Synthesis of [1,2-*a*]-fused tricyclic dihydroquinolines by palladium-catalyzed intramolecular C–N cross-coupling of polarized heterocyclic enamines

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Abstract

A simple methodology for [1,2-*a*]-fused tricyclic dihydroquinolines is established. The key step of the methodology is an intramolecular Buchwald-Hartwig amination reaction of suitable halogenated (both bromo and chloro) cyclic enaminoketones, enaminoesters and enaminonitriles with various ring size (from five- to seven-membered). Optimal reaction conditions (palladium source, base, ligand) depend on the ring size of the starting enamine, giving 65–98% yield of the tricyclic product. A treatment of the products with perchloric acid gives respective quinolinium perchlorates.

Keywords: Buchwald-Hartwig reaction, enaminones, palladium, amination, cross-coupling

Introduction

The term enaminone was first introduced by Greenhill[1] in 1977. Ever since, enaminones and related compounds (enaminoesters, enaminonitriles,…) have become very useful synthons in organic synthesis.[2–8] A privileged status among them have cyclic enaminones and their derivatives.[9,10] They can, in principle, be divided into three structural types **I**–**III** (Fig. 1).

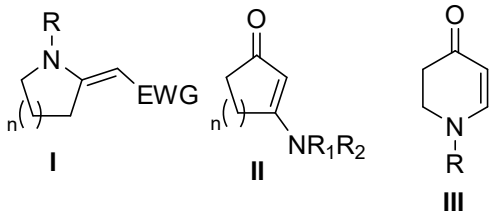
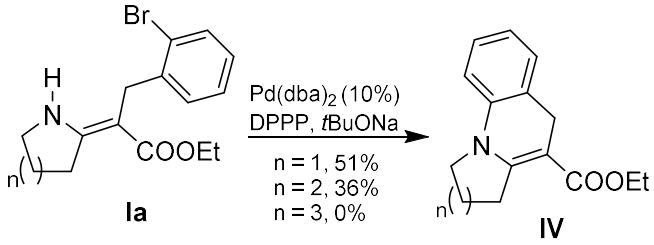


Figure 1. Structural classes of cyclic enaminones.

The synthons in Fig. 1 give access, by means of suitable synthetic transformations, to a number of structures that are the core of both natural and synthetic biologically active compounds (e.g. alkaloids and amino acids).[5,11–13] For example, intramolecular C–N cross-coupling reactions of cyclic enaminones and related compounds are an efficient method for the synthesis of polycyclic nitrogen-containing heterocycles. However, compared with the plethora of works dealing with C–N cross-coupling reactions, papers involving as substrates cyclic enaminones and related compounds are relatively rare.[14–26] Some papers dealing with the synthesis of fused indole derivatives using intramolecular C–N bond formation in cyclic enaminones appeared in the literature.[14,15,22–26] However, the situation is quite different in the case of their dihydroquinoline homologs and, to the best of our knowledge, there is only one paper[21] describing the mentioned transformation. Thus in 2003 Wang and coworkers[21] reported the Buchwald-Hartwig cross-coupling reaction of enaminoesters **Ia** providing tricyclic compounds **IV** with bridgehead nitrogen atom (Scheme 1). The yields were, however, only moderate-to-zero.



Scheme 1. Previously reported results on intramolecular C–N cross-coupling reactions of *C*-benzylated cyclic enaminoesters.[21]

Similar structural motif can be found e.g. at Ochrosamines A,B (alkaloids from the Australian rainforest tree *Ochrosia Moorei*),[27,28] Strychnozairine (an alkaloid from the African tree *Strychnos variabilis*),[29] 2,7-dihydroxyapogeissoschizine (the alkaloid isolated from the root bark of *Strychnos gossweileri*),[30] or valesiochotamine alkaloids[31] (Figure 2). Fused cyclic enaminones with bridgehead nitrogen served as intermediates in the synthesis of 10-methoxydihydrocorynantheol, 10-methoxycorynantheidol,[32] or 6-oxo-16-episilicine.[33]

