Laboratoire d'Electrochimie, Catalyse et Synthèse Organique (LECSO), CNRS-Université Paris 12 Val de Marne, UMR 7582, 2-8 rue Henri Dunant, 94320 Thiais, France

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Abstract—Numerous functionalized diarylmethylamines have been synthesized in high yield according to a one-step three-component coupling between an aromatic organozinc reagent, a secondary amine, and an aromatic aldehyde. Both organozinc species and aldehyde can bear a functional group and either aromatic or non-aromatic amines can be used in this versatile procedure.

1. Introduction

Diarylmethylamines constitute important intermediates in the synthesis of pharmacologically active compounds.[1] Although chiral diarylmethylamine blocks are found in many substances displaying a biological activity, their asymmetric synthesis has not gained much attention until these last years. Among several efficient procedures, which have been developed,[2–5] there is a particular emphasis on stereoselective additions of carbon nucleophiles to imines.[3–5] Thus, it was shown that arylmethylamine derivatives can be obtained in good yields and enantiomeric excesses either starting from chiral imines[4] or using chiral mediators.[5] The antihistamine agent cetirizine was obtained under its enantiomerically-pure form via a resolution technique employing tartaric acid.[6] In the field of racemate synthesis, reductive procedures involving carbonyl compounds were employed for the synthesis of several diarylmethylamines[7,8] and other methods like arylation of iminium salts,[9] displacement of polymer-supported benzotriazole[10] using aromatic organomagnesium reagents, or addition of phenyllithium to selenoamides[11] have been also reported.

Multi-component reactions are known to be among the most powerful building tools available in organic synthesis, since they rapidly increase the complexity of final products starting from simple precursors. In the field of multi-component processes leading to arylmethylamine derivatives, aromatic Mannich reactions[12] have been set as evident candidates since they allow the potential synthesis of benzylamines, mixed alkylarylmethylamines, or diarylmethylamines simply depending on starting compounds, which are involved in the reaction. Thus, several years ago, Lubben and Feringa described the aminomethylation of phenol derivatives through a Mannich-type reaction among phenol derivatives, amines and formaldehyde.[13] Organoboronic acids were employed in three-component couplings with salicylaldehydes[14] or heteroaromatic aldehydes[15] and amines to provide arylmethylamine derivatives in moderate to good yield. Recently, some diarylmethylamines were also efficiently obtained using organotrifluoroborates instead of arylboronic acids in a Petasis-related reaction.[16] Despite their indubitable interest, these methods suffer from some limitations. Indeed, aromatic Mannich reactions require the use of electron-rich benzene derivatives to proceed and no control of the regioselectivity of the carbon–carbon bond formation can be envisaged. In the organoboronic Mannich reaction,[14–16] only aldehydes bearing an activating group (OH or N atom) at the position α to the CHO function undergo the three-component coupling.

In a recent paper,[17] we reported preliminary results about the possible use of aromatic organozinc reagents[18] as nucleophiles in expedient three-component couplings with aromatic aldehydes and secondary amines leading to diarylmethylamines. It was shown that organozinc reagents constitute valuable nucleophiles in this process and that the reaction is efficient even with non-activated benzaldehyde derivatives. In order to clarify the scope of the procedure,

Keywords: Diarylmethylamines; Multi-component reaction; Aromatic organozinc reagents; Aromatic aldehydes; Secondary amines.
* Corresponding author. Tel.: +33 149781136; fax: +33 149781148; e-mail: legall@glvt-cnrs.fr

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several other experiments were realized and we report herein our whole results concerning the possible use of aromatic organozinc reagents in this multi-component reaction.

2. Results and discussion

In a previous work, we had noticed the possibility of using aromatic organozinc reagents as nucleophiles in Bruylants-type reactions with α-aminonitriles derived from piperidine, yielding diarylmethylamines.[19] Considering that α-aminonitriles are stable iminium equivalents, we anticipated that organozinc compounds would also react with iminium intermediates, which could be for instance generated in situ from an aromatic aldehyde and a secondary amine. Hence we undertook to scan the possibilities provided by a Mannich-type reaction in which an organozinc reagent would be used as the carbon nucleophile. Indeed, such a method could allow the synthesis of numerous diarylmethylamines simply according to the starting compounds.

In a first time, we had envisaged to form α-aminonitriles in situ using a Strecker-type reaction.[20] Unfortunately, protic conditions found in classical syntheses[20,21] are incompatible with the subsequent use of organozinc reagents, which are very basic species. Thus, in a second time we envisaged to synthesize diarylmethylamines following a two-steps procedure: in a first step, a transient hemiaminal formed by reaction between an aldehyde and an amine would be *O*-methylated into an α-aminoether. In a second step, an organozinc reagent would be used as nucleophile for the displacement of the methoxy group. As outlined in Scheme 1, experiments were achieved starting from piperidine, benzaldehyde, and 4-methoxyphenylzinc bromide, prepared separately in acetonitrile according to a procedure inspired from the cobalt-catalyzed process previously developed in the laboratory.[22]

Curiously, it was shown that the corresponding diarylmethylamine was obtained only when the methoxylating agent MeI was used in understoichiometric amount. We then envisaged to add the arylzinc compound to a solution containing only piperidine and benzaldehyde and remarked that reaction products started appearing within a few minutes when at least 1 equiv of the arylzinc compound was used. Furthermore, the optimum value for an efficient coupling was found to be at least 2 equiv of the arylzinc reagent, the reaction being almost quantitative beyond this value. The need for such quantities of the organozinc may account for a base-assisted elimination on the intermediate hemiaminal leading to a formal iminium ion, which is further attacked by the remaining arylzinc compound.

We then attempted to enhance the reaction rate by adding copper salts to the reaction medium.[23] We observed that coupling occurred faster when CuI was added in catalytic amount to the 4-methoxyphenylzinc bromide solution before introduction of piperidine and benzaldehyde. Furthermore, the reaction appeared to be more selective in the presence of cuprous salts, fewer side products being detected.

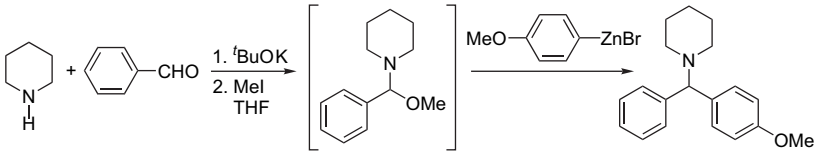
Consequently, we envisaged to extend the reaction to several organozinc compounds. These reagents were prepared efficiently (77–97% GC yield) starting from 30 mmol of various aromatic bromides. We made the observation that in a general manner, electron-rich organozinc species can be activated with cuprous iodide (coupling method A) whereas electron-deficient organozinc fast produces dimeric biaryl compounds upon addition of cuprous iodide. The redox-type mechanism of this unwanted reaction could be clearly confirmed by the concomitant production of copper powder. Starting from electron-poor organozinc compounds, best conditions for an efficient coupling were found as Barbier-like reaction conditions. It consisted in the dropwise addition of the organozinc into a pre-heated mixture of piperidine and benzaldehyde (coupling method B). We could also remark that this coupling method B was more versatile than coupling method A since it could be applied to any organozinc reagent, independently from its reactivity and stability.

Results are presented in Table 1.

Diarylmethylamines are obtained in moderate to excellent yields (40–95%). The reaction proceeds efficiently with both electron-donating substituents (entries 2–7 of Table 1) and electron-withdrawing groups (entries 8–11 of Table 1) connected to the phenyl ring.

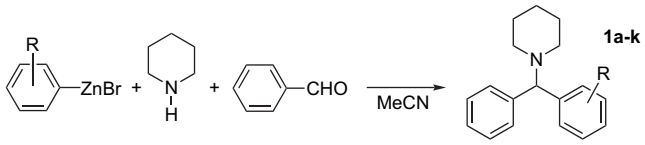
Considering the presence of a nitrogen atom on the final diarylmethylamine structures, the simplest work-up was found as an acid–base treatment, which ensured the removal of most by-products. Indeed, these compounds (hydrodehalogenation products ArH, biaryl Ar–Ar, or alcohol sometimes arise from the addition of the organozinc to the aldehyde) were easily separated from the diarylmethylamine using this method provided they do not contain nitrogen.

