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Direct Aminoalkylation of Arenes, Heteroarenes, and Alkenes via Ni-Catalyzed Negishi Cross-Coupling Reactions

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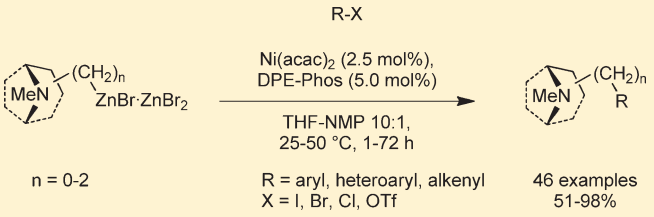
Supporting Information

ABSTRACT: A room-temperature Ni-catalyzed cross-coupling of aryl, heteroaryl, and alkenyl electrophiles with aminoalkylzinc bromides, readily available from the corresponding aminoalkyl chlorides via Grignard reagents, was developed. The reaction allows a convenient one-step preparation of various aminoalkyl products, including piperidine and tropane derivatives. Such functionalized amine moieties are widely present in various biologically active molecules. Aryl, heteroaryl, and alkenyl iodides, bromides, chlorides and triflates are suitable electrophiles. A short total synthesis of two natural products, (±)-galipinine and (±)-cusparine, is also reported.



INTRODUCTION

One of the most frequently occurring functionalities in biologically or pharmacologically active compounds is the aminoalkyl moiety.[1] The basic trialkylamine is one of the most important pharmacophore groups.[2] A method for the simple, direct, and convenient introduction of these aminoalkyl residues into funtionalized compounds would therefore be of great interest.[3] For aryl, heteroaryl, or alkenyl structures this task can be easily accomplished by using cross-coupling chemistry. Whereas many reports dealing with cross-coupling reactions of alkyl organometallics derivatives bearing an amide or sulfonamide nitrogen have been published,[4] no coupling procedures of an aminoalkyl zinc or magnesium organometallic species bearing a basic nitrogen are known. Molander described a direct Pd-catalyzed cross-coupling of aminoalkyl groups to arenes and heteroarenes using potassium aminoalkyltrifluoroborates.[5a] The high potential of this protocol for the synthesis of biologically active molecules was also demonstrated. This reaction is so far described for primary alkylamines.[5b,c] Recently, we reported a novel aminoalkylation based on a Ni-catalyzed cross-coupling reaction between aminoalkylzinc compounds and various aryl and heteroaryl bromides, chlorides, and triflates.[6] This method allows a direct introduction of both primary and secondary aminoalkyl groups possessing a basic nitrogen. Herein, we describe the full scope of this cross-coupling. Furthermore, we report a total synthesis of two natural products, (±)-galipinine and (±)-cusparine, demonstrating the utility of the cross-coupling.

RESULTS AND DISCUSSION

The alkylzinc halides required as nucleophiles for the Negishi cross-coupling are easily accessed from the corresponding chlorides via a Grignard reagent and transmetalation with $ZnCl_2$. Therefore, treatment of commercial 3-dimethylaminopropyl chloride hydrochloride (**1**) with LiH (2.0 equiv) in THF, followed by filtration, resulted in a solution of the corresponding chloramines. Insertion of magnesium turnings activated with DIBAL-H[7] (3 mol %) in the presence of LiCl[8] (2 equiv) in THF (reflux, 2 h) afforded the organomagnesium compound. A subsequent transmetalation using $ZnBr_2$ (2 equiv, 1.0 M in THF/NMP 10:1)[9] gave 3-dimethylaminopropylzinc bromide (**2a**) in 82% yield, as determined by iodometric titration[10] (Scheme 1). The presence of $ZnBr_2$ was essential for the success of the cross-coupling (see below).

Palladium catalysts, previously used to perform sp^3-sp^2 Negishi cross-couplings,[11] were not very promising. Only traces of the cross-coupling product were detected using $Pd_2(dba)_3$ (2.5 mol %) and PPh_3, $P(o\text{Tol})_3$,[11a] $PtBu_3$,[11b] or tri(2-furyl)-phosphine[11c,d] in the model reaction of the zinc reagent **2a** with *m*-bromoanisole (**3a**, Table 1, entry 1). $Pd(dppf)Cl_2$[11f] gave the product **4a** in merely 37% yield at 25 °C within 16 h, and also the highly active PEPPSI[11f−h] catalyst provided better but still unsatisfactory yields (entry 11). Since inexpensive Ni catalysts recently showed remarkable high activities in the Negishi cross-coupling,[12] we have tested several common phosphine ligands in the presence of $Ni(acac)_2$ or $NiCl_2$ (2.5 mol %). We found that electron-rich phosphine ligands such as $P(o\text{Tol})Ph_2$ (entry 6), $n\text{BuPAd}_2$[13a] (entry 7), $P(O\text{iPr})_3$[13b] (entry 9), or $P(p\text{Tol})_3$ (entry 12) gave the best results. Among the ligands screened, bis(2-diphenylphosphinophenyl)ether (DPE-Phos)[14] turned out to be the most active and robust, affording the cross-coupling product **4a** in almost quantitative yield (entry 14). Further optimization revealed that the optimal ratio of the ligand to nickel was 2:1 (entry 15), and the optimal amount of $ZnBr_2$ was 2 mol per mol of the Grignard reagent (entry 16).[15]

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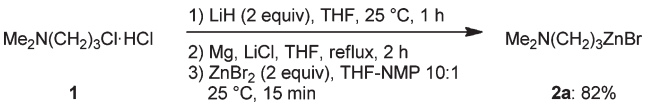
Having established the optimized conditions for the cross-coupling reaction, we investigated the behavior of other primary and secondary aminoalkylzinc reagents. Following the same protocol, aminoalkylzinc reagents **2a**−**e** were prepared starting from commercially available hydrochlorides (for **2a**−**d**) or from tropanol (for **2e**). Noteworthy, the corresponding aminoalkylmagnesium chlorides solutions in THF are relatively stable and can be stored at 0 °C (titration after 6 months revealed the loss of active magnesium species being less than 20%).

Cross-Coupling Reactions of Aminoalkylzinc Reagent 2a Leading to Products 4b−j. Hence we used 3-dimethylaminopropylzinc bromide (**2a**) in the presence of $Ni(acac)_2$ (2.5 mol %) and DPE-Phos (5.0 mol %) in the optimized solvent mixture (THF/NMP 10:1)[12c,d] at 25 °C for the cross-coupling reaction with various functionalized aryl and heteroaryl bromides and chlorides, and we obtained the products **4b**−**j** in good to excellent yields within 1−3 h (Scheme 2).

Trisubstituted aryl bromides **3b** and **3c** underwent the coupling reaction within 1−3 h, and the corresponding alkylated arenes **4b** and **4c** were obtained in 79−83% yield (Table 2, entries 1 and 2). A ketone function is compatible with the reaction conditions, and we isolated the *p*-keto-substituted alkylbenzene **4d** in 90% yield from the reaction of zinc reagent **2a** with 1-(4-bromophenyl)pentan-1-one (**3d**, 1 h, entry 3). Also the bromopyridine **3e** bearing an ester function and 4-bromoisoquinoline (**3f**) were submitted to the cross-coupling protocol and furnished the pyridine **4e** and the aminoalkylated isoquinoline **4f** in 80−84% yield within 3 h (entries 4 and 5). 6-Bromoquinoxaline (**3g**) and the Boc-protected indole **3h** were cross-coupled with **2a** within 1−2 h and led to heterocycles **4g** and **4h** in 86−98% yield (entries 6 and 7). Finally, the brominated furan **3i** and 2-chloroquinoline (**3j**) were suitable electrophiles for the

Scheme 1. Preparation of 3-Dimethylaminopropylzinc Bromide (2a)



Scheme 2. Ni-Catalyzed Cross-Coupling Reaction of Aminoalkylzinc Reagent 2a

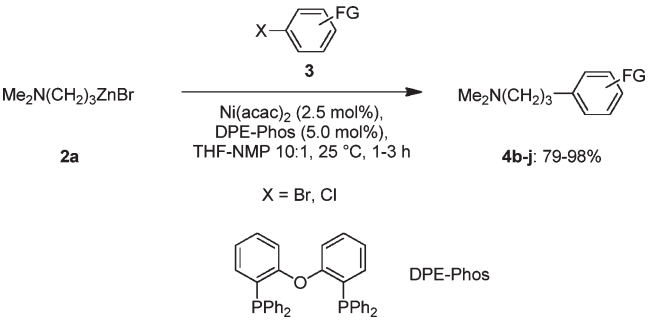
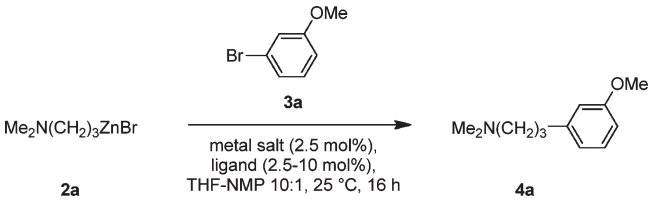
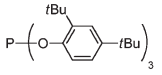


Table 1. Ligand Screening in the Cross-Coupling Reaction of 3-Dimethylaminopropylzinc Bromide (2a) with 3-Bromoanisole (3a)



Entry	Metal salt (2.5 mol%)	Ligand (2.5-10 mol%)	Ratio salt to ligand	Yield of **4a** [%][a]
1	$Pd_2(dba)_3$	P(2-fur)$_3$	1:2	4
2	$Ni(acac)_2$	P*t*Bu$_3$·HBF$_4$	1:2	12
3	$Ni(acac)_2$	IPr·HCl	1:1	17
4	$NiCl_2$	dppp	1:1	33
5	$PdCl_2$	dppf	1:1	37
6	$Ni(acac)_2$	P(*o*Tol)Ph$_2$	1:2	49
7	$Ni(acac)_2$	*n*BuPAd$_2$	1:2	50
8	$Ni(acac)_2$	P(*o*Tol)$_3$	1:2	54
9	$Ni(acac)_2$	P(O*i*Pr)$_3$	1:3	73
10	$Ni(acac)_2$	PPh_3	1:3	79
11	PEPPSI	-	-	84
12	$Ni(acac)_2$	P(*p*Tol)$_3$	1:4	87
13	$Ni(acac)_2$		1:3	88
14	$Ni(acac)_2$	DPE-Phos	1:1	93
15	$Ni(acac)_2$	DPE-Phos	1:2	97
16	$Ni(acac)_2$	DPE-Phos	1:2	99[b]

[a] GC yield using tridecane as internal standard. [b] 2.0 equiv of $ZnBr_2$ used.

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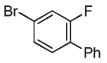
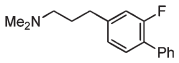
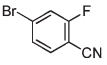
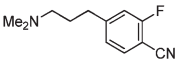
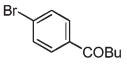
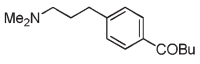
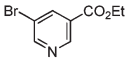
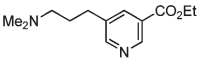
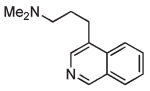
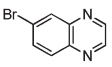
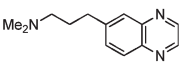
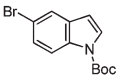
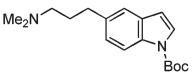
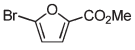
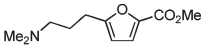
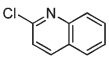
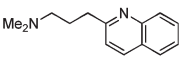
Table 2. Preparation of Products 4b−j Obtained by Cross-Coupling (THF, 25 °C) Using Zinc Reagent 2a

Entry	Electrophile	Product, [h][a]	Yield [%][b]
1	 **3b**	 **4b** (3)	83
2	 **3c**	 **4c** (1)	79
3	 **3d**	 **4d** (1)	90
4	 **3e**	 **4e** (3)	80
5	 **3f**	 **4f** (3)	84
6	 **3g**	 **4g** (1)	98
7	 **3h**	 **4h** (2)	86
8	 **3i**	 **4i** (3)	84
9	 **3j**	 **4j** (3)	88

[a] Reaction time. [b] Yield of isolated, analytically pure product after aqueous workup without chromatographical purification.

protocol and led to the 2,5-disubstituted furan **4i** and quinoline derivative **4j** in 84−88% yield (entries 8 and 9).

Cross-Coupling Reactions of Primary Aminoalkylzinc Reagents 2b and 2c Leading to Products 5a−f and 6a−d. The primary aminoalkylzinc bromides **2b** and **2c**, prepared via the usual procedure in 56−77% yield, were used for the cross-coupling reaction with various aryl and heteroaryl bromides or chlorides and led to the aminoalkyl products **5a−f** and **6a−d** in in 56−95% yield within 1−48 h (Scheme 3).

Hence the reaction of **2b** with 3-bromoanisole (**3a**) or 1-bromo-3-(trifluoromethoxy)benzene (**3k**) or the biphenyl derivative **3b** furnished the corresponding alkylated arenes **5a−c** in 70−80% yield within 3−48 h (Table 3, entries 1−3). Performing the reaction with ethyl 5-bromonicotinate (**3e**) led to the pyridine derivative **5d** in 95% yield (entry 4). The protected 5-bromoindole **3h** and the chloro-substituted quinoline **3j** led to the heterocyclic piperidinyl derivatives **5e** and **5f** in 56−95% yield (entries 5 and 6). ((1-Methylpiperidin-3-yl)methyl)zinc bromide (**2c**) underwent the Ni-catalyzed cross-coupling reaction in a similar fashion, and the reaction with anisole derivative **3a** or the bis-halogenated benzonitrile **3c** proceeded smoothly and yielded the alkylbenzene derivatives **6a** and **6b** in 56−66% yield (entries 7 and 8). Additionally, the heterocyclic bromide **3h** and 2-chloro-6-methoxypyridine (**3l**) gave, after cross-coupling with **2c**, the piperidinyl compounds **6c** and **6d** in 60−90% yield (entries 9 and 10).