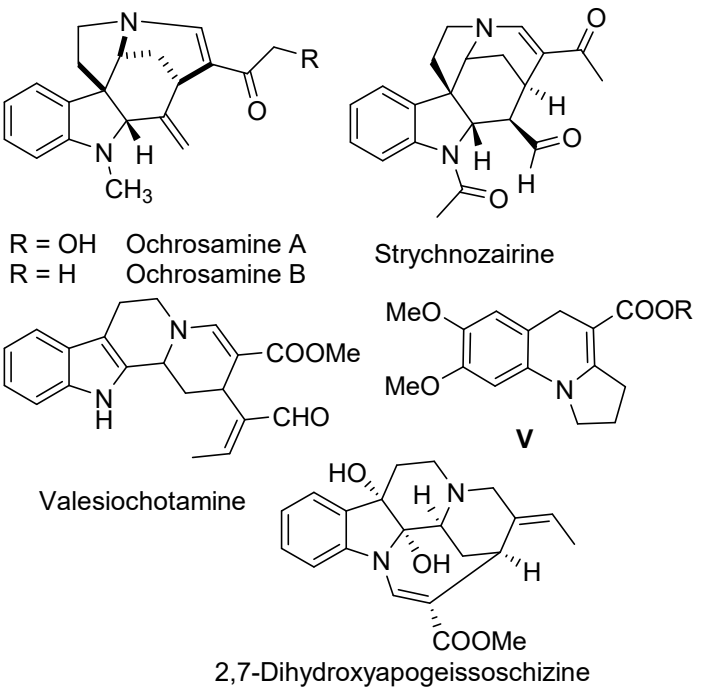
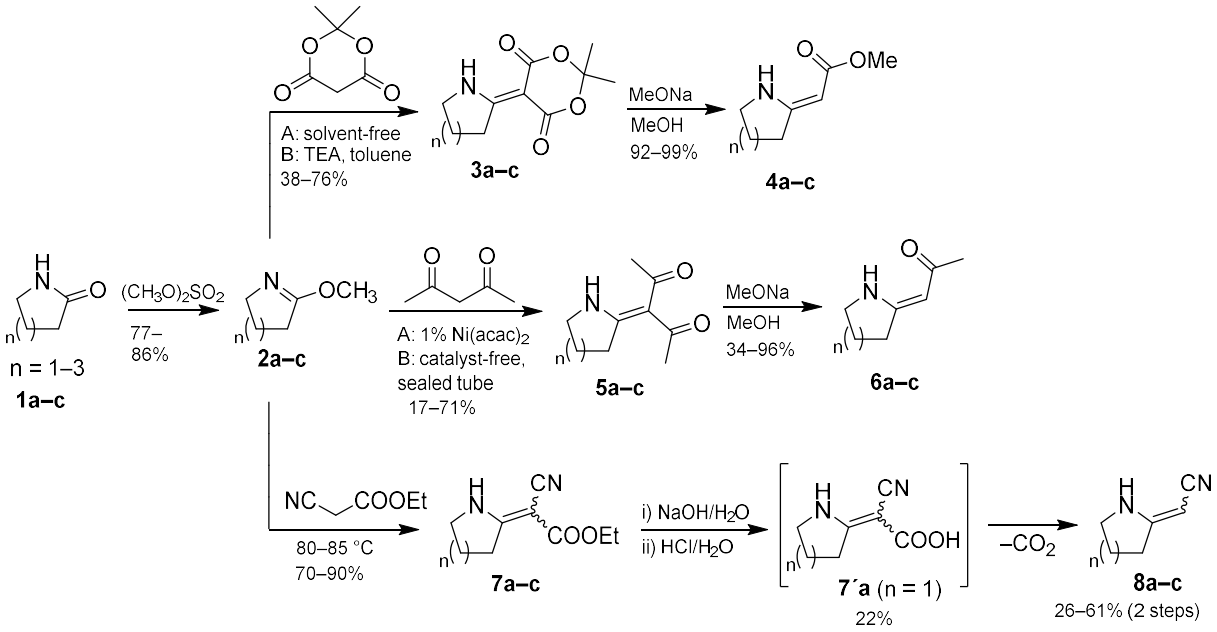


Figure 2. Some natural and synthetic fused enaminones.

Thus, tricyclic compounds like **IV** can be suitable scaffolds for further synthetic transformations leading to both natural and synthetic compounds with favourable biological activity. Recently Levacher et al.[34] suggested tricyclic fused 1,4-dihydroquinolines **V** (Fig. 2) as new chemical delivery agents for the transfer of AChE inhibitor galantamine to the brain. In this work we present a simple and superior protocol enabling to synthesize fused tricyclic dihydroquinolines by means of an intramolecular, palladium catalysed, C–N cross-coupling reaction of exocyclic enaminones, enaminoesters and enaminonitriles.

Results and Discussion

Synthesis of the starting enamines. The starting enamines **9** were prepared according to Scheme 2 and Scheme 3. All the procedures started from lactim ethers **2a–c**, prepared in an ordinary way from the corresponding lactams **1a–c** (Scheme 2). Enaminoesters **4a–c** were prepared by means of modified literature[35] procedure through intermediates **3a–c** using Meldrum's acid as C2 synthon. The decomposition of **3a–c** by sodium methoxide gives **4a–c** in high yields.