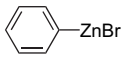
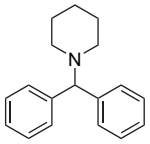
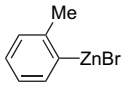
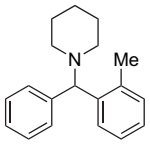
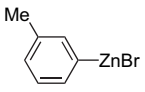
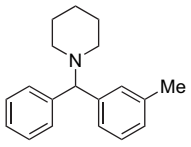
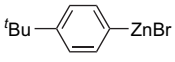
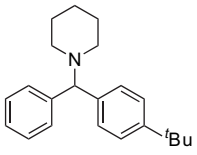
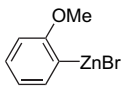
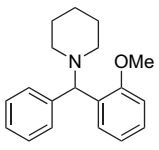
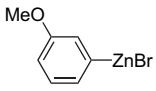
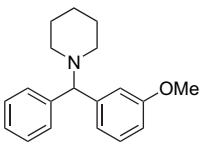
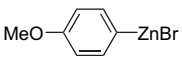
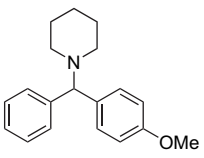
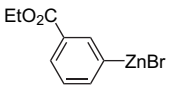
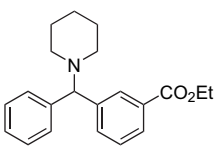
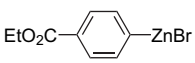
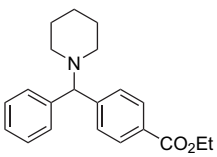
Additional experiments were conducted using commercial solutions of phenylzinc bromide and 4-methoxyphenylzinc iodide in tetrahydrofuran[24] following typical experimental conditions of coupling method A as well as conditions of coupling method B. Only traces of the expected product were observed, even with a large excess of the starting organozinc (3 equiv). The addition of catalytic amounts of cobalt and zinc bromide did not improve the production of diarylmethylamine. In order to confirm that cobalt salts were not involved in the reaction mechanism, benzylzinc bromide was synthesized in acetonitrile in the absence of a cobalt catalyst. The organozinc thus obtained was allowed to react with benzaldehyde and piperidine at room temperature for



Scheme 1.

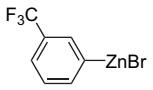
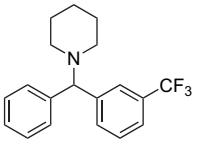
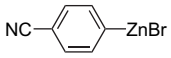
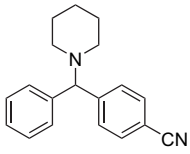
Table 1. Coupling of functionalized organozinc reagents with piperidine and benzaldehyde



Entry	Organozinc and GC yield (%)		Reaction time (h)	Product		Isolated yield (%)[a]
1		80	18[b]		**1a**	59
2		97	18[b], 4[c]		**1b**	71[b], 77[c]
3		93	18[b]		**1c**	56
4		82	18[b]		**1d**	75
5		95	18[b]		**1e**	95
6		92	18[b]		**1f**	62
7		89	3[b]		**1g**	88
8		93	4[c]		**1h**	40
9		92	4[c]		**1i**	70

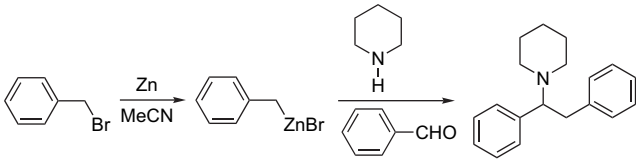
(*continued*)

Table 1. (*continued*)

Entry	Organozinc and GC yield (%)	Reaction time (h)	Product	Isolated yield (%)[a]
10	 95	4[c]	 **1j**	83
11	 77	4[c]	 **1k**	72

[a] Yields based on initial amine and aldehyde amounts (10 mmol).
[b] Coupling method A: CuI (ca. 0.3 equiv vs ArZnX) was added at room temperature into the organozinc (>20 mmol) solution before addition of the amine (10 mmol) and the aldehyde (10 mmol).
[c] Coupling method B: The organozinc-containing (>20 mmol) solution was added dropwise into the pre-heated mixture (70 °C) of the amine (10 mmol) and the aldehyde (10 mmol) in acetonitrile (15 mL).

3 h giving rise to the almost quantitative formation of the Mannich reaction product (Scheme 2).



Scheme 2.

This result clearly shows that the very poor reactivity of these commercial organozinc compounds cannot be linked with the absence of cobalt salts in the reaction medium. This may account for a possible role of the solvent in the reaction course. Considering the experimental conditions used in coupling method B, in which a limited amount of tetrahydrofuran is added in the acetonitrile solution in order to stabilize the organozinc reagent during the course of time, one can imagine that important amounts of tetrahydrofuran can also noticeably slow down the coupling reaction. Nevertheless, the absence of reactivity of commercial organozinc reagents may not be solely explained by solvent effects.

In order to test the reactivity of Grignard reagents in this three-component procedure, an experiment involving phenylmagnesium bromide was conducted. As it could be anticipated, the use of phenylmagnesium bromide in a coupling reaction with piperidine and benzaldehyde did not led to the formation of the corresponding diarylmethylamine but gave rise to an exclusive addition of phenylmagnesium bromide to benzaldehyde producing diphenylmethanol.

It should also be mentioned that an attempt to synthesize compound **1g** in a one-step reaction was realized. Thus, piperidine and benzaldehyde were placed along with 4-methoxyphenyl bromide in the reaction mixture containing cobalt salts and zinc dust. No cuprous iodide was added in that case since the only result would have been the production of copper(0) and zinc salts upon redox reaction of copper(I) with zinc dust. An exothermic reaction occurred fast and after 1 h at room temperature, the additional heating at 50 °C for 1 h allowed the formation of compound **1g** in 85% GC yield. This procedure might be efficient especially with electron-rich organozinc compounds since they react clearly faster than electron-deficient organozinc compounds and do not have a so affirmed tendency to yield biaryls upon heating. Nevertheless, additional tests might be necessary to clarify the scope of this one-step reaction.

Another series of experiments, involving benzaldehyde as the aldehyde and 4-methoxyphenylzinc bromide as the model organozinc reagent, was realized in order to test the effect of the secondary amine on the course of the reaction.

Results are presented in Table 2.

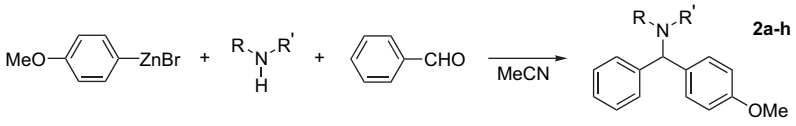
Diarylmethylamines are again obtained in moderate to excellent yields (50–96%). Both aromatic (entries 7 and 8 of Table 2) and non-aromatic amines (entries 1–6 of Table 2) are convenient substrates in this procedure, yields being just a bit lower in the case of aromatic amines. This result is consistent with their generally admitted lower reactivity as nucleophiles. It is important to note that piperazine derivatives, which are known to exhibit various biological activities, can be obtained using this procedure (entry 3 of Table 2). Yield is only moderate in that case but the coupling product showed a lower stability during work-up and even after purification, this compound fast darkened when exposed to air and/or light. More accurate conditions for the reaction and the isolation of products might certainly increase yields for this class of compounds.

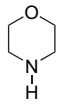
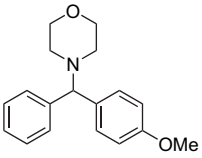
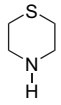
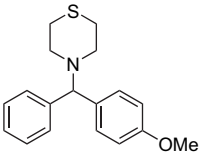
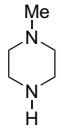
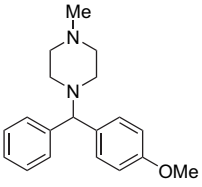
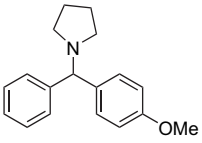
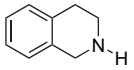
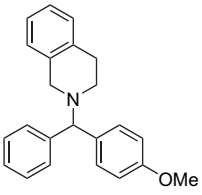
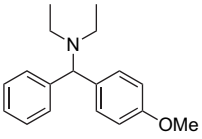
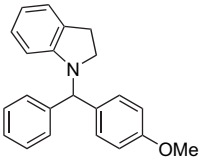
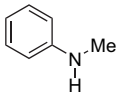
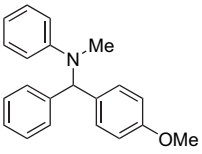
In a third series of experiments, we employed substituted benzaldehydes to ensure that functionalities can be present on the related phenyl ring. Moreover, we investigated the possible use of heteroaromatic aldehydes in the process.