Cross-Coupling Reactions of Secondary Aminoalkylzinc Reagents 2d and 2e Leading to Products 7a−i and 8a−e. The secondary aminoalkylzinc bromides **2d** and **2e** could be prepared via magnesium insertion and subsequent transmetalation using $ZnBr_2$. To our delight, they performed equally well in the cross-coupling protocol with various halides and triflates,

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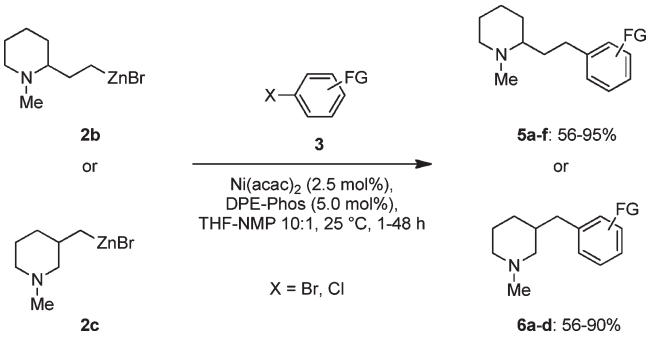
Scheme 3. Ni-Catalyzed Cross-Coupling Reaction of Aminoalkylzinc Reagents 2b and 2c



furnishing within 1−48 h the corresponding products **7a**−**i** and **8a**−**e** in 55−96% yield (Scheme 4).[16]

The reaction of (1-methylpiperidin-4-yl)zinc bromide (**2d**) with the 5-iodo-uracil derivative **3m** at 25 °C for 48 h gave the uracil derivative **7a** in 60% yield (Table 4, entry 1). Similarly, the cyano-, acetonitrile-, or keto-substituted bromobenzenes **3c,d,n,o** furnished the corresponding piperidine derivatives **7b**−**e** in 84−96% yield (1−8 h, entries 2−5). 6-Bromoquinoxaline (**3g**) and the methoxy-substituted 2-pyridinyl chloride **3l** smoothly underwent the coupling within 3 h and afforded the N-heterocyclic compounds **7f** and **7g** in 55−79% yield (entries 6 and 7). Noteworthy, aryl or heteroaryl triflates react well. Hence, the electron-rich naphthyl triflate **3p** reacted with (1-methylpiperidin-4-yl)zinc bromide (**2d**) for 48 h, leading to the alkylated product **7h** in 93% yield (entry 8). Finally, quinolin-2-yl trifluoromethanesulfonate (**3q**) furnishes the 2-piperidinyl quinoline **7i** (25 °C, 8 h) in 95% yield (entry 9).

Remarkably, the cross-coupling of 8-methyl-8-azabicyclo-[3.2.1]octylzinc species derived from tropanol gave exclusively *exo*-3-aryltropanes, as confirmed by NOESY experiments. We assume that this selectivity results from the stereospecific formation of the intermediate chelate stabilized Grignard reagent, and that the cross-coupling reaction proceeds with retention of configuration.[17] So the electron-rich 3-bromoanisole (**3a**) and also the electron-deficient 2-(4-bromophenyl)acetonitrile (**3o**) reacted smoothly with the zinc reagent **2e**, leading to the arylated tropane derivatives **8a** and **8b** in 55−92% yield (entries 10 and 11). Also a chloropyridine such as **3l** is a suitable substrate and delivered the heterocyclic product **8c** in 68% yield (72 h, entry 12). Finally, the triflates **3p,r** reacted with the zinc reagent **2e** affording the 3-naphthyl and the aryl-substituted tropane derivatives **8d** and **8e** in 62−73% yield (entries 13 and 14).

Cross-Coupling Reactions of Aminoalkylzinc Reagents 2a and 2d with Alkenyl Electrophiles Leading to Products 9a−e and 10a−e. Further studies showed that the $Ni(acac)_2$/DPE-Phos system catalyzed also the cross-coupling with alkenyl halides or triflates leading to the expected aminoalkylated products. Using the amino-substituted zinc reagents **2a,d** we have obtained the corresponding substituted alkenes **9a**−**e** and **10a**−**e** in 51−81% yield (25−50 °C, 10−24 h, Scheme 5).

The cross-coupling of β-bromostyrene (**3s**) with 3-dimethylaminopropylzinc bromide (**2a**) in the presence of $Ni(acac)_2$ (2.5 mol %) and DPE-Phos (5.0 mol %) for 16 h led to the styrene **9a** in 66% yield (Table 5, entry 1). The reaction of α-bromostyrene (**3t**) produced the geminal substituted ethene **9b** in 51% yield (16 h, entry 2). The coupling of the 4-chlorophenyl-substituted triflate **3u** or triflate **3v** bearing a nitrile group with aminoalkylzinc halide **2a** led to *para*-functionalized styrenes **9c,d** in 54−69% yield (entries 3 and 4). The triflate **3w** derived from tetralone was aminoalkylated with **2a**, yielding the functionalized dihydronaphthalene **9e** in 75% yield (entry 5). Likewise, secondary aminoalkylzinc bromides reacted with alkenyl halides, and the cross-coupling between **2d** and (*E*)-1-iodooct-1-ene (**3x**) provided the substituted piperidine **10a** in 58% yield within 24 h (entry 6). The Ni-catalyzed reaction of zinc reagent **2d** with 2-bromostyrene **3s** or (2-bromoethene-1,1-diyl)dibenzene (**3y**) furnished the bi- and trisubstituted piperidinylethylenes **10b** and **10c** in 77−81% yield (entries 7 and 8). (1-Methylpiperidin-4-yl)zinc bromide (**2d**) reacted with the triflates **3u** and **3w** leading to the corresponding products **10d** and **10e** in 54−56% yield (20 h, entries 9 and 10).

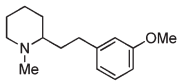
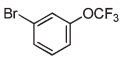
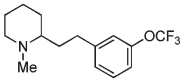
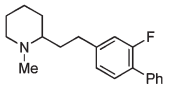
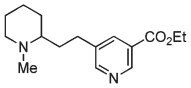
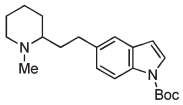
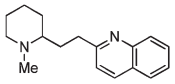
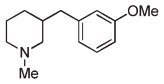
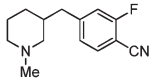
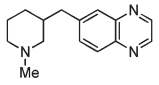
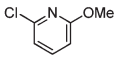
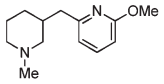
Synthesis of (±)-Cusparine (11) and (±)-Galipinine (12) Using a Ni-Catalyzed Cross-Coupling. Tetrahydroquinolines are an important structure found in many natural products. While the 3- and 4-substituted derivatives are easily accessible via a Grieco condensation,[18] the synthesis of 2-functionalized tetrahydroquinolines is often problematic. Cuspareine (**11**) and galipinine (**12**) are two recently discovered natural compounds showing interesting pharmacological profiles. They are found in the bark of *Galipea officinalis* Hancock, a shrubby tree from Venezuela,[19] and exhibit promising antibacterial activities against *Plasmodium falciparum*, the parasite causing malaria.[20] Several routes for their total synthesis have been devised,[21] including asymmetric approaches.[22] We have developed an alternative synthetic path toward these two tetrahydroquinolines, using the aminoalkyl cross-coupling as a key step.

Starting from commercial quinaldine (**13**), a hydroxymethylation with paraformaldehyde furnished 2-(quinolin-2-yl)ethanol (**14**) in 73% after recrystallization from *n*-heptane (Scheme 6).[23] Reduction of the quinoline ring with $NaBH_4$ in the presence of $NiCl_2$ (18 mol %) led to piperidine **15** in 87% yield,[24] which was submitted to an aminoalkylation using formaldehyde and $Na(BH_3)CN$,[25] yielding the corresponding *N*-methyl-piperidine **16** in quantitative yields. A chlorination with thionyl chloride in CH_2Cl_2[26] gave the amine **17** in 83% yield. Magnesium insertion facilitated by LiCl[8] gave access to the aminoalkylmagnesium chloride **18** (25 °C, 3 h) in 69% yield as determined by titration.[10] Transmetalation with $ZnBr_2$ (2.0 equiv) in THF/NMP 10:1 and Negishi coupling with 4-bromoveratrole (**19**) or 5-bromobenzo[*d*][1,3]dioxole (**20**) at 25 °C for 18−22 h led to (±)-cusparine (**11**), which was isolated in 88% yield, and (±)-galipinine (**12**) in 81% yield, 29−32% overall yield over the 6 steps of this racemic synthesis.

■ CONCLUSIONS

In summary, we have developed a general method for the one-pot aminoalkylation of arenes, heteroarenes, and ethenes, using a Ni-catalyzed Negishi cross-coupling reaction of primary as well as secondary aminoalkylzinc bromides. These reagents are easily available from the corresponding aminoalkyl chlorides. Aryl, heteroaryl, and alkenyl iodides, bromides, chlorides, and triflates are appropriate coupling electrophiles. A total synthesis of two natural products bearing this important structure, (±)-cusparine and (±)-galipinine, that includes the cross-coupling protocol as key step was also accomplished. Further development of this method is currently underway in our laboratories.

Table 3. Preparation of Products 5a−f and 6a−d Obtained by Cross-Coupling (THF, 25 °C) Using Zinc Reagents 2b and 2c

Entry	Electrophile	Product, [h][a]	Yield [%][b]
1	**3a**	 **5a** (18)	73
2	 **3k**	 **5b** (3)	80
3	**3b**	 **5c** (48)	70
4	**3e**	 **5d** (3)	95
5	**3h**	 **5e** (48)	56[c]
6	**3j**	 **5f** (1)	95
7	**3a**	 **6a** (30)	56[c]
8	**3c**	 **6b** (10)	66[c]
9	**3h**	 **6c** (10)	60[c]
10	 **3l**	 **6d** (20)	90

[a] Reaction time. [b] Yield of isolated, analytically pure product after aqueous workup without chromatographical purification. [c] An additional purification by column chromatography was necessary.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes that were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H

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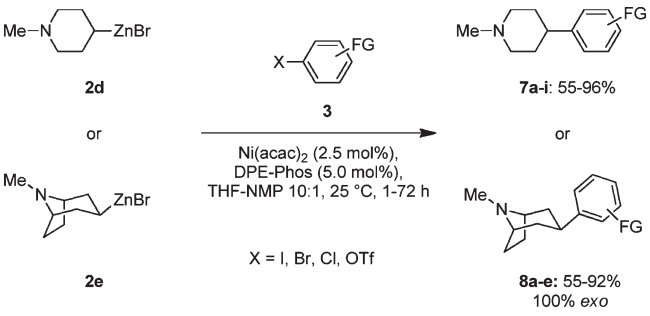
Scheme 4. Ni-Catalyzed Cross-Coupling Reaction of Aminoalkylzinc Reagents 2d and 2e



NMR (25 °C) and capillary GC. Purification via column chromatography was performed using silica gel 60 (40−63 μm 230−400 mesh ASTM). All reagents were obtained from commercial sources. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or C_6D_6 and chemical shifts (δ) are reported in parts per million (ppm). Mass spectra and high resolution mass spectra (HRMS) were recorded using electrospray ionization except where otherwise noted.

Preparation of $ZnBr_2$ Solution. $ZnBr_2$ solution (1.0 M in THF) was prepared by drying $ZnBr_2$ (22.5 g, 100 mmol) in a Schlenk flask under vacuum at 140 °C for 5 h. After cooling, THF (100 mL) was added, and stirring was continued until all salts were dissolved.

Typical Procedure for Preparation Aminoalkylmagnesium Chlorides 2a−e by Insertion of Magnesium (TP1). In a dry and argon-flushed Schlenk flask, equipped with a stirring bar and a pressure vent, were placed the hydrochloride (1.0 equiv) and LiH (3.0 equiv). THF (500 mL per 1 mol of the hydrochloride) was slowly added at room temperature under vigorous stirring, keeping the hydrogen formation at a controlled rate. After complete addition of the solvent, the mixture was stirred at room temperature for 1 h, then filtered through a Schlenk frit, and used without further purification.

Magnesium turnings (1.2 equiv) and LiCl (2.0 equiv) were placed in an argon-flushed three-necked flask and dried for 10−20 min at 130 °C under vacuum (1 mbar). The flask was refilled with argon and then cooled under argon. After the addition of THF (500 mL per 1 mol of the alkyl chloride) and DIBAL-H (20% in hexane, 3 mol %), the alkyl chloride dissolved in THF (500 mL per 1 mol) was added dropwise so that the mixture was gently boiling. Then, the reaction mixture was refluxed for another 2 h. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.3 to 0.8 M in THF was obtained.

Typical Procedure for Cross-Coupling of the Aminoalkylmagnesium Chlorides with Aryl Electrophiles Using Ni(acac)$_2$ and DPE-Phos (TP2). A dry and argon-flushed Schlenk flask, equipped with a septum and a magnetic stirring bar, was charged with a solution of $ZnBr_2$ (2 equiv, 2 mL, 1.0 M in THF) and *N*-methylpyrrolidone (0.3 mL). The mixture was stirred at room temperature for 15 min. The aminoalkylmagnesium chloride (1.2 mmol) was added, and the mixture was stirred at room temperature for 15 min. The electrophile (1.0 mmol), DPE-Phos (27 mg, 5 mol %), and Ni(acac)$_2$ (9 mg, 2.5 mol %) dissolved in THF (1 mL) were added, and the mixture was stirred at room temperature until the complete consumption of the electrophile was observed by GC analysis. The reaction mixture was quenched with satd aq K_2CO_3 solution (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were extracted with 2 N HCl (2 × 20 mL) and water (20 mL). The acidic aqueous layer was basified with satd K_2CO_3 and extracted with diethyl ether (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4). After filtration, the solvent was evaporated *in vacuo*, and the compound purified by column chromatography, if necessary.