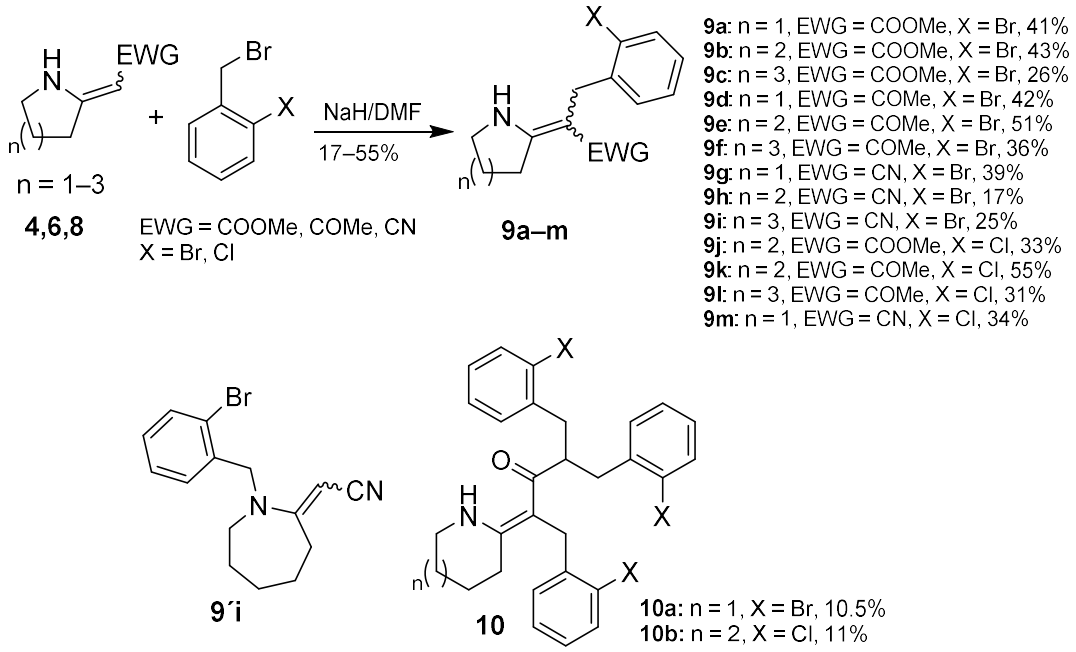


Scheme 2. Synthesis of exocyclic enamines.

Similarly, the reaction of **2a–c** with acetylacetone furnished enaminoketones **6a–c** in two steps. Two methodologies for the synthesis of intermediates **5a–c** were used. The published[36] procedure using catalytic amount of nickel(II) acetylacetonate (Method A) provided only low yields of **5** (17% for **5a**, 23% for **5c**). Catalyst- and solvent-free modification performed in a sealed tube (Method B) led to a substantially higher yield of **5c** (71%). The synthesis of **5b** proved to be the most problematic. Partial deacetylation took place during the condensation step to give 5:4 mixture of **5b** and **6b**. As **6b** was the aim of the whole synthetic sequence the mixture was not separated and was used in the next reaction step. Deacetylation of **5a–c** was performed in a similar way as in the case of **3a–c** giving enaminoketones **6a–c**.

The synthesis of exocyclic enaminonitriles **8a–c** was carried out in the analogous way as in the previous cases (Scheme 2). However, intermediates **7b,c**, synthesized from **2b,c** upon heating with ethyl cyanoacetate in a pressure tube, contained 10–30% of methylester, probably generated via transesterification of **7b,c** by methanol formed from **2**. No such a by-product was observed in the case of **7a** prepared by heating in a conventional apparatus. As the mixture of esters does not hinder the next step, they were used in the following step without purification. Saponification of **7a–c** with aqueous sodium hydroxide followed with acidification/decarboxylation led to the formation of enaminonitriles **8a–c** in moderate-to-low yields. (Upon careful neutralization of the mixture, intermediate cyanoacid **7'a** was isolated in 22% yield at pH 7). No product **8** was formed using MeONa/MeOH system. The enaminonitriles, unlike **4** and **6**, exist in $CDCl_3$ as *E/Z* mixtures (for details see Experimental). The last step for the synthesis of **9** is *C*-benzylation of enamines **4**, **6** and **8** (Scheme 3). In principle, enamines are ambident nucleophiles and can be alkylated both at the nitrogen and C2 carbon atom. Dannhardt et al.[37,38] systematically studied the alkylation of some exocyclic enaminones and specified principal factors affecting the regioselectivity of this reaction.

Lhommet et al.[39–42] described regioselective *C*-alkylation of a number of exocyclic enaminoesters. We adopted the methodology published in ref.[21] (Scheme 3) where no *N*-benzylated product was described.



Scheme 3. *C*-Benzylation of the exocyclic enamines.

In most cases the reaction proceeded chemoselectively at C2 carbon atom. Only in the case of seven-membered exocyclic enaminonitrile **8c** the procedure afforded predominantly *N*-benzylated product **9´i** (Scheme 3) with *N*-benzyl/*C*-benzyl ratio ca 2:1 (according to ^{1}H NMR). The desired product **9i** was then separated by means of column chromatography. Interestingly, the reaction of 2-bromobenzylbromide with enaminoketone **6b** gave a by-product (11%), which was identified as tris-*C*-benzylated compound **10a** (Scheme 3). The structure was confirmed by means of 1D and 2D NMR, HRMS and also X-ray crystallography (see Figure 3 and Supporting Info). Analogous product **10b** was isolated in 11% yield from enaminoketone **6c** and 2-chlorobenzylbromide.

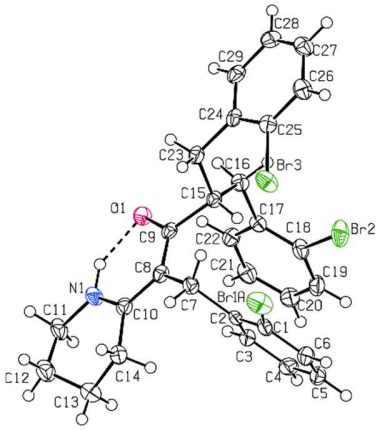


Figure 3. ORTEP view (50% probability level) of **10a**, disordered part of phenyl ring is omitted for clarity.