Results are presented in Table 3.

In most cases, yields are good to excellent (76–99%). It appears that benzaldehyde derivatives react fairly well with either electron-donating or -withdrawing groups connected to the phenyl moiety. It should nevertheless be mentioned that in some cases, electronic effects can play a role in the

Table 2. Coupling of 4-methoxyphenylzinc bromide with secondary amines and benzaldehyde

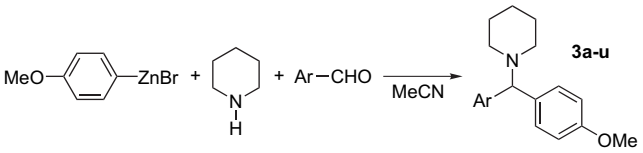


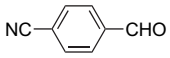
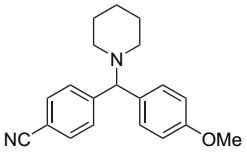
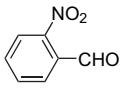
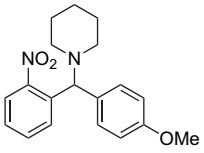
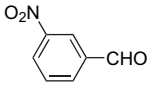
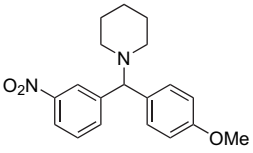
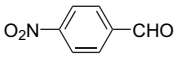
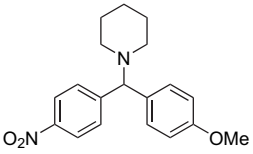
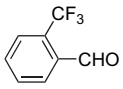
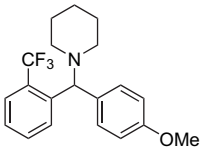
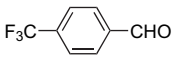
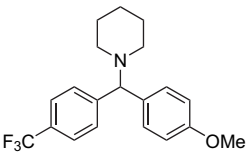
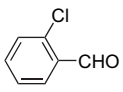
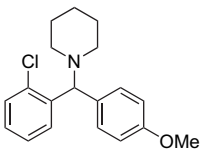
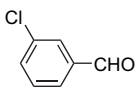
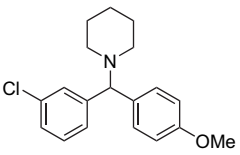
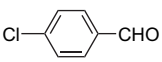
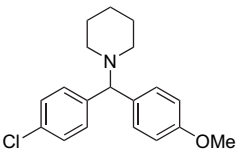
Entry	Amine	Reaction time (h)[a]	Product		Isolated yield (%)[b]
1		3		**2a**	90
2		3		**2b**	96
3		4		**2c**	50
4		3		**2d**	94
5		3		**2e**	89
6		3		**2f**	94
7		3		**2g**	80
8		6		**2h**	53

[a] Coupling method A: CuI (ca. 0.3 equiv vs ArZnX) was added at room temperature into the organozinc (>20 mmol) solution before addition of the amine (10 mmol) and the aldehyde (10 mmol).

[b] Yields based on initial amine and aldehyde amounts (10 mmol).

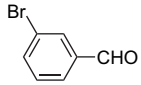
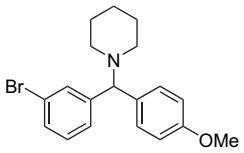
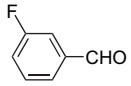
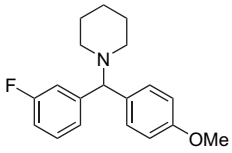
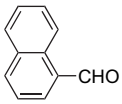
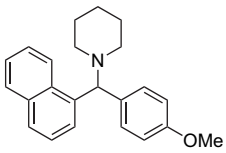
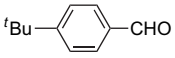
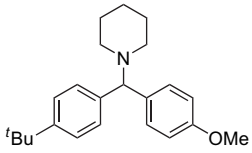
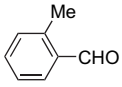
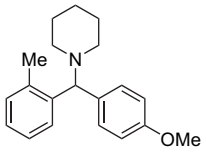
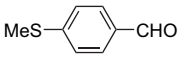
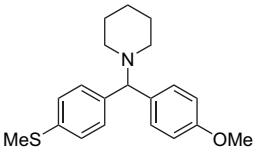
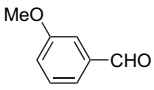
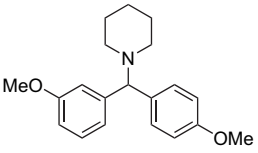
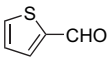
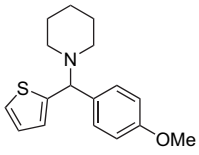
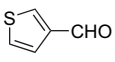
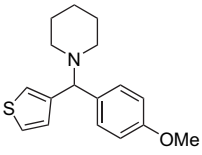
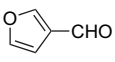
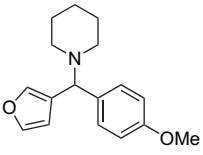
Table 3. Coupling of 4-methoxyphenylzinc bromide with piperidine and aromatic aldehydes



Entry	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
1		3[b]		**3a**	83
2		18[c]		**3b**	46
3		3[c]		**3c**	98
4		3[c]		**3d**	78
5		3[b]		**3e**	79
6		3[b]		**3f**	99
7		18[b]		**3g**	86
8		3[b]		**3h**	96
9		18[b]		**3i**	96

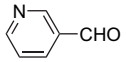
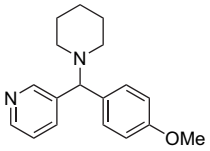
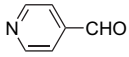
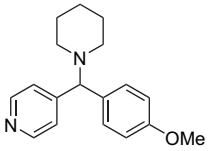
(*continued*)

Table 3. (*continued*)

Entry	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
10		3[b]		**3j**	96
11		3[b]		**3k**	98
12		18[b]		**3l**	76
13		18[b]		**3m**	84
14		18[b]		**3n**	84
15		3[b]		**3o**	98
16		18[b]		**3p**	83
17		18[b]		**3q**	76
18		18[b]		**3r**	97
19		18[b]		**3s**	91

(*continued*)

Table 3. (*continued*)

Entry	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
20		18[b]		**3t**	92[d]
21		18[b]		**3u**	87[d]

[a] Yields based on initial amine and aldehyde amounts (10 mmol).
[b] Coupling method A: CuI (ca. 0.3 equiv vs ArZnX) was added at room temperature into the organozinc (>20 mmol) solution before addition of the amine (10 mmol) and the aldehyde (10 mmol).
[c] Coupling method B: Conditions used in coupling method A but without CuI.
[d] An additional chromatographic purification was performed over silica gel using a diethyl ether–dichloromethane: 90/10 mixture as an eluent.

course of the reaction. Indeed, with nitrobenzaldehydes, the coupling is achieved rapidly without using additional cuprous iodide (entries 3 and 4 of Table 3). *ortho*-Substituted benzaldehydes react slower than *meta*- and *para*-substituted benzaldehydes and yields are generally lower. This behavior can be particularly noticed in the case of nitrobenzaldehydes. *ortho*-Nitrobenzaldehyde leads to only 46% yield (entry 2 of Table 3) whereas couplings featuring *meta*- and *para*-benzaldehydes are very efficient (78–98%, entries 3 and 4 of Table 3). A similar behavior can be observed with heteroaromatic aldehydes derived from thiophene. Indeed, the reaction is clearly less efficient with thiophene-2-carboxaldehyde (entry 17 of Table 3) than with thiophene-3-carboxaldehyde (entry 18 of Table 3).

In the case of heteroaromatic aldehydes derived from pyridine (entries 20 and 21 of Table 3), we could also observe along the major product, diarylmethylpiperidine, the presence of the alcohol resulting from the addition of the arylzinc compound to the aldehyde function. In these limited cases, owing to the presence of nitrogen on both products, the acid–base treatment was not sufficient to separate the diarylmethylpiperidine from the alcohol. Thus, an additional chromatographic purification over silica gel was applied to the crude product.

3. Conclusion

In conclusion, the results presented in this paper show that a three-component Mannich-type reaction involving aromatic organozinc reagents as nucleophile constitute a very versatile methodology for the synthesis of diarylmethylamines. Indeed, diarylmethylamines are obtained in high yields and various functionalities can be introduced through both organozinc reagents and benzaldehyde derivatives. Heteroaromatic aldehydes are also efficient and either secondary aromatic or non-aromatic amines can be used in the process thus highlighting the important scope of the reaction. Nevertheless, additional developments might be envisaged: can enolizable aldehydes be used in the procedure and do aliphatic organozinc undergo the reaction? What would be the behavior of primary amines or amides in this reaction and furthermore would amino-acids derivatives be efficient as amines? Additionally, could they induce stereoselectivity in the reaction and in a general manner, can enantioselective syntheses be realized toward the use of chiral mediators?