Synthesis of Aminoalkylmagnesium Chlorides 2a−e. *3-(Dimethylamino)propylmagnesium Chloride (**2a**).* (3-Chloropropyl)-dimethylamine (12.16 g, 100 mmol) reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.80 M in THF was obtained in 82% yield.

*2-(1-Methylpiperidin-2-yl)ethylmagnesium Chloride (**2b**).* 2-(2-Chloroethyl)-1-methylpiperidine (16.17 g, 100 mmol) reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.71 M in THF was obtained in 66% yield.

*(1-Methylpiperidin-3-yl)methylmagnesium Chloride (**2c**).* 3-(Chloromethyl)-1-methylpiperidine (14.77 g, 100 mmol) reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.50 M in THF was obtained in 77% yield.

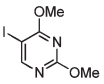
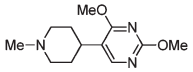
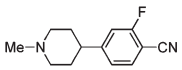
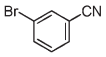
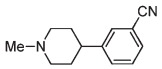
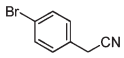
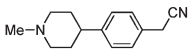
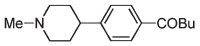
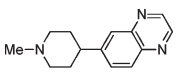
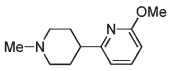
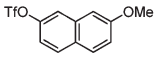
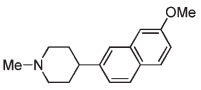
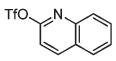
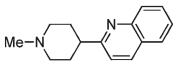
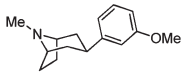
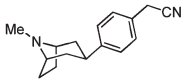
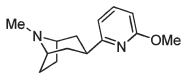
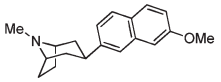
*(1-Methylpiperidin-4-yl)magnesium Chloride (**2d**).* 4-Chloro-1-methylpiperidine (13.36 g, 100 mmol) reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.62 M in THF was obtained in 56% yield.

3-Chloro-8-methyl-8-azabicyclo[3.2.1]octane. A solution of tropine (28.3 g, 200 mmol) in $CHCl_3$ (250 mL) was cooled to −30 °C. Thionyl chloride (47.6 g, 400 mmol) was added slowly, and the solution was stirred at reflux temperature for 3 h and then for an additional 16 h at room temperature. The solution was carefully mixed with 6 N NaOH, and the aqueous phase was extracted with CH_2Cl_2/Et_2O (1:1) and washed with satd aq K_2CO_3 solution (100 mL). The K_2CO_3 solution was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic layers were dried (Na_2SO_4). After removal of the solvent *in vacuo*, the crude product was purified by fractionated distillation, which furnished 3-chloro-8-methyl-8-azabicyclo[3.2.1]octane (14.9 g, 93.0 mmol, 47% yield) as a colorless oil. Bp (°C) 80 (12 mbar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 4.18−4.06 (m, 1H), 3.18−3.16 (m, 2H), 2.31 (s, 3H), 2.07−1.90 (m, 6H), 1.58−1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 61.4, 53.3, 41.1, 38.7, 26.7; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (vs), 2878 (s), 2798 (m), 1449 (m), 1336 (s), 1301 (m), 1238 (s), 1129 (w), 1042 (m), 1027 (s), 866 (m), 832 (m), 762 (s), 640 (m); MS (EI, 70 eV) *m*/*z* (%) 159 (7, M^+), 124 (100), 96 (11), 94 (3), 82 (8), 67 (7); HRMS (EI) calcd for $C_8H_{14}ClN$ 159.0815, found 159.0813. The analytical data match those from the literature: Archer, S.; Bell, M. R.; Lewis, T. R.; Schulenberg, J. W.; Unser, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 6337−6338.

*8-Methyl-8-azabicyclo[3.2.1]octyl-3-magnesium Chloride (**2e**).* 3-Chloro-8-methyl-8-azabicyclo[3.2.1]octane (15.97 g, 100 mmol) reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP1**. The fresh solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.3 M in THF was obtained, 35% yield.

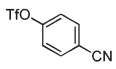
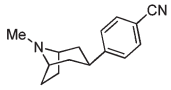
Synthesis of Aminoalkyl Cross-Coupling Products of Type 4. *3-(3-Methoxyphenyl)-N,N-dimethylpropan-1-amine (**4a**).* 3-Bromoanisole (**3a**; 187 mg, 1.00 mmol) reacted with 3-(dimethylamino)-propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished 3-(3-methoxyphenyl)-*N*,*N*-dimethylpropan-1-amine (**4a**; 188 mg, 97% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.21−7.15 (m, 1H), 6.79−6.70 (m, 3H), 3.78 (s, 3H), 2.63−2.58 (t, J = 7.8 Hz, 2H), 2.31−2.26 (t, J = 7.3 Hz, 2H), 2.21 (s, 6H), 1.83−1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 159.9, 144.2, 129.5, 121.0, 114.4, 111.3, 59.5, 55.4, 45.7, 34.0, 29.6; IR (ATR) $\tilde{\nu}$/cm^{-1} 3382 (vs), 3014

Table 4. Preparation of Products 7a−i and 8a−e Obtained by Cross-Coupling (THF, 25 °C) Using Zinc Reagents 2d and 2e

Entry	Electrophile	Product, [h][a]	Yield [%][b]
1	 **3m**	 **7a** (48)	60
2	**3c**	 **7b** (1)	88
3	 **3n**	 **7c** (8)	96
4	 **3o**	 **7d** (8)	94
5	**3d**	 **7e** (2)	84
6	**3g**	 **7f** (3)	79
7	**3l**	 **7g** (3)	55
8	 **3p**	 **7h** (48)	93
9	 **3q**	 **7i** (8)	95
10	**3a**	 **8a** (22)	55[c]
11	**3o**	 **8b** (72)	92[c]
12	**3l**	 **8c** (72)	68[c]
13	**3p**	 **8d** (72)	62[c]

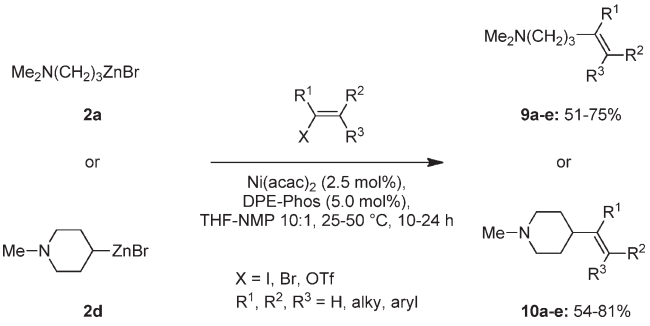
dx.doi.org/10.1021/jo201630e |*J. Org. Chem.* 2011, 76, 8891–8906

Table 4. Continued

Entry	Electrophile	Product, [h][a]	Yield [%][b]
14	 **3r**	 **8e** (8)	73[c]

[a] Reaction time. [b] Yield of isolated, analytically pure product after aqueous workup without chromatographical purification. [c] An additional purification by column chromatography was necessary.

Scheme 5. Ni-Catalyzed Cross-Coupling Reaction of Aminoalkylzinc Reagents 2a and 2d with Alkenyl Electrophiles



(m), 2942 (s), 2836 (m), 1600 (s), 1584 (s), 1486 (vs), 1466 (s), 1438 (s), 1258 (vs), 1154 (s), 1038 (s), 916 (m), 886 (w), 784 (m), 696 (m); MS (EI, 70 eV) *m*/*z* (%) 193 (43, M^+), 122 (11), 121 (8), 91 (7), 59 (4), 58 (100); HRMS (EI) calcd for $C_{12}H_{19}NO$ 193.1467, found 193.1466.

3-(2-Fluoro-[1,1′-biphenyl]-4-yl)-N,N-dimethylpropan-1-amine (**4b**). 4-Bromo-2-fluoro-1,1′-biphenyl (**3b**; 251 mg, 1.00 mmol) reacted with 3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished 3-(2-fluoro-[1,1′-biphenyl]-4-yl)-*N*,*N*-dimethylpropan-1-amine (**4b**; 213 mg, 83% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.50−7.48 (m, 2H), 7.39−7.34 (m, 2H), 7.32−7.27 (m, 2H), 7.00−6.93 (m, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.33 (t, *J* = 7.3 Hz, 2H), 2.23 (s, 6H), 1.85−1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 161.5, 158.2, 144.0, 136.0, 130.7, 129.1, 128.6, 127.6, 124.6, 116.3, 116.0, 59.1, 45.4, 33.2, 30.9, 29.0; IR (ATR) $\tilde{\nu}$/cm^{-1} 3398 (w), 2942 (w), 2860 (w), 2816 (w), 2766 (w), 1660 (m), 1626 (m), 1484 (m), 1416 (m), 1266 (m), 1124 (m), 1038 (w), 1010 (w), 828 (m), 766 (s), 740 (w), 722 (m), 696 (vs), 640 (w); MS (EI, 70 eV) *m*/*z* (%) 257 (7, M^+), 185 (4), 183 (4), 170 (3), 58 (100); HRMS (EI) calcd for $C_{17}H_{20}FN$ 257.1580, found 257.1564.

4-(3-(Dimethylamino)propyl)-2-fluorobenzonitrile (**4c**). 4-Bromo-2-fluorobenzonitrile (**3c**; 200 mg, 1.00 mmol) reacted with 3-(dimethylamino)-propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 1 h, according to **TP2**. Aqueous workup furnished 4-(3-(dimethylamino)propyl)-2-fluorobenzonitrile (**4c**; 163 mg, 79% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.46−7.41 (m, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 10.6 Hz, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.19 (t, *J* = 7.3 Hz, 2H), 2.13 (s, 6H), 1.75−1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 165.0, 161.6, 151.7, 133.4, 125.3, 116.5, 114.4, 58.7, 45.5, 33.7, 28.8; IR (ATR) $\tilde{\nu}$/cm^{-1} 2944 (m), 2860 (w), 2818 (m), 2768 (m), 2234 (m), 1622 (vs), 1568 (m), 1500 (m), 1430 (vs), 1252 (s), 1112 (s), 1038 (m), 830 (s), 736 (m), 634 (m); MS (EI, 70 eV) *m*/*z* (%) 206 (6, M^+), 134 (3), 106 (2), 71 (3), 58 (100); HRMS (EI) calcd for $C_{12}H_{15}FN_2$ 206.1219, found 206.1217.

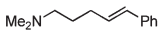
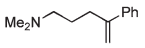
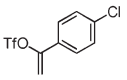
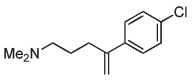
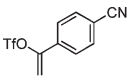
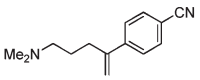
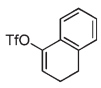
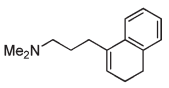
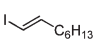
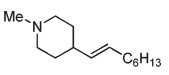
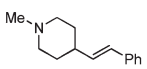
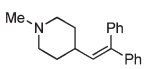
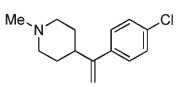
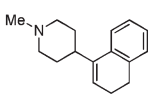
1-(4-(3-(Dimethylamino)propyl)phenyl)pentan-1-one (**4d**). 1-(4-Bromo-phenyl)-pentan-1-one (**3d**; 241 mg, 1.00 mmol) reacted with (3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 1 h, according to **TP2**. Aqueous workup furnished 1-(4-(3-(dimethylamino)propyl)phenyl)pentan-1-one (**4d**; 223 mg, 90% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.84 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.18 (s, 6H), 1.81−1.81 (m, 2H), 1.73−1.63 (m, 2H), 1.43−1.31 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 200.3, 148.1, 135.2, 128.8, 128.4, 59.2, 45.7, 38.4, 33.8, 29.3, 26.8, 22.7, 14.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (m), 2860 (m), 2814 (w), 2764 (m), 1680 (vs), 1606 (s), 1460 (m), 1412 (m), 1266 (m), 1214 (m), 1180 (s), 1012 (m), 968 (m), 846 (m); MS (EI, 70 eV) *m*/*z* (%) 247 (3, M^+), 145 (3), 115 (2), 91 (1), 58 (100); HRMS (EI) calcd for $C_{16}H_{25}NO$ 247.1936, found 247.1913.

Ethyl 5-(3-(Dimethylamino)propyl)nicotinate (**4e**). Ethyl 5-bromonicotinate (**3e**; 230 mg, 1.00 mmol) reacted with (3-(dimethylamino)-propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished ethyl 5-(3-(dimethylamino)propyl)nicotinate (**4e**; 189 mg, 80% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.92−8.91 (m, 1H), 8.48−8.47 (m, 1H), 8.00−7.99 (m, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.15 (t, *J* = 7.3 Hz, 2H), 2.08 (s, 6H), 1.73−1.63 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 165.6, 153.7, 148.6, 137.5, 136.8, 126.1, 61.4, 58.7, 45.5, 30.4, 29.0, 14.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2942 (w), 2860 (w), 2816 (w), 2766 (w), 1720 (vs), 1598 (w), 1576 (w), 1458 (m), 1368 (m), 1284 (vs), 1204 (s), 1106 (s), 1026 (s), 968 (w), 938 (w), 910 (w), 862 (w), 766 (s), 732 (m), 708 (m); MS (EI, 70 eV) *m*/*z* (%) 236 (3, M^+), 191 (4), 120 (2), 59 (3), 58 (100); HRMS (EI) calcd for $C_{13}H_{20}N_2O_2$ 236.1525, found 236.1527.