The intramolecular C–N cross-coupling. Wang et al.[21] described the intramolecular cyclization of exocyclic enamino esters **Ia** to the corresponding tricyclic compounds **IV** (Scheme 1) using $Pd(dba)_2$/DPPP/*t*BuONa system in toluene. The reactions were strongly affected by the ring size of the starting substrate and the yields for five, six and seven-membered tricyclic compounds were 51%, 36% and 0% respectively.

Optimization study. Starting from these results and with the aim to improve the efficiency of the catalytic system, we chose to reinvestigate the intramolecular C–N bond forming reaction using enamino ester **9b** as the model substrate. Firstly, we turned our attention to 2nd generation XPhos palladacycle precatalyst (**L1**, Fig. 4), introduced by Buchwald's group.[43] Three molar per cents of this precatalyst in the presence of common base (Cs_2CO_3) in *t*BuOH at 80 °C provided quantitative conversion of **9b** to **11b** in 7 h (Table 1, Entry 1). Half amount of the precatalyst was still capable to complete the reaction in a reasonable time of 13 h (Table 1, Entry 2). Changing the base to the cheaper potassium carbonate, however, substantially worsen the results (Table 1, Entry 3). The best results were obtained using cheap tribasic potassium phosphate as the base (Table 1, Entry 4) providing quantitative conversion of **9b** in 10 h. Moreover, no reaction was observed in the absence of **L1** (Table 1, Entry 5).

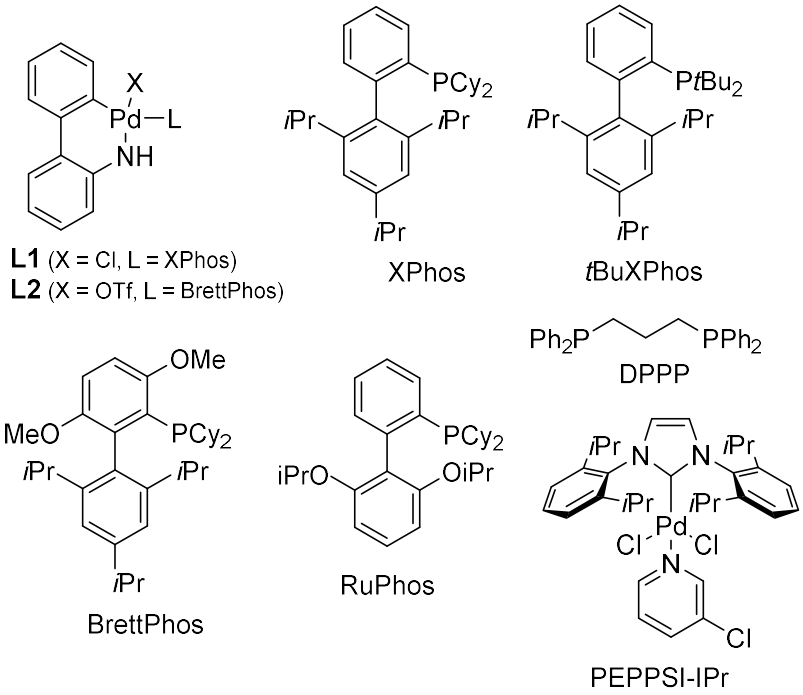
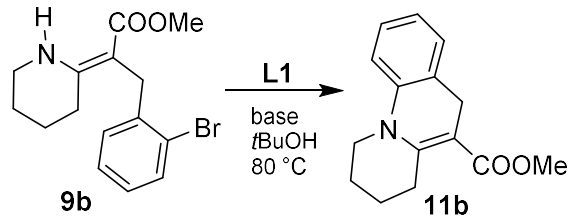


Figure 4. Ligands and precatalysts used in this work.

Table 1. Optimization study for palladacycle-catalysed cyclization of six-membered exocyclic enamino ester[a]



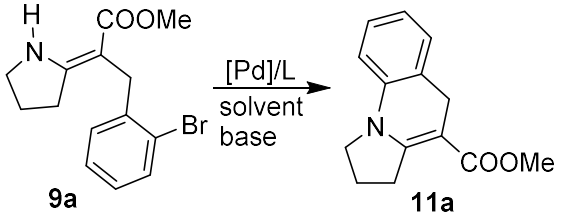
Entry	[%]**L1**	Base	Time [h]	Conv.[b]/Yield[c]
1	3	Cs_2CO_3	7	>99/97
2	1.5	Cs_2CO_3	10	>99/94
3	1.5	K_2CO_3	16	51
4	1.5	K_3PO_4	13	>99/95
5	0	Cs_2CO_3	24	0

[a]Conditions: substrate 0.5 mmol, *t*BuOH (2 mL), base (2 eq.). [b]Determined from ^{1}H NMR. [c]Isolated yield.