4. Experimental

4.1. General

Solvents (acetonitrile and THF in analytical grades) and starting materials were purchased from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using a Varian *3400* chromatograph equipped with a 5 m SGE *BP1* column. Melting points (mp) were determined on a Kofler apparatus and were not corrected. Infrared spectra were recorded in $CHCl_3$ on a Perkin–Elmer *Spectrum BX* FTIR spectrometer. NMR spectra were recorded in $CDCl_3$ at 200 MHz (^1H), 50 MHz (^{13}C), and 188 MHz (^{19}F) on a Bruker *AC200* spectrometer. In the case of fluoride-containing compounds **1j**, **3e**, **3f**, and **3k**, in order to determine accurately C–F coupling constants, ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz using a Bruker *Avance II 400* spectrometer. Data are presented as follows: chemical shift (multiplicity, coupling constants, integration). Mass spectra were recorded on a Finnigan GC–MS *GCQ* spectrometer. High-resolution mass spectra were recorded at the 'Service central d'analyses', Vernaison, France. The mode of ionization used was electrospray (ES^+). Compounds, which have been previously described in the literature are linked to relevant bibliographic references whereas compounds labeled by asterisk (*) are, to the best of our knowledge, new compounds.

4.2. Typical experimental procedure for the synthesis of organozinc reagents

A dried 100 mL tricol was flushed with argon and charged with acetonitrile (40 mL). Dodecane (0.2 mL, used as internal standard), cobalt bromide (0.66 g, 3 mmol), zinc

bromide (0.68 g, 3 mmol), phenyl bromide (0.32 mL, 3 mmol), and zinc dust (6 g, 92 mmol) were added to the solution. Trifluoromethanesulfonic acid (0.2 mL) was added to the mixture under vigorous stirring. After ca. 15 min, the aryl bromide (30 mmol) was added to the solution and as soon as the exothermic reaction had began (ca. 5 min), a water bath at room temperature was used to moderate the temperature of the medium. The reaction time, which was monitored using gas chromatography, did not exceed 30 min in most cases. Yield of organozinc compounds thus obtained were estimated as follows: a sample of the reaction medium was exposed to iodine crystals then sodium thiosulfate, and extracted with diethyl ether. The amount of iodinated product was compared to the amount of the starting aryl bromide via the internal standard using gas chromatography (GC). After completion of the reaction, the acetonitrile solution was taken up using a syringe whenever possible or filtered over Celite at 0 °C.

4.3. Typical coupling method A

To the solution of the organozinc reagent was added under stirring CuI (1.2 g, 6 mmol) and 5 min later, benzaldehyde (1 mL, 10 mmol) and piperidine (1 mL, 10 mmol). Stirring was continued for additional 3 h at room temperature.

4.4. Typical coupling method B

To the solution of the organozinc reagent was added 5 mL THF. The resulting solution was added dropwise (2 h) under stirring to a pre-heated mixture (ca. 70 °C) of benzaldehyde (1 mL, 10 mmol) and piperidine (1 mL, 10 mmol) in acetonitrile (15 mL). Stirring was continued for additional 2 h at 70 °C.

4.5. Typical acid–base work-up

The reaction mixture was poured in 150 mL of a 5% sodium hydroxide aqueous solution and extracted with dichloromethane (2×100 mL). The combined organic fractions were concentrated to dryness and diethyl ether (150 mL) was added to the residue. After complete dissolution, concentrated sulfuric acid (0.5–0.75 mL) was added carefully to the vigorously stirred solution and allowed to react for 5 min. The resulting ammonium salt was filtered and washed with diethyl ether (2×50 mL). The solid was then poured, under stirring, into a mixture of a 5% sodium hydroxide aqueous solution (100 mL) and dichloromethane (100 mL). After complete dissolution, the aqueous phase was extracted with additional 100 mL of dichloromethane. The combined organic fractions were dried over sodium sulfate and concentrated to dryness yielding analytically pure (>97% GC) diarylmethylamines. In the case of diarylmethylamines **3t** and **3u** derived from pyridine carboxaldehydes, an additional chromatographic purification was performed over silica gel (SDS 70–200 μm) using a diethyl ether–dichloromethane: 90/10 mixture as an eluent.

4.6. Analytical data

4.6.1. 1-Benzhydrylpiperidine (1a).[8,11] Pale yellow solid, mp: 70 °C; ^{1}H NMR, δ (ppm): 1.50–1.70 (m, 6H), 2.30–2.50 (m, 4H), 4.36 (s, 1H), 7.20–7.61 (m, 10H); ^{13}C NMR, δ (ppm): 24.84, 26.39, 53.29, 76.88, 126.78, 128.13, 128.43, 143.38; MS, *m/z* (relative intensity): 251 (19), 175 (14), 174 (100), 168 (12), 167 (60), 166 (12), 165 (38), 152 (19), 91 (10), 84 (20); HRMS calcd for $C_{18}H_{22}N$ $[M+H]^+$: 252.1752, found: 252.1761.

4.6.2. 1-(Phenyl(2-tolyl)methyl)piperidine (1b).[1c,17] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 7H), 4.38 (s, 1H), 6.99–7.91 (m, 9H); ^{13}C NMR, δ (ppm): 20.12, 25.03, 26.51, 53.66, 71.07, 126.37, 126.79, 127.37, 127.61, 128.38, 128.93, 130.62, 135.93, 141.82, 142.52; MS, *m/z* (relative intensity): 266 (7), 265 (17), 189 (6), 188 (35), 187 (27), 186 (11), 182 (12), 181 (72), 180 (100), 179 (61), 178 (17), 175 (6), 174 (45), 167 (14), 166 (65), 165 (65), 153 (7), 152 (6), 105 (7), 91 (10), 86 (30), 84 (7); HRMS calcd for $C_{19}H_{24}N$ $[M+H]^+$: 266.1909, found: 266.1927.

4.6.3. 1-(Phenyl(3-tolyl)methyl)piperidine (1c)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.40–1.80 (m, 6H), 2.20–2.60 (m, 7H), 4.36 (s, 1H), 7.12–7.61 (m, 9H); ^{13}C NMR, δ (ppm): 21.59, 24.82, 26.35, 53.31, 76.62, 125.16, 126.66, 127.53, 128.34, 128.70, 137.80, 143.27, 143.48; MS, *m/z* (relative intensity): 266 (7), 265 (20), 189 (11), 188 (88), 182 (26), 181 (100), 179 (11), 178 (12), 175 (11), 174 (79), 167 (27), 166 (72), 165 (69), 153 (9), 152 (7), 105 (10), 91 (12), 84 (56); HRMS calcd for $C_{19}H_{24}N$ $[M+H]^+$: 266.1909, found: 266.1928.

4.6.4. 1-((4-*tert*-Butylphenyl)(phenyl)methyl)piperidine (1d)*. Pale yellow solid, mp: 89 °C; ^{1}H NMR, δ (ppm): 1.32 (s, 9H), 1.38–1.70 (m, 6H), 2.30–2.45 (m, 4H), 4.26 (s, 1H), 7.16–7.50 (m, 9H); ^{13}C NMR, δ (ppm): 24.74, 26.28, 31.40, 53.16, 76.36, 125.12, 126.51, 127.50, 127.81, 128.13, 140.07, 143.50, 149.21; MS, *m/z* (relative intensity): 308 (5), 307 (19), 231 (18), 230 (87), 224 (21), 223 (100), 208 (19), 193 (24), 181 (6), 179 (8), 178 (16), 174 (23), 167 (25), 166 (6), 165 (16), 91 (6), 84 (16); HRMS calcd for $C_{22}H_{30}N$ $[M+H]^+$: 308.2378, found: 308.2384.