3-(Isoquinolin-4-yl)-N,N-dimethylpropan-1-amine (**4f**). 4-Bromoisoquinoline (**3f**; 208 mg, 1.00 mmol) reacted with (3-(dimethylamino)-propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished 3-(isoquinolin-4-yl)-*N*,*N*-dimethylpropan-1-amine (**4f**; 180 mg, 84% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.05 (s, 1H), 8.33 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.65−7.60 (m 1H), 7.53−7.48 (m, 1H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.17 (s, 6H), 1.88−1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 151.4, 142.9, 134.9, 131.5, 130.3, 128.6, 128.4, 126.9, 123.1, 59.5, 45.7, 28.9, 27.9; IR (ATR) $\tilde{\nu}$/cm^{-1} 2942 (m), 2858 (w), 2814 (m), 2764 (m), 1622 (m), 1582 (w), 1502 (w), 1458 (m), 1388 (m), 1262 (w), 1230 (m), 1148 (w), 1042 (m), 1020 (m), 958 (w), 894 (m), 862 (m), 786 (m), 748 (vs); MS (EI, 70 eV) *m*/*z* (%) 214 (3, M^+), 156 (7), 115 (3), 70 (5), 58 (100); HRMS (EI) calcd for $C_{14}H_{18}N_2$ 214.1470, found 214.1469.

N,N-Dimethyl-3-(quinoxalin-6-yl)propan-1-amine (**4g**). 6-Bromoquinoxaline (**3g**; 209 mg, 1.00 mmol) reacted with (3-(dimethylamino)-propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 1 h, according to **TP2**. Aqueous workup furnished *N*,*N*-dimethyl-3-(quinoxalin-6-yl)propan-1-amine (**4g**; 211 mg, 98% yield)

Table 5. Preparation of Products 9a−e and 10a−e Obtained by Cross-Coupling of Zinc Reagents 2a and 2d with Alkenyl Halides and Triflates

Entry	Electrophile	Product, [h][a], [°C][b]	Yield [%][c]
1	 **3s**	 **9a** (16, 25)	66
2	 **3t**	 **9b** (16, 25)	51
3	 **3u**	 **9c** (20, 50)	54
4	 **3v**	 **9d** (20, 50)	69
5	 **3w**	 **9e** (20, 50)	75
6	 **3x**	 **10a** (24, 50)	58
7	**3s**	 **10b** (24, 50)	77
8	 **3y**	 **10c** (10, 25)	81
9	**3u**	 **10d** (20, 50)	54
10	**3w**	 **10e** (20, 50)	56

[a] Reaction time. [b] Temperature. [c] Yield of isolated, analytically pure product after aqueous workup without chromatographical purification.

as an orange-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.64−8.62 (m, 2H), 7.87−7.86 (m, 1H), 7.75−7.74 (m, 1H), 7.48−7.47 (m, 1H), 2.72 (t, J = 7.7 Hz, 2H), 2.17 (t, J = 7.3 Hz, 2H), 2.07 (s, 6H), 1.81−1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 145.0, 144.3, 143.2, 141.8, 131.7, 129.3, 127.8, 59.1, 45.6, 33.7, 29.0; IR (ATR) $\tilde{\nu}$/cm^{-1} 2940 (m), 2856 (m), 2814 (m), 2764 (m), 1620 (m), 1498 (s), 1452 (s), 1368 (m), 1132 (m), 1024 (vs), 958 (s), 896 (m), 864 (s), 830 (s), 664 (m); MS (EI, 70 eV) m/z (%) 215 (6, M^+), 169 (1), 142 (4), 71 (9), 58 (100); HRMS (EI) calcd for $C_{13}H_{17}N_3$ 215.1422, found 215.1422.

tert-Butyl 5-(3-(Dimethylamino)propyl)-1H-indole-1-carboxylate (***4h***). *tert*-Butyl 5-bromo-1*H*-indole-1-carboxylate (**3h**; 296 mg, 1.00 mmol) reacted with (3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 2 h, according to **TP2**. Aqueous workup furnished *tert*-butyl 5-(3-(dimethylamino)propyl)-1*H*-indole-1-carboxylate (**4h**; 260 mg, 86% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.05 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 4.0 Hz, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.15 (dd, J = 8.4 Hz, 1.4 Hz, 1H), 6.49 (d, J = 4.0 Hz, 1H), 2.72 (t, J = 7.7 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.22 (s, 6H), 1.88−1.78 (m, 2H), 1.65 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 150.0, 136.9, 131.0, 126.2, 125.2, 120.5, 115.2, 107.4, 83.6, 59.5, 45.8, 33.8, 30.2, 28.5; IR (ATR) $\tilde{\nu}$/cm^{-1} 2974 (w), 2936 (m), 2856 (w), 2814 (w), 2764 (w), 1730 (vs), 1468 (s), 1370 (vs), 1348 (s),

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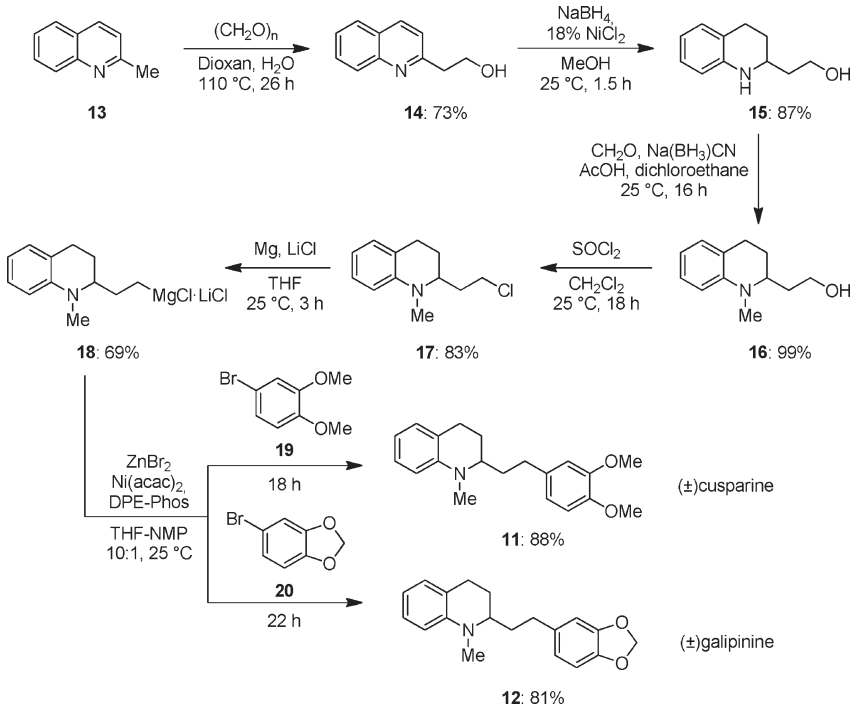
Scheme 6. Total Synthesis of (±)-Cusparine (11) and (±)-Galipinine (12) Using the Cross-Coupling Reaction Protocol



1326 (s), 1254 (s), 1218 (m), 1162 (vs), 1128 (vs), 1098 (w), 1082 (s), 1022 (s), 766 (s), 724 (m); MS (EI, 70 eV) *m*/*z* (%) 303 (100, M + H$^+$), 247 (22), 203 (1), 158 (1), 97 (8); HRMS (EI) calcd for $C_{18}H_{27}N_2O_2^+$ 303.2067, found 303.2062.

*Methyl 5-(3-(Dimethylamino)propyl)furan-2-carboxylate (**4i**).* Methyl 5-bromofuran-2-carboxylate (**3i**; 205 mg, 1.00 mmol) reacted with (3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 2 h, according to **TP2**. Aqueous workup furnished methyl 5-(3-(dimethylamino)propyl)furan-2-carboxylate (**4i**; 178 mg, 84% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.01 (d, J = 3.6 Hz, 1H), 6.06 (d, J = 3.6 Hz, 1H), 3.78 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.21 (t, J = 7.3 Hz, 2H), 2.13 (s, 6H), 1.81−1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 161.2, 159.4, 143.1, 119.4, 107.9, 59.0, 51.8, 45.6, 26.3, 26.0; IR (ATR) $\tilde{\nu}$/cm^{-1} 2946 (w), 2860 (w), 2816 (w), 2766 (w), 1720 (vs), 1594 (w), 1530 (s), 1520 (s), 1460 (m), 1436 (m), 1382 (w), 1302 (vs), 1204 (s), 1138 (s), 1018 (s), 990 (m), 926 (m), 796 (m), 760 (vs), 732 (m); MS (EI, 70 eV) *m*/*z* (%) 211 (5, M$^+$), 71 (2), 59 (3), 58 (100); HRMS (EI) calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1212.

*N,N-Dimethyl-3-(quinolin-2-yl)propan-1-amine (**4j**).* 2-Chloroquinoline (**3j**; 164 mg, 1.00 mmol) reacted with (3-(dimethylamino)propyl magnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 25 °C for 3 h, according to **TP2**. Aequous workup furnished *N,N*-dimethyl-3-(quinolin-2-yl)propan-1-amine (**4j**; 189 mg, 88% yield) as a brownish oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.97−7.92 (m, 2H), 7.66−7.63 (m, 1H), 7.60−7.54 (m, 1H), 7.38−7.33 (m, 1H), 7.19 (d, J = 8.4 Hz, 1H), 2.91 (t, J = 7.8 Hz, 2H), 2.30 (t, J = 8.0 Hz, 2H), 2.15 (s, 6H), 1.98−1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 162.5, 148.1, 136.4, 129.5, 129.0, 127.7, 126.9, 125.9, 121.6, 59.4, 45.6, 37.1, 27.9; IR (ATR) $\tilde{\nu}$/cm^{-1} 2940 (m), 2858 (w), 2814 (m), 2764 (m), 1618 (m), 1600 (s), 1562 (m), 1504 (s), 1462 (m), 1426 (s), 1140 (m), 1040 (m), 826 (vs), 748 (vs), 618 (m); MS (EI, 70 eV) *m*/*z* (%) 170 (6, M$^+$), 143 (100), 128 (17), 115 (7), 72 (19), 58 (80); HRMS (EI) calcd for $C_{14}H_{18}N_2$ 214.1470, found 214.1477.

Synthesis of Aminoalkyl Cross-Coupling Products of Type 5. *2-(3-Methoxyphenethyl)-1-methylpiperidine (**5a**).* 3-Bromoanisole (**3a**; 187 mg, 1.00 mmol) reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (**2b**; 1.69 mL, 1.20 mmol, 0.71 M in THF) at 25 °C for 18 h, according to **TP2**. Aqueous workup furnished 2-(3-methoxyphenethyl)-1-methylpiperidine (**5a**; 170 mg, 73% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.20−7.14 (m, 1H), 6.77−6.75 (m, 1H), 6.72−6.69 (m, 2H), 3.77 (s, 3H), 2.88−2.84 (m, 1H), 2.73−2.63 (m, 1H), 2.56−2.46 (m, 1H), 2.28 (s, 3H), 2.16−2.07 (m, 1H), 2.01−1.83 (m, 2H), 1.79−1.68 (m, 2H), 1.64−1.55 (m, 2H), 1.48−1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 158.6, 143.3, 128.3, 119.7, 113.1, 109.9, 62.4, 56.0, 54.1, 41.7, 33.3, 30.4, 29.3, 24.6, 23.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 3400 (w), 2934 (m), 1600 (s), 1584 (s), 1488 (s), 1452 (s), 1436 (s), 1258 (vs), 1152 (s), 1042 (s), 782 (s), 694 (vs); MS (EI, 70 eV) *m*/*z* (%) 233 (1, M$^+$), 120 (2), 111 (2), 98 (100), 70 (3); HRMS (EI) calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1770.

*1-Methyl-2-(3-(trifluoromethoxy)phenethyl)piperidine (**5b**).* 1-Bromo-3-(trifluoromethoxy)benzene (**3k**; 241 mg, 1.00 mmol) reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (**2b**; 1.69 mL, 1.20 mmol, 0.71 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished 1-methyl-2-(3-(trifluoromethoxy)phenethyl)piperidine (**5b**; 231 mg, 80% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.31−7.25 (m, 1H), 7.12−7.10 (m, 1H), 7.04−7.01 (m, 2H), 2.87−2.69 (m, 2H), 2.64−2.53 (m, 1H), 2.27 (s, 3H), 2.12−2.04 (m, 1H), 1.95−1.66 (m, 4H), 1.63−1.54 (m, 2H), 1.45−1.21 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 145.5, 129.7, 126.9, 120.9, 118.3, 63.4, 57.4, 43.1, 34.7, 31.1, 30.8, 26.0, 24.6; IR (ATR) $\tilde{\nu}$/cm^{-1} 2934 (m), 2858 (w), 2778 (w), 1612 (w), 1588 (w), 1490 (w), 1444 (w), 1252 (vs), 1212 (vs), 1154 (vs), 1032 (m), 1002 (w), 864 (w), 792 (w), 700 (m), 634 (m); MS (EI, 70 eV) *m*/*z* (%) 287 (2, M$^+$), 232 (2), 175 (4), 111 (2), 98 (100), 70 (7); HRMS (EI) calcd for $C_{15}H_{20}F_3NO$ 287.1497, found 287.1519.