An attempt to apply the best conditions from Table 1 to achieve the transformation of five-membered analogue **9a** to **11a** failed (Table 2, Entry 1). Neither increasing the amount of the palladacycle **L1** nor changing the base improved the situation (Table 2, Entries 2, 3). The change

for 3rd generation BrettPhos palladacycle (**L2**, X = OTf, Fig. 4) did not improve the situation at all (Table 2, Entry 4). An improvement took place on using well-known $Pd_2(dba)_3$ as the metal source although relative high amounts (5%) were required (Table 2, Entries 5–10). The best results were obtained with 1,3-bis(diphenylphosphino)propane (DPPP, Fig. 4) as the ligand. It allowed to lower the amount of the catalyst to 3.5% with the same conversion (Table 2, Entry 9). The conditions and results are very similar to those obtained in ref.[21] with lower amount of palladium in our protocol (10% $Pd(dba)_2$, DPPP, *t*BuONa, toluene vs. 3.5% $Pd_2(dba)_3$, DPPP, *t*BuONa, toluene). Decline in the amount of the metal source to 1.5% led to decrease in the conversion (Table 2, Entry 10). Palladium diacetate, pre-activated by the methodology developed by Buchwald's group[44] also showed to be promising (Table 2, Entries 11, 12). Increase in the catalyst loading and temperature led to the quantitative conversion in a short time (Table 2, Entry 13). The protocol, however, suffered from difficulties during the purification of the reaction mixture (large amount of the ligand). We therefore preferred the conditions shown in Table 2, Entry 9. PEPPSI family of ligands is another important class of ligands widely used for cross-coupling reactions.[45,46] We tested PEPPSI-IPr (Fig. 4) for the transformation of **9a** to **11a**. The performance under the conditions studied was worse than in the case of $Pd_2(dba)_3$ (Table 2, Entries 14, 15). The optimization study thus furnished two protocols for the cyclization of **9**: $Pd_2(dba)_3$/DPPP/*t*BuONa/toluene/100 °C (Table 2, Entry 9) for five-membered representatives and **L1**/K_3PO_4/*t*BuOH/80 °C for six-membered ones (Table 1, Entry 4).

Table 2. Optimization study for palladium-catalysed cyclization of bromo-substituted five-membered exocyclic enamino ester[a]



9a **11a**

Entry	[Pd]/%	[L]/%	Base/eq.	Solvent	T/°C	Time/h	Conv./%
1	**L1**/1.5		K_3PO_4/2	*t*BuOH	80	15	17
2	**L1**/3		K_3PO_4/2	*t*BuOH	80	15	19
3	**L1**/3		Cs_2CO_3/2	*t*AmOH	100	18	13
4	**L2**/3		Cs_2CO_3/2	*t*AmOH	100	24	21
5	$Pd_2(dba)_3$/5	XPhos/10	Cs_2CO_3/2	toluene	80	48	87
6	$Pd_2(dba)_3$/5	XPhos/10	*t*BuONa/1.2	toluene	80	48	87
7	$Pd_2(dba)_3$/5	BINAP/10	*t*BuONa/1.2	toluene	80	48	95
8	$Pd_2(dba)_3$/5	DPPP/10	*t*BuONa/1.2	toluene	100	24	>99
9	$Pd_2(dba)_3$/3.5	DPPP/7	*t*BuONa/1.2	toluene	100	24	>99
10	$Pd_2(dba)_3$/1.5	DPPP/3	*t*BuONa/1.2	toluene	100	36	72

Table 2 (continued)

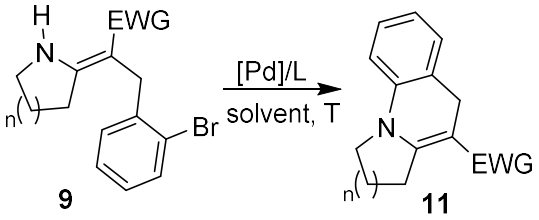
Entry	[Pd]/%	[L]/%	Base/eq.	Solvent	T/°C	Time/h	Conv./%
11[b]	$Pd(OAc)_2$/3	XPhos/9	*t*BuONa/1.6	*t*BuOH	80	3	54
12[b]	$Pd(OAc)_2$/3	XPhos/9	*t*BuONa/1.6	*t*BuOH	80	16	83
13[b]	$Pd(OAc)_2$/5	XPhos/15	*t*BuONa/1.6	*t*AmOH	100	3	>99
14	PEPPSI-IPr/2		*t*BuONa/1.5	toluene	80	48	65
15	PEPPSI-IPr/10		*t*BuONa/1.5	toluene	80	48	80

[a]Conditions: substrate 0.5 mmol, solvent 2 mL. [b]Water-mediated preactivation.

Conditions for **9b** (Table 1, Entry 4) worked well also for seven-membered homolog **9c** (Table 3).

The optimized reaction conditions, mentioned above, represent not only a substantial improvement of the methodology published by Wang,[21] (95% yield vs. 36%, **9a**) but it worked also in the case of seven-membered ester **9c** (yield 97%) where Wang's protocol failed. The protocols were further used for the cyclization of other enamines (enaminoesters, enaminoketones, enaminonitriles) (Table 3).