4.6.5. 1-((2-Methoxyphenyl)(phenyl)methyl)piperidine (1e)*. Pale yellow solid, mp: 100 °C; ^{1}H NMR, δ (ppm): 1.40–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.69 (s, 3H), 4.77 (s, 1H), 6.70–7.66 (m, 9H); ^{13}C NMR, δ (ppm): 24.90, 26.36, 53.23, 55.41, 67.32, 110.77, 120.72, 126.32, 127.26, 128.06, 128.26, 131.72, 143.46, 157.13; MS, *m/z* (relative intensity): 282 (10), 281 (39), 280 (16), 238 (6), 205 (13), 204 (100), 198 (17), 197 (70), 196 (17), 195 (8), 188 (5), 181 (19), 179 (15), 175 (8), 174 (51), 169 (8), 167 (6), 166 (6), 165 (25), 153 (9), 152 (20), 121 (6), 92 (6), 91 (90), 86 (28), 84 (11); HRMS calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1861.

4.6.6. 1-((3-Methoxyphenyl)(phenyl)methyl)piperidine (1f)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.40–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.76 (s, 3H), 4.30 (s, 1H), 6.75–7.54 (m, 9H); ^{13}C NMR, δ (ppm): 25.02, 26.56, 53.40, 55.10, 76.82, 112.00, 113.95, 120.60, 127.00, 128.10, 128.45, 129.58, 143.35, 145.26, 159.91; MS, *m/z* (relative intensity): 282 (6), 281 (11), 280 (6), 205 (12), 204 (77), 199 (15), 198 (100), 197 (78), 183 (19), 182 (44), 181 (20), 179 (10), 175 (13), 174 (80), 169 (21), 168

(8), 167 (29), 166 (29), 165 (55), 164 (8), 155 (8), 154 (20), 153 (26), 152 (19), 121 (9), 91 (18), 84 (100); HRMS calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1869.

4.6.7. 1-((4-Methoxyphenyl)(phenyl)methyl)piperidine (1g).[17] Pale yellow solid, mp: 60 °C; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.65 (s, 3H), 4.17 (s, 1H), 6.77 (d, J=8.7 Hz, 2H), 7.06–7.40 (m, 9H); ^{13}C NMR, δ (ppm): 24.81, 26.36, 53.17, 55.17, 75.95, 113.74, 126.61, 128.37, 129.021, 135.40, 143.69, 158.41; MS, m/z (relative intensity): 281 (15), 204 (20), 198 (17), 197 (100), 182 (11), 167 (5), 166 (7), 165 (16), 154 (7), 153 (11), 152 (6); HRMS calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1874.

4.6.8. Ethyl 3-(phenyl(piperidin-1-yl)methyl)benzoate (1h)*. Pale yellow viscous oil; IR, ν (cm^{-1}): 1710; ^1H NMR, δ (ppm): 1.20–1.60 (m, 9H), 2.20–2.40 (m, 4H), 4.20–4.40 (m, 3H), 7.09–8.07 (m, 9H); ^{13}C NMR, δ (ppm): 14.44, 24.76, 26.31, 53.22, 60.94, 76.41, 126.99, 128.09, 128.57, 129.19, 129.43, 130.69, 132.37, 142.77, 143.95, 166.70; MS, m/z (relative intensity): 324 (8), 323 (33), 322 (9), 294 (5), 247 (20), 246 (100), 240 (9), 239 (32), 218 (21), 211 (8), 195 (12), 194 (8), 193 (35), 175 (15), 174 (100), 168 (8), 167 (59), 166 (32), 165 (71), 164 (9), 152 (11), 91 (11), 84 (45); HRMS calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1964, found: 324.1964.

4.6.9. Ethyl 4-(phenyl(piperidin-1-yl)methyl)benzoate (1i).[17] Pale yellow solid, mp: 98 °C; IR, ν (cm^{-1}): 1710; ^1H NMR, δ (ppm): 1.20–1.60 (m, 9H), 2.20–2.40 (m, 4H), 4.20–4.40 (m, 3H), 7.10–7.97 (m, 9H); ^{13}C NMR, δ (ppm): 14.20, 24.53, 26.08, 52.97, 60.59, 76.24, 126.88, 127.70, 128.32, 128.85, 129.59, 142.16, 145.58, 166.29; MS, m/z (relative intensity): 324 (8), 323 (33), 322 (8), 278 (5), 247 (17), 246 (100), 240 (9), 239 (45), 218 (19), 193 (6), 175 (9), 174 (79), 168 (8), 167 (55), 166 (38), 165 (62), 164 (5), 152 (14), 91 (10), 84 (41); HRMS calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1964, found: 324.1940.

4.6.10. 1-(Phenyl(3-(trifluoromethyl)phenyl)methyl)-piperidine (1j).[17] Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 4.28 (s, 1H), 7.10–7.71 (m, 9H); ^{13}C NMR, δ (ppm): 24.61, 26.20, 53.05, 76.38, 123.72 (q, J=4 Hz), 124.50 (q, J=271 Hz), 124.78 (q, J=4 Hz), 127.25, 128.19, 128.68, 128.92, 130.85 (q, J=31 Hz), 131.47, 142.30, 144.73; ^{19}F NMR, δ (ppm): −62.18; MS, m/z (relative intensity): 320 (11), 319 (40), 318 (12), 243 (13), 242 (85), 236 (11), 235 (45), 233 (6), 217 (11), 216 (8), 215 (49), 214 (9), 195 (13), 175 (16), 174 (100), 167 (13), 166 (39), 165 (61), 164 (6), 159 (10), 91 (11), 84 (45); HRMS calcd for $C_{19}H_{21}F_3N$ $[M+H]^+$: 320.1626, found: 320.1634.

4.6.11. 4-(Phenyl(piperidin-1-yl)methyl)benzonitrile (1k)*. Pale yellow viscous oil; IR, ν (cm^{-1}): 2230; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 4.27 (s, 1H), 7.14–7.35 (m, 5H), 7.52 (s, 4H); ^{13}C NMR, δ (ppm): 24.55, 26.16, 53.02, 76.18, 110.42, 118.95, 127.29, 128.05, 128.53, 132.23, 141.54, 149.13; MS, m/z (relative intensity): 276 (20), 275 (6), 200 (11), 199 (97), 193 (23), 192 (78), 191 (32), 190 (47), 177 (8), 175 (14), 174 (100), 166 (10), 165 (66), 164 (10), 163 (7), 152 (6), 116 (7), 91 (10), 84 (38); HRMS calcd for $C_{19}H_{21}N_2$ $[M+H]^+$: 277.1705, found: 277.1720.

4.6.12. 4-((4-Methoxyphenyl)(phenyl)methyl)morpholine (2a).[10] Pale yellow solid, mp: 66 °C; ^1H NMR, δ (ppm): 2.25–2.40 (m, 4H), 3.60–3.75 (m, 7H), 4.12 (s, 1H), 6.77 (d, J=8.7 Hz, 2H), 7.08–7.42 (m, 7H); ^{13}C NMR, δ (ppm): 52.55, 54.96, 67.06, 75.85, 113.81, 126.83, 127.70, 128.46, 128.85, 134.29, 142.65, 158.50; MS, m/z (relative intensity): 283 (7), 198 (17), 197 (100), 182 (10), 166 (7), 165 (15), 154 (6), 153 (11), 152 (6); HRMS calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651, found: 284.1648.

4.6.13. 4-((4-Methoxyphenyl)(phenyl)methyl)thiomorpholine (2b).[17] Pale brown solid, mp: 78 °C; ^1H NMR, δ (ppm): 2.62 (s, 8H), 3.67 (s, 3H), 4.31 (s, 1H), 6.78 (d, J=8.7 Hz, 2H), 7.08–7.36 (m, 7H); ^{13}C NMR, δ (ppm): 28.12, 53.50, 55.06, 75.11, 113.82, 126.80, 127.85, 128.38, 129.02, 134.09, 142.54, 158.51; MS, m/z (relative intensity): 299 (9), 271 (6), 198 (16), 197 (100), 182 (8), 166 (7), 165 (13), 153 (9), 152 (6); HRMS calcd for $C_{18}H_{22}NOS$ $[M+H]^+$: 300.1422, found: 300.1432.

4.6.14. 1-((4-Methoxyphenyl)(phenyl)methyl)-4-methylpiperazine (2c).[1b] Pale yellow solid, mp: 78 °C; ^1H NMR, δ (ppm): 2.24 (s, 3H), 2.41 (br s, 8H), 3.65 (s, 3H), 4.16 (s, 1H), 6.76 (d, J=8.7 Hz, 2H), 7.10–7.42 (m, 7H); ^{13}C NMR, δ (ppm): 46.05, 51.97, 55.11, 55.51, 75.58, 113.89, 126.79, 127.82, 128.52, 128.95, 134.97, 143.27, 158.56; MS, m/z (relative intensity): 296 (20), 239 (7), 238 (41), 237 (100), 236 (32), 225 (11), 224 (42), 210 (7), 198 (11), 197 (60), 182 (12), 181 (8), 167 (5), 166 (10), 165 (25), 154 (10), 153 (22), 152 (10), 121 (5), 99 (17), 70 (8), 56 (13); HRMS calcd for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1967, found: 297.1950.