*2-(2-(2-Fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1-methylpiperidine (**5c**).* 4-Bromo-2-fluoro-1,1′-biphenyl (**3b**; 251 mg, 1.00 mmol) reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (**2b**; 1.69 mL, 1.20 mmol, 0.71 M in THF) at 25 °C for 48 h, according to **TP2**. Aqueous workup furnished 2-(2-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1-methylpiperidine (**5c**; 209 mg, 70% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.54−7.51 (m, 2H), 7.43−7.38 (m, 2H), 7.35−7.29 (m, 2H), 7.03−6.95 (m, 2H), 2.88−2.69 (m, 2H), 2.64−2.53

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(m, 1H), 2.28 (s, 3H), 2.13−2.02 (m, 1H), 1.98−1.66 (m, 5H), 1.63−1.55 (m, 2H), 1.44−1.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 161.6, 158.3, 144.9, 136.1, 130.8, 129.1, 128.6, 127.6, 124.5, 116.2, 115.9, 63.5, 57.4, 43.2, 34.7, 30.9, 26.1, 24.7; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (m), 2854 (w), 2776 (w), 1484 (m), 1416 (m), 1268 (m), 1126 (m), 1032 (m), 824 (m), 764 (s), 732 (m), 696 (vs); MS (EI, 70 eV) m/z (%) 297 (1, M^+), 185 (4), 169 (1), 111 (1), 98 (100), 70 (4); HRMS (EI) calcd for $C_{20}H_{24}FN$ 297.1893, found 297.1897.

*Ethyl 5-(2-(1-Methylpiperidin-2-yl)ethyl)nicotinate (**5d**).* Ethyl 5-bromonicotinate (**3e**; 230 mg, 1.00 mmol) reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (**2b**; 1.69 mL, 1.20 mmol, 0.71 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished ethyl 5-(2-(1-methylpiperidin-2-yl)ethyl)nicotinate (**5d**; 263 mg, 95% yield) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.92 (s, 1H), 8.49 (m, 1H), 7.99 (m, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.76−2.62 (m, 2H), 2.57−2.47 (m, 1H), 2.15 (s, 3H), 2.02−1.92 (m, 1H), 1.87−1.54 (m, 5H), 1.49−1.42 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.24−1.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 165.6, 153.6, 148.5, 138.1, 136.6, 126.1, 63.1, 61.5, 57.2, 43.1, 34.5, 30.7, 28.1, 25.9, 24.5, 14.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (m), 2856 (w), 2776 (w), 1720 (vs), 1444 (m), 1368 (m), 1280 (s), 1204 (s), 1106 (s), 1026 (s), 766 (s), 708 (m); MS (EI, 70 eV) m/z (%) 275 (1, M − H^+), 231 (4), 119 (1), 111 (1), 98 (100), 70 (6); HRMS (EI) calcd for $C_{16}H_{23}N_2O_2^+$ 275.1754, found 275.1732.

*tert-Butyl 5-(2-(1-Methylpiperidin-2-yl)ethyl)-1H-indole-1-carboxylate (**5e**).* *tert*-Butyl 5-bromo-1*H*-indole-1-carboxylate (**3h**; 296 mg, 1.00 mmol) reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (**2b**; 1.69 mL, 1.20 mmol, 0.71 M in THF) at 25 °C for 48 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) furnished *tert*-butyl 5-(2-(1-methylpiperidin-2-yl)ethyl)-1*H*-indole-1-carboxylate (**5e**; 193 mg, 56% yield) as an orange-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.02 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 3.5 Hz, 1H), 7.35 (d, J = 1.5 Hz, 1H), 7.13 (dd, J = 8.4 Hz, 1.5 Hz, 1H), 6.49 (d, J = 3.5 Hz, 1H), 2.87−2.74 (m, 2H), 2.68−2.58 (m, 1H), 2.27 (s, 3H), 2.11−2.02 (m, 1H), 2.00−1.86 (m, 2H), 1.80−1.69 (m, 2H), 1.65 (s, 9H), 1.62−1.55 (m, 2H), 1.46−1.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 148.8, 136.1, 129.8, 124.9, 123.8, 119.1, 113.9, 106.1, 82.4, 62.4, 56.2, 42.0, 34.3, 30.2, 29.7, 27.7, 24.9, 23.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (s), 2856 (w), 2776 (m), 1730 (vs), 1468 (m), 1442 (m), 1370 (s), 1346 (s), 1326 (s), 1254 (m), 1218 (m), 1162 (s), 1128 (s), 1080 (m), 1022 (m), 764 (m), 722 (m); MS (EI, 70 eV) m/z (%) 343 (100, [M + H^+]), 249 (7), 229 (11), 159 (19), 137 (30), 102 (1); HRMS (EI) calcd for $C_{21}H_{31}N_2O_2^+$ 343.2380, found 343.2371.

*2-(2-(1-Methylpiperidin-2-yl)ethyl)quinoline (**5f**).* 2-Chloroquinoline (**3j**; 164 mg, 1.00 mmol) reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (**2b**; 1.69 mL, 1.20 mmol, 0.71 M in THF) at 25 °C for 1 h, according to **TP2**. Aqueous workup furnished 2-(2-(1-methylpiperidin-2-yl)ethyl)quinoline (**5f**; 241 mg, 95% yield) as an orange-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.99−7.94 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.62−7.56 (m, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H), 3.05−2.95 (m, 1H), 2.91−2.75 (m, 2H), 2.23 (s, 3H), 2.13−1.79 (m, 4H), 1.75−1.64 (m, 2H), 1.56−1.48 (m, 2H), 1.42−1.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 163.1, 148.1, 136.4, 129.5, 129.1, 127.7, 126.9, 125.8, 121.5, 63.6, 57.4, 43.3, 35.0, 33.0, 30.9, 26.1, 24.6; IR (ATR) $\tilde{\nu}$/cm^{-1} 2930 (s), 2854 (m), 2776 (m), 1618 (m), 1600 (s), 1502 (s), 1442 (m), 1426 (m), 1374 (m), 1138 (m), 1118 (m), 1032 (m), 824 (vs), 756 (s), 618 (m); MS (EI, 70 eV) m/z (%) 253 (1, M − H^+), 168 (3), 155 (3), 143 (100), 112 (58), 98 (45), 70 (3); HRMS (EI) calcd for $C_{17}H_{21}N_2^+$ 253.1699, found 253.1701.

Synthesis of Aminoalkyl Cross-Coupling Products of Type 6. *3-(3-Methoxybenzyl)-1-methylpiperidine (**6a**).* 3-Bromoanisole (**3a**; 187 mg, 1.00 mmol) reacted with (1-methylpiperidin-3-yl)methylmagnesium chloride (**2c**; 2.40 mL, 1.20 mmol, 0.50 M in THF) at 25 °C for 30 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 3-(3-methoxybenzyl)-1-methylpiperidine (**6a**; 123 mg, 56% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.13 (t, J = 7.7 Hz, 1H), 6.70 (s, 1H), 6.66 (m, 2H), 3.74 (s, 3H), 2.78 (t, J = 11.0 Hz, 2H), 2.44 (d, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.95−1.89 (m, 2H), 1.71−1.56 (m, 4H), 0.95−0.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 159.8, 141.8, 129.4, 121.7, 114.9, 111.5, 61.9, 56.3, 55.3, 46.5, 41.3, 37.8, 30.2, 25.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2930 (m), 2846 (m), 2774 (m), 1600 (m), 1584 (s), 1488 (s), 1452 (m), 1438 (m), 1258 (vs), 1152 (vs), 1044 (s), 872 (m), 774 (s), 738 (m), 696 (vs); MS (EI, 70 eV) m/z (%) 219 (27, M^+), 122 (6), 97 (100), 82 (4), 58 (7), 43 (5); HRMS (EI) calcd for $C_{14}H_{21}NO$ 219.1623, found 219.1614.

*2-Fluoro-4-((1-methylpiperidin-3-yl)methyl)benzonitrile (**6b**).* 4-Bromo-2-fluorobenzonitrile (**3c**; 200 mg, 1.00 mmol) reacted with (1-methylpiperidin-3-yl)methylmagnesium chloride (**2c**; 2.40 mL, 1.20 mmol, 0.50 M in THF) at 25 °C for 10 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 2-fluoro-4-((1-methylpiperidin-3-yl)methyl)benzonitrile (**6b**; 154 mg, 66% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.47−7.42 (m, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 10.1 Hz, 1H), 2.70−2.58 (m, 2H), 2.51 (d, J = 7.1 Hz, 2H), 2.16 (s, 3H), 1.87−1.80 (m, 2H), 1.63−1.39 (m, 4H), 0.94−0.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 165.0, 161.5, 149.7, 133.3, 125.8, 117.1, 114.4, 61.7, 56.2, 46.7, 41.1, 37.8, 30.2, 25.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (s), 2850 (m), 2778 (m), 2236 (m), 1622 (vs), 1568 (m), 1500 (m), 1430 (s), 1284 (m), 1252 (m), 1160 (m), 1148 (m), 1112 (s), 1092 (m), 822 (m); MS (EI, 70 eV) m/z (%) 232 (50, M^+), 134 (14), 111 (8), 97 (100), 84 (8), 71 (14); HRMS (EI) calcd for $C_{14}H_{17}FN_2$ 232.1376, found 232.1364.

*6-((1-Methylpiperidin-3-yl)methyl)quinoxaline (**6c**).* 6-Bromoquinoxaline (**3g**; 209 mg, 1.00 mmol) reacted with (1-methylpiperidin-3-yl)methylmagnesium chloride (**2c**; 2.40 mL, 1.20 mmol, 0.50 M in THF) at 25 °C for 10 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 6-((1-methylpiperidin-3-yl)methyl)quinoxaline (**6c**; 145 mg, 60% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.73−8.71 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 2.75−2.68 (m, 4H), 2.17 (s, 3H), 2.04−1.83 (m, 2H), 1.72−1.50 (m, 4H), 0.98−0.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 145.1, 144.5, 143.2, 143.0, 142.0, 132.1, 129.4, 128.8, 61.9, 56.2, 46.6, 41.3, 37.8, 30.2, 25.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2930 (s), 2848 (m), 2776 (m), 1618 (m), 1498 (s), 1448 (s), 1368 (m), 1284 (m), 1132 (m), 1092 (m), 1022 (vs), 956 (m), 896 (m), 866 (s), 824 (m), 780 (m), 668 (m); MS (EI, 70 eV) m/z (%) 241 (6, M^+), 169 (8), 143 (7), 115 (4), 97 (100), 58 (11), 43 (10); HRMS (EI) calcd for $C_{15}H_{19}N_3$ 241.1579, found 241.1568.

*2-Methoxy-6-((1-methylpiperidin-3-yl)methyl)pyridine (**6d**).* 2-Chloro-6-methoxypyridine (**3l**; 144 mg, 1.00 mmol) reacted with (1-methylpiperidin-3-yl)methylmagnesium chloride (**2c**; 2.40 mL, 1.20 mmol, 0.50 M in THF) at 25 °C for 20 h, according to **TP2**. Aqueous workup furnished 2-methoxy-6-((1-methylpiperidin-3-yl)methyl)pyridine (**6d**; 198 mg, 90% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38−7.33 (m, 1H), 6.58 (d, J = 7.1 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.68 (d, J = 11.0 Hz, 2H), 2.49 (d, J = 7.1 Hz, 2H), 2.14 (s, 3H), 2.12−2.00 (m, 1H), 1.83−1.75 (m, 1H), 1.64−1.42 (m, 4H), 0.93−0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 163.8, 158.5, 138.6, 116.0, 107.7, 62.3, 56.5, 53.3, 46.9, 43.1, 36.7, 30.6, 25.7; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (m), 2848 (w), 2774 (m), 1598 (s), 1578 (s), 1464 (vs), 1438 (s), 1414 (s), 1302 (s), 1262 (s), 1146 (m), 1032 (s), 798 (s), 780 (s), 746 (m); MS (EI, 70 eV) m/z (%) 219 (8, [M − H^+]), 123 (100), 98 (26), 70 (2), 58 (2), 43 (4); HRMS (EI) calcd for $C_{13}H_{20}N_2O$ 220.1576, found 220.1581.

Synthesis of Aminoalkyl Cross-Coupling Products of Type 7. *2,4-Dimethoxy-5-(1-methylpiperidin-4-yl)pyrimidine (**7a**).* 5-Iodo-2,4-dimethoxypyrimidine (**3m**; 266 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 48 h, according to **TP2**. Aqueous workup

furnished 2,4-dimethoxy-5-(1-methylpiperidin-4-yl)pyrimidine (**7a**; 142 mg, 60% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.98 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.92−2.89 (m, 2H), 2.60−2.50 (m, 1H), 2.25 (s, 3H), 2.03−1.94 (m, 2H), 1.75−1.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 169.2, 164.0, 155.1, 119.1, 56.4, 54.8, 54.0, 46.6, 33.4, 31.5; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (w), 2780 (w), 1598 (s), 1564 (s), 1462 (s), 1402 (s), 1372 (vs), 1290 (s), 1256 (s), 1234 (m), 1200 (m), 1138 (m), 1072 (s), 1016 (s), 994 (m), 794 (s), 762 (m); MS (EI, 70 eV) m/z (%) 237 (81, M$^+$), 193 (11), 140 (5), 97 (100), 70 (32), 57 (9), 43 (13); HRMS (EI) calcd for $C_{12}H_{19}N_3O_2$ 237.1477, found 237.1476.