Table 3. Intramolecular Buchwald-Hartwig amination of bromo-substituted exocyclic enamines[a,b]



9 **11**

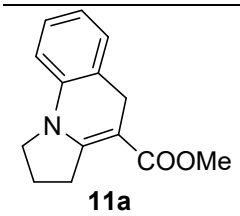
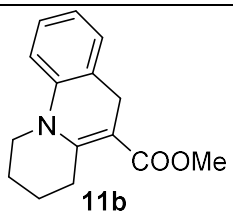
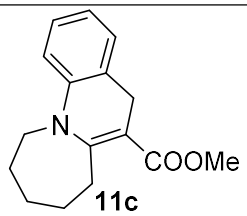
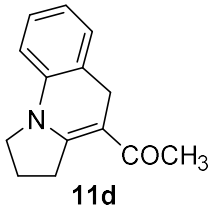
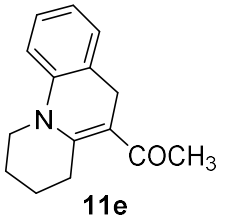
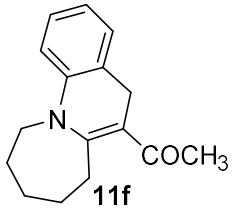
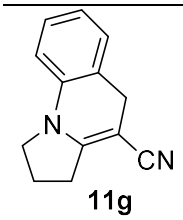
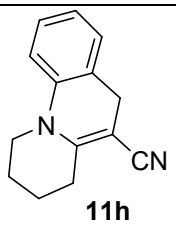
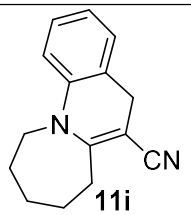
 **11a**	 **11b**	 **11c**
Method A, 24 h, 65%	Method B, 16 h, 95%	Method B, 16 h, 97%
 **11d**	 **11e**	 **11f**
Method A, 36 h, 87%	Method B, 24 h, 98%	Method B, 24 h, 96%

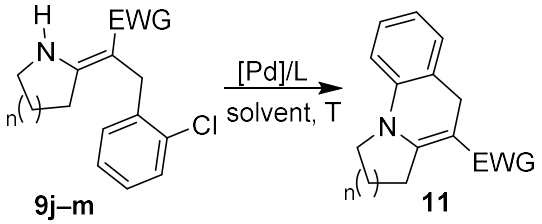
Table 3 (continued)

 **11g** Method A, 36 h, 67%	 **11h** Method B, 24 h, 97%	 **11i** Method B, 24 h, 98%

[a]**Method A:** substrate **9** (0.5 mmol), $Pd_2(dba)_3$ (3.5–5 mol.%), DPPP (7–10 mol.%), *t*BuONa (0.6 mmol, 1.2 eq.), toluene (2 mL), 100 °C 24–36 h. **Method B:** substrate **9** (0.5 mmol), **L1** (1.5–2 mol.%), K_3PO_4 (1 mmol, 2 eq.), *t*BuOH (2 mL), 80 °C, 16–24 h. [b]Isolated yields given

Having an efficient protocol for the cyclization of bromo derivatives in hand, we turned our attention to the chloro derivatives. The optimization study (Table 4) provided available protocol to bring about the cyclization of chloro substituted exocyclic enamines: $Pd_2(dba)_3$/RuPhos/Cs_2CO_3 in toluene.

Table 4. Cyclization of chloro derivatives[a]



9j–m **11**

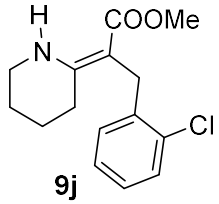
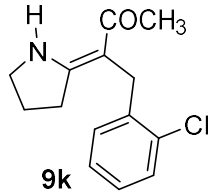
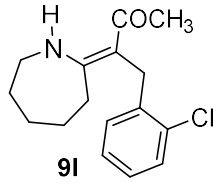
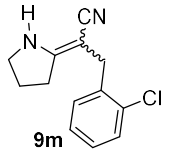
Entry	Substrate	Product	[Pd]/%	[L]/%	Base/eq.	Cond.[a]	Conv./ Yield[b]
1	 **9j**	**11b**	**L1**/3		K_3PO_4/2	*t*BuOH, 80 °C, 24 h	0
2			$Pd_2(dba)_3$/5	RuPhos /10	Cs_2CO_3/ 1.4	DMF, 100 °C, 24 h	23
3			$Pd_2(dba)_3$/5	RuPhos /10	Cs_2CO_3/ 1.4	Toluene, 100 °C, 24 h	>99/87
4	 **9k**	**11d**	$Pd_2(dba)_3$/5	RuPhos /10	Cs_2CO_3/ 1.4	Toluene, 100 °C, 72 h	67
5			$Pd_2(dba)_3$/5	DPPP /10	*t*BuONa/ 1.2	Toluene, 100 °C, 48 h	23

Table 4 (continued)

Entry	Substrate	Product	[Pd]/%	[L]/%	Base/eq.	Cond.[a]	Conv./ Yield[b]
6	 **9l**	**11f**	$Pd_2(dba)_3$/5	RuPhos /10	Cs_2CO_3/ 1.4	Toluene, 100 °C, 60 h	>99/91
7			$Pd_2(dba)_3$/5	*t*BuXPhos/10	Cs_2CO_3/ 1.4	*t*AmOH, 100 °C, 60 h	19
8	 **9m**	**11g**	$Pd_2(dba)_3$/5	RuPhos /10	Cs_2CO_3/ 1.4	Toluene, 100 °C, 48 h	>99/71
9			$Pd_2(dba)_3$/5	DPPP /10	*t*BuONa/ 1.2	Toluene, 100 °C, 48 h	>99/75

[a]Conditions: 0.5 mmol of the substrate, 2 mL of the solvent. [b]Conversion estimated from ^{1}H NMR, isolated yield.