4.6.15. 1-((4-Methoxyphenyl)(phenyl)methyl)pyrrolidine (2d).[9] Pale yellow solid, mp: 54 °C; ^1H NMR, δ (ppm): 1.80–2.00 (m, 4H), 2.50–2.70 (m, 4H), 3.76 (s, 3H), 4.28 (s, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.22–7.64 (m, 7H); ^{13}C NMR, δ (ppm): 23.66, 53.66, 54.94, 75.80, 113.77, 126.74, 127.38, 128.50, 136.70, 144.79, 158.49; MS, m/z (relative intensity): 267 (8), 198 (17), 197 (100), 190 (27), 182 (10), 165 (11), 154 (6), 153 (8), 152 (5); HRMS calcd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1701, found: 268.1713.

4.6.16. 2-((4-Methoxyphenyl)(phenyl)methyl)-1,2,3,4-tetrahydro isoquinoline (2e)*. Pale yellow solid, mp: 96 °C; ^1H NMR, δ (ppm): 2.75–2.92 (m, 2H), 2.93–3.08 (m, 2H), 3.74 (s, 2H), 3.78 (s, 3H), 4.52 (s, 1H), 6.94–7.66 (m, 13H); ^{13}C NMR, δ (ppm): 29.63, 49.42, 55.34, 75.27, 75.56, 114.21, 125.80, 126.26, 127.09, 127.82, 128.11, 128.94, 129.26, 134.34, 135.27, 135.60, 143.63, 158.87; MS, m/z (relative intensity): 329 (5), 252 (7), 198 (22), 197 (100), 182 (10), 167 (5), 166 (8), 165 (14), 154 (6), 153 (10), 133 (7), 132 (36); HRMS calcd for $C_{23}H_{24}NO$ $[M+H]^+$: 330.1858, found: 330.1878.

4.6.17. *N*,*N*-Diethyl-*N*-((4-methoxyphenyl)(phenyl)-methyl)amine (2f)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.11 (t, J=7.1 Hz, 6H), 2.71 (q, J=7.1 Hz, 4H), 3.73 (s, 3H), 4.83 (s, 1H), 6.91 (d, J=8.7 Hz, 2H), 7.20–7.60

(m, 7H); ^{13}C NMR, δ (ppm): 11.60, 43.24, 55.15, 70.89, 113.94, 126.79, 128.15, 128.44, 129.43, 135.72, 144.18, 158.72; MS, *m/z* (relative intensity): 269 (5), 198 (17), 197 (100), 192 (10), 182 (10), 167 (5), 166 (7), 165 (11), 154 (5), 153 (8); HRMS calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1858, found: 270.1865.

4.6.18. 1-((4-Methoxyphenyl)(phenyl)methyl)indoline (2g).[17] Pale brown viscous oil; ^{1}H NMR, δ (ppm): 3.23 (t, J=8.1 Hz, 2H), 3.55 (t, J=8.1 Hz, 2H), 4.01 (s, 3H), 5.89 (s, 1H), 6.60 (d, J=7.8 Hz, 1H), 6.95–7.74 (m, 12H); ^{13}C NMR, δ (ppm): 28.69, 51.75, 55.30, 66.30, 108.56, 114.13, 117.91, 124.62, 127.55, 128.80, 130.07, 130.64, 133.67, 142.05, 152.30, 159.11; MS, *m/z* (relative intensity): 315 (14), 198 (16), 197 (100), 182 (11), 166 (7), 165 (15), 154 (7), 153 (10), 152 (6); HRMS calcd for $C_{22}H_{22}NO$ $[M+H]^+$: 315.1701, found: 316.1705.

4.6.19. *N*-((4-Methoxyphenyl)(phenyl)methyl)-*N*-methylaniline (2h)*. Pale brown solid, mp: 110 °C; ^{1}H NMR, δ (ppm): 2.67 (s, 3H), 3.69 (s, 3H), 6.09 (s, 1H), 6.62–6.80 (m, 5H), 7.01–7.30 (m, 9H); ^{13}C NMR, δ (ppm): 34.33, 55.11, 66.48, 112.37, 112.97, 113.75, 116.76, 127.06, 128.49, 129.15, 129.97, 132.73, 141.05, 150.18, 158.75; MS, *m/z* (relative intensity): 303 (9), 198 (16), 197 (100), 182 (13), 166 (8), 165 (17), 154 (6), 153 (11), 152 (6); HRMS calcd for $C_{21}H_{22}NO$ $[M+H]^+$: 304.1701, found: 304.1702.

4.6.20. 4-((4-Methoxyphenyl(piperidin-1-yl)methyl)benzonitrile (3a).[17] Pale yellow viscous oil; IR, ν (cm^{-1}): 2230; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.74 (s, 3H), 4.23 (s, 1H), 6.81 (AB, J=8.7 Hz, 2H), 7.22 (AB, J=8.7 Hz, 2H), 7.52 (s, 4H); ^{13}C NMR, δ (ppm): 24.64, 26.24, 53.04, 55.23, 75.60, 110.34, 114.05, 119.07, 128.49, 129.19, 132.28, 133.60, 149.63, 158.86; MS, *m/z* (relative intensity): 306 (9), 223 (18), 222 (100), 204 (20), 190 (9), 178 (7); HRMS calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$: 307.1810, found: 307.1816.

4.6.21. 1-((4-Methoxyphenyl)(2-nitrophenyl)methyl)-piperidine (3b)*. Pale orange viscous oil; IR, ν (cm^{-1}): 1527, 1247; ^{1}H NMR, δ (ppm): 1.39–1.51 (m, 6H), 2.27 (br s, 4H), 3.70 (s, 3H), 4.82 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.19–7.33 (m, 3H), 7.46–7.62 (m, 2H), 8.02 (d, J=8.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.44, 26.03, 52.78, 54.92, 68.45, 113.60, 123.80, 127.15, 129.49, 129.67, 132.29, 137.66, 149.98, 158.61; MS, *m/z* (relative intensity): 326 (6), 310 (20), 309 (100), 279 (16), 278 (69), 242 (6), 227 (7), 226 (35), 225 (7), 211 (11), 196 (13), 195 (7), 183 (10), 181 (8), 165 (8), 154 (6), 153 (9), 152 (12), 135 (13), 123 (10), 84 (39); HRMS calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1709, found: 327.1700.

4.6.22. 1-((4-Methoxyphenyl)(3-nitrophenyl)methyl)-piperidine (3c)*. Pale orange viscous oil; IR, ν (cm^{-1}): 1530, 1353; ^{1}H NMR, δ (ppm): 1.42–1.62 (m, 6H), 2.31 (br s, 4H), 3.74 (s, 3H), 4.31 (s, 1H), 6.82 (AB, J=8.7 Hz, 2H), 7.26 (AB, J=8.7 Hz, 2H), 7.40 (t, J=7.9 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 8.01 (d, J=7.8 Hz, 1H), 8.29 (br s, 1H); ^{13}C NMR, δ (ppm): 24.61, 26.22, 52.98, 55.21, 75.16, 114.06, 121.74, 122.69, 129.18, 133.57, 133.84, 134.17, 146.34, 148.48, 158.86; MS, *m/z* (relative intensity): 327 (9), 326 (30), 243 (18), 242 (100), 226 (6), 225 (30), 204 (36), 196 (18), 195 (13), 181 (5), 165 (6), 153 (18), 152 (14), 84 (8); HRMS calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1709, found: 327.1712.

4.6.23. 1-((4-Methoxyphenyl)(4-nitrophenyl)methyl)-piperidine (3d)*. Pale orange viscous oil; IR, ν (cm^{-1}): 1516, 1345; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.72 (s, 3H), 4.29 (s, 1H), 6.81 (AB, J=8.7 Hz, 2H), 7.24 (AB, J=8.7 Hz, 2H), 7.57 (AB, J=8.8 Hz, 2H), 8.09 (AB, J=8.8 Hz, 2H); ^{13}C NMR, δ (ppm): 24.64, 26.25, 53.06, 55.21, 75.39, 114.10, 123.75, 128.45, 129.20, 133.40, 146.68, 151.82, 158.92; MS, *m/z* (relative intensity): 326 (9), 243 (16), 242 (100), 219 (5), 212 (8), 204 (19), 196 (20), 153 (8), 152 (7); HRMS calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1709, found: 327.1716.