2-Fluoro-4-(1-methylpiperidin-4-yl)benzonitrile (***7b***). 4-Bromo-2-fluorobenzonitrile (**3c**; 200 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 1 h, according to **TP2**. Aqueous workup furnished 2-fluoro-4-(1-methylpiperidin-4-yl)benzonitrile (**7b**; 198 mg, 88% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.45 (dd, J = 7.9 Hz, 7.1 Hz, 2H), 7.04 (dd, J = 8.2 Hz, 1.5 Hz, 1H), 6.98 (dd, J = 10.4 Hz, 1.5 Hz, 2H), 2.92−2.85 (m, 2H), 2.52−2.41 (m, 1H), 2.22 (s, 3H), 2.00−1.92 (m, 2H), 1.78−1.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 164.0, 160.5, 154.3, 132.3, 122.5, 113.9, 113.7, 113.1, 97.8, 54.8, 45.3, 42.2, 31.9; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (s), 2848 (m), 2782 (s), 2738 (m), 2236 (m), 1620 (vs), 1568 (m), 1500 (m), 1446 (m), 1430 (s), 1380 (s), 1280 (m), 1250 (m), 1112 (m), 956 (m), 828 (m), 760 (m); MS (EI, 70 eV) m/z (%) 218 (77, M$^+$), 217 (100), 157 (4), 134 (10), 97 (8), 83 (23), 70 (44), 43 (56); HRMS (EI) calcd for $C_{13}H_{15}FN_2$ 218.1219, found 218.1192.

3-(1-Methylpiperidin-4-yl)benzonitrile (***7c***). 3-Bromobenzonitrile (**3n**; 182 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 8 h, according to **TP2**. Aqueous workup furnished 3-(1-methylpiperidin-4-yl)-benzonitrile (**7c**; 192 mg, 96% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39 (m, 3H), 7.32 (m, 1H), 2.88−2.84 (m, 2H), 2.45−2.37 (m, 1H), 2.21 (s, 3H), 1.98−1.90 (m, 2H), 1.71−1.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 147.4, 131.2, 130.3, 129.6, 129.0, 118.7, 112.1, 55.7, 46.1, 41.4, 32.9; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (m), 2844 (w), 2780 (m), 2736 (w), 2228 (m), 1466 (m), 1446 (m), 1378 (m), 1280 (m), 1134 (m), 1068 (m), 996 (m), 798 (s), 768 (m), 692 (vs); MS (EI, 70 eV) m/z (%) 200 (68, M$^+$), 199 (100), 116 (2), 97 (2), 83 (4), 70 (13), 57 (7), 43 (9); HRMS (EI) calcd for $C_{13}H_{16}N_2$ 200.1313, found 200.1293.

2-(4-(1-Methylpiperidin-4-yl)phenyl)acetonitrile (***7d***). 2-(4-Bromophenyl)acetonitrile (**3o**; 196 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 8 h, according to **TP2**. Aqueous workup furnished 2-(4-(1-methylpiperidin-4-yl)phenyl)acetonitrile (**7d**; 200 mg, 94% yield) as an orange solid. Mp (°C) 57−58; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.16−7.13 (m, 4H), 3.62−3.61 (m, 2H), 2.90−2.86 (m, 2H), 2.44−2.34 (m, 1H), 2.23 (s, 3H), 2.00−1.89 (m, 2H), 1.74−1.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 146.5, 128.2, 127.9, 127.8, 118.2, 56.5, 46.7, 41.8, 33.7, 23.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2938 (s), 2848 (m), 2780 (m), 2764 (s), 2738 (m), 2244 (w), 1682 (w), 1514 (m), 1462 (m), 1380 (m), 1280 (s), 1134 (s), 1074 (s), 992 (s), 820 (s), 760 (vs); MS (EI, 70 eV) m/z (%) 214 (74, M$^+$), 213 (100), 115 (6), 97 (18), 83 (7), 69 (28), 57 (11), 43 (16); HRMS (EI) calcd for $C_{14}H_{18}N_2$ 214.1470, found 214.1458.

1-(4-(1-Methylpiperidin-4-yl)phenyl)pentan-1-one (***7e***). 1-(4-Bromophenyl)pentan-1-one (**3d**; 241 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 2 h, according to **TP2**. Aqueous workup furnished 1-(4-(1-methylpiperidin-4-yl)phenyl)pentan-1-one (**7e**; 218 mg, 84% yield) as an orange solid. Mp (°C) 37−38; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.80 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 2.89−2.81 (m, 4H), 2.49−2.38 (m, 1H), 2.22 (s, 3H), 2.00−1.91 (m, 2H), 1.75−1.68 (m, 4H), 1.66 (m, 2H), 1.37−1.24 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 200.3, 151.9, 135.4, 128.5, 127.2, 56.3, 46.6, 42.3, 38.4, 33.4, 26.8, 22.7, 14.1; IR (ATR) $\tilde{\nu}$/cm^{-1} 2934 (m), 2872 (m), 2778 (m), 1678 (vs), 1606 (s), 1464 (m), 1444 (m), 1378 (m), 1278 (m), 1212 (m), 1182 (m), 1134 (m), 992 (m), 976 (m), 844 (m), 764 (m); MS (EI, 70 eV) m/z (%) 259 (90, M$^+$), 258 (100), 202 (4), 97 (15), 83 (5), 70 (13), 43 (3); HRMS (EI) calcd for $C_{17}H_{25}NO$ 259.1936, found 260.1947.

6-(1-Methylpiperidin-4-yl)quinoxaline (***7f***). 6-Bromoquinoxaline (**3g**; 209 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 3 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 6-(1-methylpiperidin-4-yl)quinoxaline (**7f**; 163 mg, 79% yield) as a red solid. Mp (°C) 176−178; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.77−8.75 (m, 2H), 7.99 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 3.26−3.22 (m, 2H), 2.90−2.79 (m, 1H), 2.54 (s, 3H), 2.25−2.11 (m, 2H), 2.01−1.97 (m, 2H), 1.43−1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 146.3, 144.1, 143.6, 142.1, 141.1, 128.8, 128.6, 125.5, 54.5, 52.0, 44.2, 40.0, 30.7, 27.7; IR (ATR) $\tilde{\nu}$/cm^{-1} 2948 (s), 2924 (s), 2622 (s), 2606 (s), 2494 (vs), 1618 (m), 1496 (m), 1474 (s), 1442 (m), 1396 (m), 1374 (s), 1262 (m), 1172 (m), 1024 (s), 932 (m), 894 (m), 806 (m); MS (EI, 70 eV) m/z (%) 227 (99, M$^+$), 156 (8), 115 (5), 97 (7), 83 (12), 70 (100), 57 (12), 42 (35); HRMS (EI) calcd for $C_{14}H_{17}N_3$ 227.1422, found 227.1413.

2-Methoxy-6-(1-methylpiperidin-4-yl)pyridine (***7g***). 2-Chloro-6-methoxypyridine (**3l**; 144 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 3 h, according to **TP2**. Aqueous workup furnished 2-methoxy-6-(1-methylpiperidin-4-yl)pyridine (**7g**; 113 mg, 55% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.45−7.40 (m, 1H), 6.67 (d, J = 7.1 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.96−2.90 (m, 2H), 2.57−2.46 (m, 1H), 2.28 (s, 3H), 2.06−1.94 (m, 2H), 1.91−1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 163.7, 163.1, 138.9, 113.5, 108.0, 56.3, 53.3, 46.8, 43.6, 32.1; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (m), 2846 (w), 2778 (m), 2734 (w), 1578 (vs), 1462 (vs), 1412 (s), 1378 (m), 1278 (s), 1246 (s), 1142 (m), 1046 (m), 1028 (s), 954 (m), 800 (s), 764 (m), 740 (m); MS (EI, 70 eV) m/z (%) 206 (8, M$^+$), 191 (23), 178 (5), 150 (11), 136 (100), 123 (6), 71 (7); HRMS (EI) calcd for $C_{12}H_{18}N_2O$: 206.1419, found 206.1433.

4-(7-Methoxynaphthalen-2-yl)-1-methylpiperidine (***7h***). 7-Methoxynaphthalen-2-yl trifluoromethanesulfonate (**3p**; 306 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 48 h, according to **TP2**. Aqueous workup furnished 4-(7-methoxynaphthalen-2-yl)-1-methylpiperidine (**7h**; 237 mg, 93% yield) as a yellow solid. Mp (°C) 94−95; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.67 (dd, J = 9.0 Hz, 4.2 Hz, 2H), 7.54 (s, 1H), 7.22 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.10−7.05 (m, 2H), 3.88 (s, 3H), 3.01−2.97 (m, 2H), 2.61−2.53 (m, 1H), 2.32 (s, 3H), 2.11−2.02 (m, 2H), 1.93−1.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 156.7, 143.3, 133.7, 128.0, 126.7, 126.6, 122.7, 122.6, 117.0, 104.6, 55.4, 54.2, 45.5, 41.2, 32.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2934 (m), 2774 (m), 2736 (w), 1628 (m), 1512 (m), 1448 (m), 1376 (m), 1258 (m), 1210 (s), 1132 (m), 1028 (s), 996 (m), 896 (m), 836 (vs), 802 (m), 776 (w), 762 (m), 710 (m), 612 (m); MS (EI, 70 eV) m/z (%) 255 (92, M$^+$), 240 (19), 184 (10), 140 (12), 97 (19), 70 (100), 43 (10); HRMS (EI) calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1609.

2-(1-Methylpiperidin-4-yl)quinoline (***7i***). Quinolin-2-yl trifluoromethanesulfonate (**3q**; 277 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 8 h, according to **TP2**. Aqueous workup furnished 2-(1-methylpiperidin-4-yl)quinoline (**7i**; 215 mg, 95% yield) as a yellow-orange solid. Mp (°C) 41−43; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.92 (dd, J = 8.4 Hz, 2.7 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.56−7.50 (m, 1H), 7.35−7.29 (m, 1H), 7.20 (dd, J = 8.4 Hz, 1.3 Hz,

1H), 2.89−2.85 (m, 2H), 2.81−2.70 (m, 1H), 2.20 (s, 3H), 2.02−1.94 (m, 2H), 1.91−1.83 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 165.4, 148.0, 136.6, 129.5, 129.1, 127.6, 127.2, 125.9, 119.3, 56.2, 46.7, 45.2, 32.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (m), 2774 (m), 2734 (m), 1686 (w), 1600 (m), 1500 (m), 1444 (m), 1428 (m), 1376 (m), 1278 (m), 1134 (s), 998 (m), 830 (s), 756 (vs), 744 (s), 622 (m); MS (EI, 70 eV) m/z (%) 226 (33, M^+), 180 (4), 170 (6), 156 (100), 128 (6), 118 (5), 69 (17); HRMS (EI) calcd for $C_{15}H_{18}N_2$ 226.1470, found 226.1459.

Synthesis of Aminoalkyl Cross-Coupling Products of Type 8. *3-(3-Methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane (**8a**).* 3-Bromoanisole (**3a**; 187 mg, 1.00 mmol) reacted with 8-methyl-8-azabicyclo[3.2.1]octyl-3-magnesium chloride (**2e**; 4.00 mL, 1.20 mmol, 0.30 M in THF) at 25 °C for 22 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 3-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3.2.1]octane (**8a**; 127 mg, 55% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.18 (t, J = 7.9 Hz, 1H), 6.86−6.83 (m, 2H), 6.73−6.69 (m, 1H), 3.77 (s, 3H), 3.36−3.32 (m, 2H), 2.89−2.77 (m, 1H), 2.40 (s, 3H), 2.14−2.02 (m, 4H), 1.79−1.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 158.7, 145.9, 128.4, 118.7, 111.8, 110.8, 61.0, 54.2, 39.1, 37.6, 33.7, 24.9; IR (ATR) $\tilde{\nu}$/cm^{-1} 2928 (s), 2796 (w), 1600 (s), 1584 (s), 1486 (m), 1452 (s), 1352 (m), 1264 (s), 1242 (m), 1158 (s), 1038 (vs), 776 (s), 760 (s), 696 (vs); MS (EI, 70 eV) m/z (%) 231 (100, M^+), 202 (61), 188 (12), 134 (6), 121 (5), 96 (27), 83 (49); HRMS (EI) calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1617.

*2-(4-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl)acetonitrile (**8b**).* 2-(4-Bromophenyl)acetonitrile (**3o**; 196 mg, 1.00 mmol) reacted with 8-methyl-8-azabicyclo[3.2.1]octyl-3-magnesium chloride (**2e**; 4.00 mL, 1.20 mmol, 0.30 M in THF) at 25 °C for 72 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 2-(4-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)phenyl)acetonitrile (**8b**; 220 mg, 92% yield) as a sand colored solid. Mp (°C) 105−106; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.09 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.48 (s, 2H), 3.27−3.25 (m, 2H), 2.72−2.62 (m, 1H), 2.32 (s, 3H), 2.14−1.98 (m, 2H), 1.67−1.64 (m, 2H), 1.50−1.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 144.2, 131.1, 128.3, 128.2, 118.3, 63.5, 39.8, 37.8, 33.7, 25.5, 23.3; IR (ATR) $\tilde{\nu}$/cm^{-1} 2934 (s), 2910 (s), 2798 (m), 2244 (w), 1512 (s), 1418 (s), 1354 (s), 1122 (s), 1052 (s), 1036 (s), 848 (vs), 800 (s), 786 (s), 768 (vs), 706 (m), 630 (m); MS (EI, 70 eV) m/z (%) 241 (100, $[M + H^+]$), 235 (1), 102 (26), 51 (1); HRMS (EI) calcd for $C^{16}H^{21}N^{2+}$ 241.1699, found 241.1691.

*3-(6-Methoxypyridin-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (**8c**).* 2-Chloro-6-methoxypyridine (**3l**; 144 mg, 1.00 mmol) reacted with 8-methyl-8-azabicyclo[3.2.1]octyl-3-magnesium chloride (**2e**; 4.00 mL, 1.20 mmol, 0.30 M in THF) at 25 °C for 72 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 3-(6-methoxypyridin-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (**8c**; 158 mg, 68% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39 (t, J = 7.7 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.21−3.17 (m, 2H), 2.93−2.81 (m, 1H), 2.29 (s, 3H), 2.05−1.94 (m, 4H), 1.68−1.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 162.5, 161.8, 137.7, 112.6, 106.6, 60.2, 52.1, 39.0, 35.8, 35.5, 25.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2946 (m), 2794 (w), 1578 (s), 1462 (s), 1438 (m), 1414 (m), 1308 (m), 1282 (m), 1256 (s), 1078 (m), 1028 (s), 794 (vs), 764 (s), 740 (m), 704 (m); MS (EI, 70 eV) m/z (%) 232 (25, $[M^+]$), 146 (18), 137 (60), 123 (20), 96 (54), 83 (100), 67 (42); HRMS (EI) calcd for $C_{14}H_{20}N_2O$ 232.1576, found 232.1558.