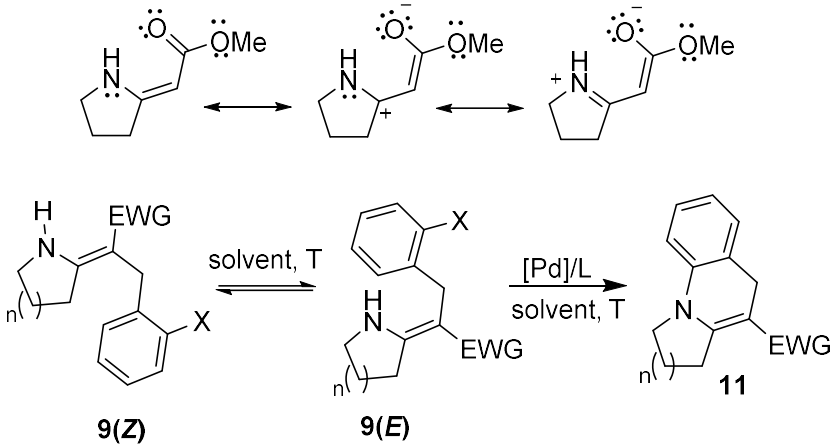
The conditions worked well for all kinds of substrates with the exception of five-membered ketone **9k** where only moderate conversion was achieved (Table 4, Entry 4). The conditions successful for the bromo derivatives failed (Table 4, Entry 1) as well as the application of *t*BuXPhos as the ligand (Table 4, Entry 7). For RuPhos and *t*BuXPhos see Figure 4.

DPPP Ligand, successful in the cyclization of five-membered bromo derivatives, brought about the cyclization in the case of nitrile **9m** (Table 4, Entry 9). On the other hand, its application for enamino ketone **9k** led to only low conversion (Table 4, Entry 5).

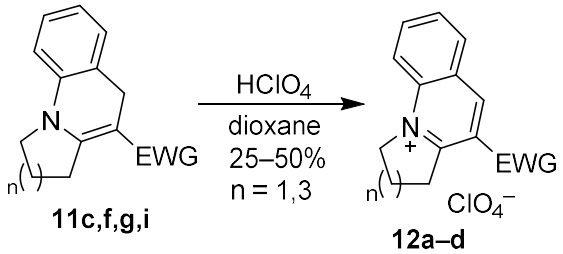
It is clear that substrates **9** must adopt *E*-configuration prior to the cyclization to **11**. However, due to the possibility of formation of an intramolecular N–H···O hydrogen bond (for enaminones and enaminoesters) one would suppose the prevalence of *Z*-configuration which is not prone to cyclize to **11**. The *Z*-configuration was in the case of **9d** proved by means of X-ray (Figure S1). Enaminonitriles **9g**–**i**,**m** are *E*/*Z*-mixtures in solution. An explanation of successful transformation of **9** to **11** lies in decreased C–C bond order of the double bond due to the push-pull effect (see mesomeric structures in Scheme 4). Energy of rotation is then also decreased[47] which facilitates mutual interconversion of *E*/*Z* isomers.

Compounds **11** are rather unstable oils. Especially unstable are five-membered derivatives **11a**,**d** that rapidly decompose on air to give dark tarry substances during few days even in a refrigerator. Recently Levacher et al.[34] have described interesting fused dihydroquinoline-quinolinium redox system potentially applicable as chemical delivery system (CDS) for brain-targeting drugs. Inspired by this work we performed preliminary study on the oxidative quarternization of selected compounds **11**. On treatment by perchloric acid compounds **11** oxidize to the corresponding quinolinium perchlorates **12** (Scheme 5) that were confirmed and characterized by means of multinuclear magnetic resonance, X-ray diffraction and HRMS (see

Supporting Info and Experimental). To the best of our knowledge, compounds **12** with n > 1 have not been prepared hitherto. The larger ring could improve the lipophilicity of the molecules which can be important, with respect to the applicability of this kind of molecules as CDS.



Scheme 4. Mesomeric structures of **4a** used for the explanation of mutual interconversion of *E*/*Z* isomers accounting for high conversions of the cross coupling even in *Z*-predominant mixtures.



Scheme 5. Oxidation of selected dihydroquinolines to the corresponding quinolinium perchlorates.