4.6.24. 1-((4-Methoxyphenyl)(2-(trifluoromethyl)-phenyl)methyl)piperidine (3e)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.44–1.52 (m, 6H), 2.16–2.37 (m, 4H), 3.68 (s, 3H), 4.60 (s, 1H), 6.78 (d, J=8.8 Hz, 2H), 7.17 (t, J=7.6 Hz, 1H), 7.38–7.54 (m, 4H), 8.08 (d, J=7.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.76, 26.40, 53.25, 55.11, 69.70, 113.75, 124.71 (q, J=272 Hz), 125.57 (q, J=6 Hz), 126.51, 128.05 (q, J=29 Hz), 129.51, 129.63, 132.09, 134.47, 143.45, 158.60; ^{19}F NMR, δ (ppm): −56.14; MS, *m/z* (relative intensity): 349 (20), 266 (17), 265 (100), 250 (7), 245 (10), 205 (6), 204 (30), 181 (6), 153 (6); HRMS calcd for $C_{20}H_{23}F_3NO$ $[M+H]^+$: 350.1732, found: 350.1711.

4.6.25. 1-((4-Methoxyphenyl)(4-(trifluoromethyl)-phenyl)methyl) piperidine (3f)*. Pale yellow solid, mp: 59 °C; ^{1}H NMR, δ (ppm): 1.40–1.55 (m, 6H), 2.26–2.29 (m, 4H), 3.71 (s, 3H), 4.23 (s, 1H), 6.80 (AB, J=8.7 Hz, 2H), 7.26 (AB, J=8.7 Hz, 2H), 7.51 (s, 4H); ^{13}C NMR, δ (ppm): 24.69, 26.29, 53.28, 55.27, 75.66, 113.97, 124.39 (q, J=270 Hz), 125.37 (q, J=4 Hz), 128.10, 128.83 (q, J=32 Hz), 129.15, 134.26, 148.11, 158.78; ^{19}F NMR, δ (ppm): −62.18; MS, *m/z* (relative intensity): 349 (21), 330 (6), 266 (21), 265 (100), 250 (6), 233 (6), 204 (27), 196 (5), 181 (6), 165 (5), 153 (8); HRMS calcd for $C_{20}H_{23}F_3NO$ $[M+H]^+$: 350.1732, found: 350.1741.

4.6.26. 1-((2-Chlorophenyl)(4-methoxyphenyl)methyl)-piperidine (3g)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.41–1.54 (m, 6H), 2.28–2.30 (m, 4H), 3.67 (s, 3H), 4.70 (s, 1H), 6.76 (d, J=8.7 Hz, 2H), 6.98–7.37 (m, 5H), 7.82 (d, J=7.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.67, 26.16, 53.07, 54.96, 70.40, 113.52, 126.92, 127.26, 128.59, 128.90, 129.35, 129.58, 133.63, 141.15, 158.38; MS, *m/z* (relative intensity): 317 (8), 316 (6), 315 (25), 234 (6), 233 (29), 232 (17), 231 (100), 204 (31), 197 (12), 196 (22), 195 (15), 181 (15), 165 (9), 153 (15), 152 (18), 84 (6); HRMS calcd for $C_{19}H_{23}ClNO$ $[M+H]^+$: 316.1468, found: 316.1459.

4.6.27. 1-((3-Chlorophenyl)(4-methoxyphenyl)methyl)-piperidine (3h).[17] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.71 (s, 3H), 4.14 (s, 1H), 6.79 (d, J=8.6 Hz, 2H), 7.05–7.40 (m, 6H); ^{13}C NMR, δ (ppm): 24.79, 26.35, 53.13, 55.23, 75.53, 113.93, 126.02, 126.76, 127.92, 129.17, 129.77, 134.37, 146.09, 158.69; MS, *m/z* (relative intensity): 315 (12), 234 (7), 233 (33), 232 (17), 231 (100), 204 (26), 197 (7), 196

(29), 195 (7), 181 (10), 165 (6), 153 (7), 152 (6); HRMS calcd for $C_{19}H_{23}ClNO$ $[M+H]^+$: 316.1468, found: 316.1470.

4.6.28. 1-((4-Chlorophenyl)(4-methoxyphenyl)methyl)-piperidine (3i)*. Pale yellow solid, mp: 94 °C; ^1H NMR, δ (ppm): 1.40–1.54 (m, 6H), 2.25–2.28 (m, 4H), 3.74 (s, 3H), 4.15 (s, 1H), 6.80 (d, J=8.7 Hz, 2H), 7.19–7.51 (m, 6H); ^{13}C NMR, δ (ppm): 24.80, 26.17, 52.93, 55.10, 75.11, 113.72, 128.40, 128.99, 132.04, 134.61, 142.19, 145.63, 158.43; MS, m/z (relative intensity): 317 (7), 315 (16), 233 (29), 232 (15), 231 (100), 204 (9), 196 (21), 195 (6), 181 (15), 165 (8), 153 (14), 152 (10); HRMS calcd for $C_{19}H_{23}ClNO$ $[M+H]^+$: 316.1468, found: 316.1481.

4.6.29. 1-((3-Bromophenyl)(4-methoxyphenyl)methyl)-piperidine (3j)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.39–1.60 (m, 6H), 2.25–2.27 (m, 4H), 3.71 (s, 3H), 4.13 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.05–7.33 (m, 5H), 7.56 (t, J=1.7 Hz, 1H); ^{13}C NMR, δ (ppm): 24.49, 26.06, 52.87, 54.97, 75.27, 113.67, 122.34, 126.19, 128.92, 129.69, 130.42, 130.71, 134.19, 146.10, 158.42; MS, m/z (relative intensity): 361 (16), 359 (20), 278 (17), 277 (97), 276 (24), 275 (100), 205 (10), 204 (56), 197 (14), 196 (53), 195 (16), 182 (7), 181 (35), 165 (15), 153 (24), 152 (23), 84 (12); HRMS calcd for $C_{19}H_{23}BrNO$ $[M+H]^+$: 360.0963, found: 360.0950.

4.6.30. 1-((3-Fluorophenyl)(4-methoxyphenyl)methyl)-piperidine (3k).[25] Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.39–1.59 (m, 6H), 2.26–2.29 (m, 4H), 3.70 (s, 3H), 4.17 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.13–7.29 (m, 6H); ^{13}C NMR, δ (ppm): 24.72, 26.29, 53.07, 55.17, 75.49, 113.46 (d, J=22 Hz), 113.84, 114.52 (d, J=21 Hz), 123.52 (d, J=2 Hz), 129.14, 129.74 (d, J=8 Hz), 134.54, 146.66 (d, J=6 Hz), 158.63, 163.05 (d, J=243 Hz); ^{19}F NMR, δ (ppm): −112.80; MS, m/z (relative intensity): 299 (18), 216 (16), 215 (100), 204 (26), 200 (8), 184 (8), 183 (14), 172 (7), 171 (12), 170 (5), 165 (6), 84 (6); HRMS calcd for $C_{19}H_{23}FNO$ $[M+H]^+$: 300.1764, found: 300.1771.

4.6.31. 1-((4-Methoxyphenyl)(naphthalen-1-yl)methyl)-piperidine (3l)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.43–1.61 (m, 6H), 2.37–2.46 (m, 4H), 3.60 (s, 3H), 4.98 (s, 1H), 6.74 (d, J=8.7 Hz, 2H), 7.34–7.53 (m, 5H), 7.68–7.81 (m, 2H), 8.02 (d, J=7.2 Hz, 1H), 8.44 (d, J=8.2 Hz, 1H); ^{13}C NMR, δ (ppm): 24.70, 26.47, 53.71, 55.00, 71.53, 113.58, 123.78, 124.90, 125.78, 127.33, 128.87, 129.62, 131.64, 134.13, 134.56, 139.50, 145.56, 158.32; MS, m/z (relative intensity): 331 (13), 248 (27), 247 (100), 233 (5), 232 (16), 231 (7), 217 (9), 216 (15), 215 (26), 204 (15), 203 (13), 202 (14), 84 (21); HRMS calcd for $C_{23}H_{26}NO$ $[M+H]^+$: 332.2014, found: 332.2018.