*3-(7-Methoxynaphthalen-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (**8d**).* 7-Methoxynaphthalen-2-yl trifluoromethanesulfonate (**3p**; 306 mg, 1.00 mmol) reacted with 8-methyl-8-azabicyclo[3.2.1]octyl-3-magnesium chloride (**2e**; 4.00 mL, 1.20 mmol, 0.30 M in THF) at 25 °C for 72 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 3-(7-methoxynaphthalen-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (**8d**; 174 mg, 62% yield) as a sand colored solid. Mp (°C) 100−102; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.64 (dd, J = 9.0 Hz, 4.2 Hz, 2H), 7.56 (m, 1H), 7.24 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.07−7.03 (m, 2H), 3.86 (s, 3H), 3.28−3.26 (m, 2H), 3.02−2.90 (m, 1H), 2.35 (s, 3H), 2.12−2.00 (m, 4H), 1.75−1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 158.0, 144.0, 135.0, 129.3, 128.0, 127.9, 124.6, 124.2, 118.2, 105.9, 62.0, 55.5, 40.6, 39.2, 35.2, 26.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (m), 2844 (w), 2796 (w), 1630 (m), 1604 (m), 1512 (m), 1464 (m), 1392 (m), 1350 (m), 1258 (m), 1212 (vs), 1170 (m), 1118 m), 1028 (s), 892 (m), 838 (vs), 726 (m); MS (EI, 70 eV) m/z (%) 281 (88, M^+), 252 (33), 170 (10), 141 (9), 96 (30), 83 (100); HRMS (EI) calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1759.

*4-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)benzonitrile (**8e**).* 4-Cyanophenyl trifluoromethanesulfonate (**3r**; 251 mg, 1.00 mmol) reacted with 8-methyl-8-azabicyclo[3.2.1]octyl-3-magnesium chloride (**2e**; 4.00 mL, 1.20 mmol, 0.30 M in THF) at 25 °C for 8 h, according to **TP2**. Column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) furnished 4-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)benzonitrile (**8e**; 164 mg, 73% yield) as an orange solid. Mp (°C) 78−81; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.50 (d, J = 7.7 Hz, 2H), 7.31 (d, J = 7.7 Hz, 2H), 3.24 (m, 2H), 2.92−2.80 (m, 1H), 2.29 (s, 3H), 2.08−2.06 (m, 2H), 1.93−1.85 (m, 2H), 1.67−1.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 151.5, 132.4, 128.4, 119.2, 110.0, 61.8, 40.7, 38.9, 35.2, 26.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2936 (s), 2876 (m), 2838 (m), 2790 (m), 2222 (s), 1608 (m), 1470 (m), 1448 (m), 1350 (s), 1052 (m), 1036 (s), 844 (s), 814 (vs), 784 (m), 754 (m); MS (EI, 70 eV) m/z (%) 226 (80, M^+), 197 (45), 183 (7), 115 (7), 96 (28), 83 (100), 42 (19); HRMS (EI) calcd for $C_{15}H_{18}N_2$ 226.1470, found 226.1455.

Synthesis of Aminoalkyl Cross-Coupling Products of Type 9. *(E)-N,N-Dimethyl-5-phenylpent-4-en-1-amine (**9a**).* (*E*)-(2-Bromovinyl)benzene (**3s**; 183 mg, 1.00 mmol) reacted with 3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 50 °C for 16 h, according to **TP2**. Aqueous workup furnished (*E*)-*N*,*N*-dimethyl-5-phenylpent-4-en-1-amine (**9a**; 125 mg, 66% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39−7.28 (m, 5H), 6.46−6.42 (m, 1H), 6.31−6.21 (m, 1H), 2.39−2.22 (m, 10H), 1.77−1.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 137.8, 130.5, 130.1, 128.8, 126.9, 125.9, 59.3, 45.5, 30.9, 28.1; IR (ATR) $\tilde{\nu}$/cm^{-1} 3025 (m), 2970 (m), 2939 (vs), 2857 (m), 2814 (s), 2763 (vs), 1695 (w), 1494 (w), 1464 (s), 1448 (m), 1264 (m), 1232 (w), 1098 (w), 1070 (w), 1041 (m), 963 (s), 843 (w), 739 (s), 716 (w), 691 (vs); MS (EI, 70 eV) m/z (%) 189 (42, M^+), 129 (31), 128 (11), 117 (13), 115 (24), 85 (14), 84 (100), 59 (11), 58 (40); HRMS (EI) calcd for $C_{13}H_{19}N$ 189.1517, found 189.1514.

*N,N-Dimethyl-4-phenylpent-4-en-1-amine (**9b**).* (1-Bromovinyl)-benzene (**3t**; 183 mg, 1.00 mmol) reacted with 3-(dimethylamino)-propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 50 °C for 16 h, according to **TP2**. Aqueous workup furnished *N*,*N*-dimethyl-4-phenylpent-4-en-1-amine (**9b**; 97 mg, 51% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.41−7.22 (m, 5H), 5.25 (s, 1H), 5.14 (s, 1H), 2.57−2.48 (m, 2H), 2.24−2.17(m, 8H), 1.67−1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 148.3, 141.2, 128.2, 127.3, 126.1, 112.3, 59.4, 45.4, 33.1, 26.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2941 (m), 2857 (w), 2814 (w), 2763 (m), 1627 (w), 1494 (w), 1458 (m), 1442 (m), 1264 (w), 1144 (w), 1098 (w), 1072 (w), 1028 (m), 893 (m), 840 (w), 828 (w), 777 (s), 700 (vs); MS (EI, 70 eV) m/z (%) 189 (4, M^+), 129 (5), 128 (6), 115 (11), 91 (7), 77 (7), 71 (100), 58 (36), 56 (5), 42 (5); HRMS (EI) calcd for $C_{13}H_{19}N$ 189.1517, found 189.1527.

*4-(4-Chlorophenyl)-N,N-dimethylpent-4-en-1-amine (**9c**).* 1-(4-Chlorophenyl)vinyl trifluoromethanesulfonate (**3u**; 287 mg, 1.00 mmol) reacted with 3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 50 °C for 20 h, according to **TP2**. Aqueous workup furnished 4-(4-chlorophenyl)-*N*,*N*-dimethylpent-4-en-1-amine (**9c**; 120 mg, 54% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.37−7.23 (m, 4 H), 5.23 (s, 1H), 5.09 (s, 1H), 2.51−2.45 (m, 2H), 2.24−2.17 (m, 8H), 1.63−1.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz)

δ (ppm) 147.1, 139.6, 133.1, 128.4, 127.4, 112.8, 59.2, 45.4, 33.0, 26.1; IR (ATR) $\tilde{\nu}$/cm^{-1} 2941 (m), 2857 (w), 2814 (w), 2764 (m), 1625 (w), 1492 (s), 1465 (m), 1458 (m), 1439 (m), 1263 (w), 1232 (w), 1091 (m), 1042 (m), 1012 (s), 896 (m), 833 (vs), 746 (m), 735 (m), 694 (m); MS (EI, 70 eV) *m*/*z* (%) 223 (1, M$^+$), 115 (3), 84 (3), 71 (19), 59 (3), 58 (100), 42 (3); HRMS (EI) calcd for $C_{13}H_{18}{}^{35}ClN$ 223.1118, found 223.1128.

*4-(5-(Dimethylamino)pent-1-en-2-yl)benzonitrile (**9d**).* 1-(4-Cyanophenyl)vinyl trifluoromethanesulfonate (**3v**; 277 mg, 1.00 mmol) reacted with 3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 50 °C for 20 h, according to **TP2**. Aqueous workup furnished 4-(5-(dimethylamino)pent-1-en-2-yl)benzonitrile (**9d**; 147 mg, 69% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.64−7.46 (m, 4H), 5.39 (s, 1H), 5.21 (s, 1H), 2.57−2.49 (m, 2H), 2.39−2.21 (m, 8H), 1.69−1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 146.6, 145.7, 132.2, 126.8, 118.9, 115.3, 111.0, 58.9, 45.2, 32.5, 25.8; IR (ATR) $\tilde{\nu}$/cm^{-1} 2942 (m), 2859 (w), 2816 (w), 2766 (m), 2227 (m), 1605 (m), 1460 (m), 1262 (m), 1100 (m), 1041 (m), 1032 (m), 1018 (m), 905 (m), 845 (vs), 748 (m), 695 (m); MS (EI, 70 eV) *m*/*z* (%) 214 (2, M$^+$), 140 (2), 116 (2), 71 (15), 59 (3), 58 (100), 56 (2), 44 (2), 42 (4); HRMS (EI) calcd for $C_{14}H_{18}N_2$ 214.1470, found 214.1457.

*3-(3,4-Dihydronaphthalen-1-yl)-N,N-dimethylpropan-1-amine (**9e**).* 3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate (**3w**; 278 mg, 1.00 mmol) reacted with 3-(dimethylamino)propylmagnesium chloride (**2a**; 1.50 mL, 1.20 mmol, 0.80 M in THF) at 50 °C for 20 h, according to **TP2**. Aqueous workup furnished 3-(3,4-dihydronaphthalen-1-yl)-*N*,*N*-dimethylpropan-1-amine (**9e**; 161 mg, 75% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.22−7.12 (m, 4H), 5.89−5.85 (m, 1H), 2.75−2.71 (m, 2H), 2.45−2.42 (m, 2H), 2.39−2.36 (m, 2H), 2.23−1.98 (m, 8H), 1.75−1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 136.7, 136.1, 134.8, 127.5, 126.5, 126.3, 124.9, 122.6, 59.6, 45.4, 30.4, 28.4, 26.4, 23.1; IR (ATR) $\tilde{\nu}$/cm^{-1} 2934 (m), 2856 (w), 2814 (m), 2762 (m), 1487 (m), 1450 (m), 1438 (m), 1263 (m), 1234 (m), 1041 (m), 1021 (m), 807 (m), 764 (s), 754 (s), 736 (vs), 694 (m); MS (EI, 70 eV) *m*/*z* (%) 215 (1, M$^+$), 141 (5), 128 (6), 115 (4), 71 (25), 59 (3), 58 (100); HRMS (EI) calcd for $C_{15}H_{21}N$ 215.1674, found 215.1667.

Synthesis of Aminoalkyl Cross-Coupling Products of Type 10. *(E)-1-Methyl-4-(oct-1-en-1-yl)piperidine (**10a**).* (*E*)-1-Iodooct-1-ene (**3x**; 238 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)-magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 24 h, according to **TP2**. Aqueous workup furnished (*E*)-1-methyl-4-(oct-1-en-1-yl)piperidine (**10a**; 122 mg, 58% yield) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 5.62 (s, 1H), 5.29 (s, 1H), 3.89−2.79 (m, 8H), 2.39−1.21 (m, 14H), 0.96−0.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 166.9, 114.6, 55.8, 50.8, 46.9, 35.8, 33.2, 31.7, 31.6, 29.9, 28.1, 23.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (vs), 2858 (m), 2781 (m), 1716 (s), 1669 (s), 1614 (s), 1433 (m), 1386 (m), 1278 (vs), 1211 (s), 1151 (s), 1068 (m), 1033 (m), 993 (m); MS (EI, 70 eV) *m*/*z* (%) 209 (11, M$^+$), 180 (51), 97 (38), 96 (100), 70 (85), 57 (33), 44 (52); HRMS (EI) calcd for $C_{14}H_{27}N$ 209.2143, found 209.2142.

*(E)-1-Methyl-4-styrylpiperidine (**10b**).* (*E*)-(2-Bromovinyl)benzene (**3s**; 183 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 24 h, according to **TP2**. Aqueous workup furnished (*E*)-1-methyl-4-styrylpiperidine (**10b**; 154 mg, 77% yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39−7.17 (m, 5H), 6.44−6.34 (m, 1H), 6.21 (d, *J* = 6.9 Hz, 1H), 2.93−2.87 (m, 2H), 2.31 (s, 3H), 2.13−1.51 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 137.7, 135.1, 128.5, 128.2, 127.0, 126.0, 55.7, 46.6, 38.9, 32.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (m), 2843 (w), 2778 (m), 2734 (w), 2778 (m), 2734 (w), 1493 (w), 1464 (w), 1445 (m), 1378 (m), 1278 (m), 1144 (m), 1136 (m), 1108 (w), 1069 (m), 980 (m), 964 (s), 768 (m), 745 (s), 692 (vs); MS (EI, 70 eV) *m*/*z* (%) 201 (12, M$^+$), 98 (17), 96 (100), 91 (13), 70 (25), 61 (17), 44 (14), 43 (84), 42 (13); HRMS (EI) calcd for $C_{14}H_{19}N$ 201.1517, found 201.1516.