4.6.32. 1-((4-*tert*-Butylphenyl)(4-methoxyphenyl)-methyl)piperidine (3m)*. Pale yellow solid, mp: 110 °C; ^1H NMR, δ (ppm): 1.25 (s, 9H), 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.68 (s, 3H), 4.14 (s, 1H), 6.77 (d, J=8.6 Hz, 2H), 7.20–7.40 (m, 6H); ^{13}C NMR, δ (ppm): 24.91, 26.43, 31.55, 34.47, 53.28, 55.18, 75.87, 113.75, 125.27, 127.56, 129.13, 135.76, 140.61, 149.28, 158.41; MS, m/z (relative intensity): 337 (9), 253 (100), 238 (14), 223 (15), 204 (6); HRMS calcd for $C_{23}H_{32}NO$ $[M+H]^+$: 338.2484, found: 338.2503.

4.6.33. 1-((2-Methylphenyl)(4-methoxyphenyl)methyl)-piperidine (3n)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.40–1.54 (m, 6H), 2.08–2.38 (m, 7H), 3.67 (s, 3H), 4.31 (s, 1H), 6.76 (d, J=8.7 Hz, 2H), 6.99–7.29 (m, 5H), 7.79 (d, J=7.6 Hz, 1H); ^{13}C NMR, δ (ppm): 20.04, 25.03, 26.50, 53.64, 55.23, 71.37, 113.76, 126.31, 127.16, 129.92, 130.61, 134.43, 135.80, 142.17, 158.48; MS, m/z (relative intensity): 296 (5), 295 (20), 212 (14), 211 (100), 210 (74), 209 (17), 204 (16), 196 (21), 195 (6), 188 (5), 187 (7), 181 (11), 180 (13), 179 (47), 166 (5), 165 (13), 153 (8), 152 (7), 105 (13); HRMS calcd for $C_{20}H_{26}NO$ $[M+H]^+$: 296.2014, found: 296.2012.

4.6.34. 1-((4-Methoxyphenyl)(4-(methylthio)phenyl)-methyl)piperidine (3o)*. Pale yellow solid, mp: 72 °C; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.35 (m, 4H), 2.37 (s, 3H), 3.69 (s, 3H), 4.14 (s, 1H), 6.78 (d, J=8.7 Hz, 2H), 7.10–7.32 (m, 6H); ^{13}C NMR, δ (ppm): 15.82, 24.67, 26.21, 52.96, 55.03, 75.31, 113.64, 126.71, 128.27, 128.86, 135.05, 136.14, 140.63, 158.32; MS, m/z (relative intensity): 327 (7), 245 (6), 244 (17), 243 (100), 196 (11), 195 (6), 181 (6), 153 (7), 152 (6); HRMS calcd for $C_{20}H_{26}NOS$ $[M+H]^+$: 328.1735, found: 328.1749.

4.6.35. 1-((3-Methoxyphenyl)(4-(methoxy)phenyl)-methyl)piperidine (3p)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.39–1.53 (m, 6H), 2.27–2.30 (m, 4H), 3.67 (s, 3H), 3.71 (s, 3H), 4.13 (s, 1H), 6.64–6.69 (m, 1H), 6.77 (AB, J=8.7 Hz, 2H), 6.94–6.98 (m, 2H), 7.14 (t, J=7.8 Hz, 1H), 7.28 (AB, J=8.7 Hz, 2H); ^{13}C NMR, δ (ppm): 24.76, 26.30, 49.86, 53.10, 55.00, 75.93, 111.61, 113.47, 113.64, 120.25, 128.91, 129.11, 135.17, 145.56, 158.40, 159.62; MS, m/z (relative intensity): 311 (9), 229 (5), 228 (38), 227 (100), 212 (12), 204 (22), 197 (10), 196 (15), 195 (11), 181 (6), 169 (7), 141 (5), 121 (5), 84 (16); HRMS calcd for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1964, found: 312.1957.

4.6.36. 1-((4-Methoxyphenyl)(thiophen-2-yl)methyl)-piperidine (3q)*. Pale yellow solid, mp: 60 °C; ^1H NMR, δ (ppm): 1.36–1.60 (m, 6H), 2.33–2.38 (m, 4H), 3.71 (s, 3H), 4.60 (s, 1H), 6.80–6.86 (m, 4H), 7.12–7.15 (m, 1H), 7.28–7.33 (m, 2H); ^{13}C NMR, δ (ppm): 24.66, 26.28, 52.40, 55.17, 70.65, 113.54, 124.65, 124.92, 126.19, 129.55, 133.12, 148.19, 158.72; MS, m/z (relative intensity): 287 (7), 205 (6), 204 (21), 203 (100), 172 (5), 171 (6), 160 (7); HRMS calcd for $C_{17}H_{22}NOS$ $[M+H]^+$: 288.1422 found: 288.1435.

4.6.37. 1-((4-Methoxyphenyl)(thiophen-3-yl)methyl)-piperidine (3r)*. Pale brown solid, mp: 67 °C; ^1H NMR, δ (ppm): 1.38–1.54 (m, 6H), 2.30 (br s, 4H), 3.73 (s, 3H), 4.38 (s, 1H), 6.81 (d, J=8.4 Hz, 2H), 7.02–7.29 (m, 5H); ^{13}C NMR, δ (ppm): 24.59, 26.21, 52.51, 55.02, 70.84, 113.43, 121.35, 125.24, 127.44, 129.17, 134.07, 144.26, 158.32; MS, m/z (relative intensity): 287 (11), 205 (7), 204 (24), 203 (100), 172 (6), 171 (6), 160 (5), 159 (6), 84 (5); HRMS calcd for $C_{17}H_{22}NOS$ $[M+H]^+$: 288.1422, found: 288.1433.

4.6.38. 1-(Furan-3-yl(4-methoxyphenyl)methyl)piperidine (3s)*. Pale yellow solid, mp: 60 °C; ^1H NMR, δ (ppm): 1.36–1.59 (m, 6H), 2.29–2.34 (m, 4H), 3.74 (s, 3H), 4.30 (s, 1H), 6.34 (s, 1H), 6.82 (d, J=8.7 Hz, 2H), 7.24–7.31 (m, 4H); ^{13}C NMR, δ (ppm): 24.65, 26.28,

52.15, 55.05, 66.23, 110.42, 113.45, 126.74, 129.15, 133.72, 140.09, 142.75, 158.48; MS, *m/z* (relative intensity): 271 (17), 242 (7), 188 (18), 187 (100), 159 (9), 144 (19), 115 (8); HRMS calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1651, found: 272.1656.

4.6.39. 3-((4-Methoxyphenyl)(piperidin-1-yl)methyl)pyridine (3t)*. Pale yellow solid, mp: 60 °C; ^{1}H NMR, δ (ppm): 1.40–1.60 (m, 6H), 2.30 (br s, 4H), 3.71 (s, 3H), 4.25 (s, 1H), 6.81 (AB, J=8.7 Hz, 2H), 7.15 (dd, J=7.9, 4.8 Hz, 1H), 7.26 (AB, J=8.7 Hz, 2H), 7.69 (dt, J=7.9, 1.8 Hz, 1H), 8.40 (dd, J=4.8, 1.5 Hz, 1H), 8.63 (d, J=1.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.33, 25.90, 52.68, 54.89, 73.15, 113.68, 123.13, 128.82, 133.65, 135.06, 138.63, 147.90, 149.40, 158.43; MS, *m/z* (relative intensity): 282 (13), 204 (32), 199 (21), 198 (100), 183 (17), 167 (15), 155 (17), 154 (17); HRMS calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283.1810, found: 283.1815.

4.6.40. 4-((4-Methoxyphenyl)(piperidin-1-yl)methyl)pyridine (3u)*. Pale yellow solid, mp: 70 °C; ^{1}H NMR, δ (ppm): 1.39–1.54 (m, 6H), 2.09–2.28 (m, 4H), 3.70 (s, 3H), 4.18 (s, 1H), 6.80 (AB, J=8.6 Hz, 2H), 7.23 (AB, J=8.6 Hz, 2H), 7.33 (d, J=6.0 Hz, 2H), 8.47 (d, J=6.0 Hz, 2H); ^{13}C NMR, δ (ppm): 24.36, 25.96, 52.64, 54.88, 74.69, 113.67, 122.72, 129.03, 132.84, 149.59, 152.52, 158.61; MS, *m/z* (relative intensity): 282 (23), 205 (14), 204 (100), 199 (29), 198 (85), 184 (5), 183 (19), 175 (5), 167 (24), 155 (16), 154 (15), 121 (8); HRMS calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283.1810, found: 283.1804.

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