*4-(2,2-Diphenylvinyl)-1-methylpiperidine (**10c**).* (2-Bromoethene-1,1-diyl)dibenzene (**3y**; 259 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 10 h, according to **TP2**. Aqueous workup furnished 4-(2,2-diphenylvinyl)-1-methylpiperidine (**10c**; 224 mg, 81% yield) as an orange solid. Mp (°C) 73−76; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.41−7.18 (m, 10H), 5.95 (d, *J* = 9.9 Hz, 1H), 2.87−2.81 (m, 2H), 2.25 (s, 3H), 1.92−1.79 (m, 2H), 1.65−1.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 142.6, 140.9, 140.4, 134.3, 129.7, 128.3, 128.1, 127.2, 127.0, 126.9, 55.3, 46.6, 35.9, 32.6, 29.8; IR (ATR) $\tilde{\nu}$/cm^{-1} 2361 (m), 2337 (w), 1444(w), 1278 (w), 1142 (w), 1105 (w), 1068 (m), 979 (m), 870 (w), 848 (w), 765 (s), 729 (m), 696 (vs), 678 (m), 668 (m); MS (EI, 70 eV) *m*/*z* (%) 277 (34, M$^+$), 172 (14), 110 (16), 97 (51), 96 (100), 82 (12), 70 (19), 57 (11), 42 (12); HRMS (EI) calcd for $C_{20}H_{23}N$ 277.1830, found 277.1823.

*4-(1-(4-Chlorophenyl)vinyl)-1-methylpiperidine (**10d**).* 1-(4-Chlorophenyl)vinyl trifluoromethanesulfonate (**3u**; 287 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 20 h, according to **TP2**. Aqueous workup furnished 4-(1-(4-chlorophenyl)vinyl)-1-methylpiperidine (**10d**; 126 mg, 54% yield) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.28−7.21 (m, 4H), 5.18 (s, 1H), 5.04 (s, 1H), 2.51−2.49 (m, 2H), 2.33−2.24 (m, 3H), 2.04−1.97 (m, 2H), 1.81−1.67 (m, 4H), 1.57−1.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 152.1, 140.8, 133.0, 128.9, 128.3, 111.6, 56.2, 46.3, 31.6, 29.2; IR (ATR) $\tilde{\nu}$/cm^{-1} 2935 (m), 2844 (w), 2780 (m), 2680 (w), 1683 (m), 1491 (s), 1446 (m), 1378 (m), 1278 (s), 1144 (s), 1137 (s), 1093 (s), 1068 (s), 1012 (s), 899 (m), 833 (vs), 770 (s), 734 (s), 695 (s); MS (EI, 70 eV) *m*/*z* (%) 235 (15, M$^+$), 97 (13), 96 (24), 82 (6), 71 (6), 70 (100), 57 (7), 44 (8), 43 (8); HRMS (EI) calcd for $C_{14}H_{18}{}^{35}Cl_2N$ 235.1128, found 235.1122.

*4-(3,4-Dihydronaphthalen-1-yl)-1-methylpiperidine (**10e**).* 3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate (**3w**; 278 mg, 1.00 mmol) reacted with (1-methylpiperidin-4-yl)magnesium chloride (**2d**; 1.94 mL, 1.20 mmol, 0.62 M in THF) at 25 °C for 20 h, according to **TP2**. Aqueous workup furnished 4-(3,4-dihydronaphthalen-1-yl)-1-methylpiperidine (**10e**; 126 mg, 56% yield) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.22−7.15 (m, 4H), 5.91−87 (m, 1H), 3.40−3.37 (m, 1H), 3.08−3.06 (m, 2H), 2.72−2.69 (m, 2H), 2.41 (s, 3H), 2.39−2.36 (m, 1H), 2.26−2.19 (m, 2H), 2.05−1.99 (m, 1H), 1.91−1.89 (m, 2H), 1.69−1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 139.8, 137.2, 134.5, 127.8, 126.5, 126.2, 122.9, 122.0, 56.4, 46.2, 36.1, 31.6, 28.4, 23.0; IR (ATR) $\tilde{\nu}$/cm^{-1} 2932 (m), 2777 (m), 1465 (m), 1448 (m), 1378 (m), 1279 (s), 1257 (s), 1155 (m), 1146 (s), 1136 (s), 1069 (m), 1030 (m), 1021 (m), 990 (s), 769 (vs), 743 (s), 733 (vs), 695 (m); MS (EI, 70 eV) *m*/*z* (%) 227 (28, M$^+$), 128 (6), 96 (7), 70 (100), 42 (8); HRMS (EI) calcd for $C_{16}H_{21}N$ 227.1674, found 227.1659.

Synthesis of Cusparine (11) and Galipinine (12). *2-(Quinolin-2-yl)ethanol (**14**).* Quinaldine (**13**; 50.0 g, 350 mmol) and paraformaldehyde (7.10 g, 234 mmol) was dissolved in dioxane (11.3 mL) and water (2.8 mL) at 75 °C, and the solution was stirred at 110 °C reflux for 20 h. Remaining quinaldine was distilled off and the red-brown residue was diluted with *n*-heptane 5 times and filtered off to furnish 2-(quinolin-2-yl)ethanol as a colorless solid (**14**; 13.0 g, 75.2 mmol, 72% yield based on recovered quinaldine). Mp (°C) 96−100; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.10 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.79 (dd, *J* = 8.1 Hz, 1.1 Hz, 1H), 7.74−7.66 (m 1H), 7.55−7.47 (m, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 4.15 (t, *J* = 5.4 Hz, 2H), 3.21 (t, *J* = 5.4 Hz, 2H). These data match the literature: Bucmann, G.; Wolniak, O. *J. Prakt. Chem.* **1964**, *25*, 101

*2-(1,2,3,4-Tetrahydroquinolin-2-yl)ethanol (**15**).* 2-(Quinolin-2-yl)ethanol (**14**; 8.65 g, 50.0 mmol) and $NiCl_2$ (1.10 g, 8.75 mmol)

were dissolved in methanol (200 mL), the mixture was cooled to 0 °C, and $NaBH_4$ (7.57 g, 200 mmol) was slowly added within 30 min. The reaction mixture was allowed to warm to 25 °C and stirred for 1 h, then the solvent was distilled off, and the residue dissolved in 2 N HCl and neutralized with satd aq K_2CO_3 solution. After extraction with CH_2Cl_2 (2 × 100 mL) the combined organic layers were dried (Na_2SO_4), and the solvent was distilled off. Drying in high vacuum furnished 2-(1,2,3,4-Tetrahydroquinolin-2-yl)ethanol (**15**; 7.69 g, 87% yield) as a yellow oil, which was used in the next step without purification.

*2-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethanol (**16**).* 2-(1,2,3,4-Tetrahydroquinolin-2-yl)ethanol (**15**; 7.69 g, 43.0 mmol), formaldehyde (6.45 g, 215 mmol), and acetic acid (3.87 g, 64.5 mmol) were dissolved in CH_2Cl_2 (150 mL), and $NaBH_3CN$ (4.05 g, 64.5 mmol) was added slowly. The solution was stirred at 25 °C for 16 h, the solvent was distilled off, and then the residue was dissolved in CH_2Cl_2 (100 mL) and washed with satd aq K_2CO_3 solution (2 × 100 mL). The organic layers were dried (Na_2SO_4), and the solvent was distilled off. Drying in high vacuum furnished 2-(1-methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethanol (**16**; 8.06 g, 98% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.16−7.11 (m, 1H), 7.02−6.98 (m, 1H), 6.64−6.58 (m, 2H), 3.74−3.62 (m, 2H), 3.36 (s, 3H), 2.84−2.72 (m, 1H), 2.61−2.50 (m, 1H), 1.88−1.61 (m, 3H), 1.47−1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 144.7, 129.1, 127.1, 122.0, 115.5, 111.3, 60.2, 56.0, 39.3, 35.2, 25.1, 23.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 3342 (s), 3052 (w), 3016 (w), 2922 (s), 2844 (s), 1606 (s), 1585 (m), 1487 (vs), 1446 (m), 1434 (m), 1349 (m), 1309 (s), 1275 (m), 1254 (m), 1206 (w), 1154 (w), 1118 (m), 1069 (m), 1047 (m), 1036 (m), 1015 (m), 931 (w), 869 (vw), 744 (s), 716 (w); MS (EI, 70 eV) *m*/*z* (%) 191 (33, M$^+$), 146 (100), 131 (16), 119 (9), 91 (6), 78 (7); HRMS (EI) calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1302. These data match the literature: Avemaria, F.; Vanderheiden, S.; Bräse, S. *Tetrahedron* **2003**, *59*, 6785.

*2-(2-Chloroethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**17**).* 2-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethanol (**16**; 6.79 g, 35.5 mmol) was dissolved in CH_2Cl_2 (100 mL), and $SOCl_2$ (5.07 g, 42.6 mmol) was added at 0 °C. After 2 h of stirring at 25 °C, the reaction was quenched with satd aq K_2CO_3 solution (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was distilled off. Column chromatography (silica gel, pentane) furnished 2-(2-chloroethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**17**; 6.17 g, 83% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.15−7.09 (m, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.67−6.62 (m, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 3.70−3.56 (m, 3H), 3.01 (s, 3H), 2.87−2.68 (m, 2H), 2.16−2.03 (m, 1H), 2.01−1.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 144.9, 128.8, 127.2, 121.3, 115.8, 111.1, 55.8, 42.2, 38.5, 34.6, 24.3, 23.4; IR (ATR) $\tilde{\nu}$/cm^{-1} 3055 (w), 3001 (w), 2928 (m), 2799 (s), 1588 (w), 1501 (s), 1440 (w), 1366 (s), 1302 (m), 1238 (m), 1200 (w), 1151 (w), 1138 (m), 1017 (m), 998 (m), 951 (vw), 869 (w), 741 (s), 719 (m); MS (EI, 70 eV) *m*/*z* (%) 209 (11, M$^+$), 180 (5), 147 (8), 146 (100), 144 (8), 131 (11), 130 (9), 118 (5), 77 (4), 43 (5); HRMS (EI) calcd for $C_{12}H_{16}{}^{35}ClN$ 209.0971, found 209.0962.

*(2-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethyl)magnesium Chloride (**18**).* 2-(2-Chloroethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**17**; 3.00 g, 14.3 mmol) reacted with Mg turnings (418 mg, 17.2 mmol) and LiCl (1.21 g, 28.6 mmol) according to **TP1**. The fresh solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.49 M in THF was obtained, 69% yield.

*2-(3,4-Dimethoxyphenethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**11**; Cusparine).* 4-Bromo-1,2-dimethoxybenzene (**19**; 434 mg, 2.00 mmol) reacted with (2-(1-methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethyl)-magnesium chloride (**18**; 4.90 mL, 2.40 mmol, 0.49 M in THF) at 25 °C for 18 h, according to **TP2**. Column chromatography (silica gel, pentane/Et_2O 7:3) furnished 6-((1-methylpiperidin-3-yl)methyl)-quinoxaline (**11**; 548 mg, 88% yield) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.10−7.07 (m, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.74−6.71 (m, 2H), 6.61−6.59 (m, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.31−3.28 (m, 1H), 2.92 (s, 3H), 2.88−2.83 (m, 1H), 2.72−2.65 (m, 2H), 2.56−2.51 (m, 1H), 1.98−1.89 (m, 3H), 1.77−1.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 148.8, 147.1, 145.2, 134.6, 128.6, 127.1, 121.7, 120.0, 115.3, 111.5, 111.2, 110.5, 58.4, 55.9, 55.8, 38.1, 33.0, 31.9, 24.3, 23.5; IR (ATR) $\tilde{\nu}$/cm^{-1} 2970 (w), 2933 (m), 2833 (w), 1739 (s), 1601 (m), 1513 (s), 1498 (s), 1479 (m), 1449 (m), 1417 (m), 1365 (m), 1305 (m), 1259 (s), 1232 (vs), 1217 (s), 1155 (m), 1140 (m), 1093 (m), 1028 (s), 803 (m), 743 (vs), 606 (w); MS (EI, 70 eV) *m*/*z* (%) 312 (3), 311 (13, M$^+$), 151 (6), 147 (11), 146 (100), 144 (4), 131 (7), 130 (5), 91 (3), 77 (2); HRMS (EI) calcd for $C_{20}H_{25}NO_2$ 311.1885, found 311.1881. These data match the literature: .

*2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**12**; Galipinine).* 5-Bromobenzo[*d*][1,3]dioxole (**20**; 402 mg, 2.00 mmol) reacted with (2-(1-methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethyl)magnesium chloride (**18**; 4.90 mL, 2.40 mmol, 0.49 M in THF) at 25 °C for 22 h, according to **TP2**. Column chromatography (silica gel, pentane/Et_2O 20:1) furnished 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**12**; 479 mg, 81% yield) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.12−7.10 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.54−6.50 (m, 2H), 5.93 (s, 2H), 3.31−3.29 (m, 1H), 2.93 (s, 3H), 2.90−2.83 (m, 1H), 2.74−2.63 (m, 2H), 2.55−2.50 (m, 1H), 1.98−1.90 (m, 3H), 1.76−1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 147.6, 145.6, 135.3, 128.7, 127.1, 120.9, 120.2, 108.7, 108.4, 108.1, 107.5, 101.1, 100.7, 58.2, 38.1, 33.0, 32.0, 24.2, 23.5; IR (ATR) $\tilde{\nu}$/cm^{-1} 3016 (w), 2970 (w), 2935 (w), 1739 (s), 1601 (m), 1499 (vs), 1488 (s), 1441 (s), 1365 (m), 1241 (s), 1229 (s), 1217 (vs), 1187 (m), 1092 (m), 1037 (s), 935 (m), 926 (m), 855 (w), 805 (m), 743 (vs), 702 (m), 611 (w); MS (EI, 70 eV) *m*/*z* (%) 296 (4), 295 (14, M$^+$), 147 (12), 146 (100), 144 (5), 135 (3), 131 (8), 130 (6), 91 (4), 77 (4); HRMS (EI) calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1566. These data match the literature: O'Byrne, A.; Evans, P. *Tetrahedron* **2008**, *64*, 8067.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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