Conclusions

In this work we have prepared and characterized thirteen 2-halobenzyl-substituted polarized ethylenes (enaminoesters, enaminoketones and enaminonitriles) with exocyclic double bond. The enamines were subjected to the intramolecular Buchwald-Hartwig amination reaction to give corresponding fused tricyclic dihydroquinolines **11** in good yields. The optimal reaction conditions depend both on the ring size of the starting enamines and on the type of the halogen. The five-membered substrates appeared to be more challenging than their six and seven membered analogues. The results presented here are a substantial improvement of the methodology published hitherto and extend both the possibilities for syntheses of interesting fused nitrogen heterocycles and the scope of cross-coupling reactions. Compounds **11** can be considered as β-EWG substituted

heterocyclic enamines. Due to the importance of such enamines in organic synthesis, compounds **11** could serve as useful intermediates for further synthetic transformations. For example, they can be easily oxidized to their quinolinium salts **12**. In addition to that, similar 3-EWG substituted dihydroquinolines were studied as carriers for brain-specific drug delivery[48,49] (just in the combination with their quinolinium salts), or as a novel class of ABCB1 inhibitors.[50]

Experimental Section

General. All the solvents and reagents were used commercial without further purification. PEPPSI-IPr was prepared according to the published procedure.[51] All the palladium sources, ligands and bases used in the cross-couplings were commercial (Aldrich, Acros, Strem) and stored under argon in a desiccator. Dry solvents were used commercial (Aldrich, Acros) and stored under argon using Sure/Seal™ or AcroSeal™ technology. TLC Analyses were performed on silica gel coated aluminium plates 60 F254 under UV visualization (254 or 365 nm). Column chromatography was performed using silica gel 60 (230–400 mesh) (Sigma Aldrich) containing ~ 0.1% Ca. Melting points were measured using Kofler hot plate microscope Boetius PHMK 80/2644. NMR Spectra were measured using either Bruker AVANCE III spectrometer operating at 400.13 (^{1}H) and 100.12 MHz (^{13}C) or Bruker Ascend™ spectrometer operating at 500.13 (^{1}H) and 125.15 MHz (^{13}C). Multiplicity of the signals is depicted as s (singlet), d (doublet), t (triplet), quint (quintet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), br (broad signal). Proton NMR spectra in $CDCl_3$ were calibrated using internal TMS ($\delta = 0.00$) and in DMSO-d6 on the middle signal of the solvent multiplet ($\delta = 2.50$). Carbon NMR spectra were referenced against the middle signal of the solvent multiplet ($\delta = 77.23$ for $CDCl_3$ and 39.51 for DMSO-d6). Measurement of ^{13}C NMR was done in an ordinary way using broadband proton decoupling or by means of APT pulse sequence. Elemental analyses were performed on a Flash EA 2000 CHNS automatic analyser (Thermo Fisher Scientific). HRMS were measured using dried droplet method on a MALDI LTQ Orbitrap XL (Thermo Fisher Scientific) with 2,5-dihydroxybenzoic acid (DHB) or 9-aminoacridine (9-AA) as the matrices for positive or negative mode respectively. Experimental procedures for compounds **2–8** as well as details for X-ray data are in Supporting Information.

General procedure for the synthesis of *C*-benzylated enamines 9. A modified procedure from ref.[21] was used. A dried Schlenk flask equipped with a magnetic stirring bar was charged with the starting substrate **4**, **6** or **8** (10 mmol). The flask was 3 × evacuated and backfilled with argon. Dry DMF (20 mL) was added via syringe. The apparatus was then cooled to –40 °C (acetone-dry ice bath) and sodium hydride (12 mmol, 1.2 eq.) was added in one portion. The mixture was stirred at –40 °C until foaming ceased (ca 1.5 h). 2-Bromobenzylbromide (12 mmol, 1.2 eq.) was then added in one portion under cooling. The flask was removed from cooling bath and heated under inert to 80 °C for 24 h. After cooling in an ice bath, the reaction was quenched with saturated aq. NH_4Cl

(50 mL). Organic layer was diluted with ethyl acetate (125 mL), washed with water (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulphate. Evaporation to dryness gave crude **9**. For purification see details at individual compounds.

Methyl 3-(2-bromophenyl)-2-(pyrrolidin-2-ylidene)propanoate (9a). Prepared from **4a**, crude product was suspended in ether (110 mL). The suspension was inserted into an ultrasound bath for half an hour. Solid impurities were filtered off and the filtrate was evaporated to dryness, the residue was recrystallized from *n*-hexane to give 41% of white solid with mp 106–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1H); 7.52 (dd, *J* 7.9, 1.2 Hz, 1H); 7.19 (td, *J* 7.7, 1.2 Hz, 1H); 7.10–7.09 (m, 1H); 7.04–7.00 (m, 1H); 3.61 (s, 3H); 3.59 (s, 2H); 3.56 (t, *J* 7.0 Hz, 2H); 2.49 (t, *J* 7.8 Hz, 2H); 1.95 (quint, *J* 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 166.6, 141.6, 132.5, 128.8, 127.4, 127.3, 124.9, 85.5, 50.7, 47.6, 34.0, 31.2, 22.2. HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{17}{}^{79}BrNO_2$ 310.04372 $[M+H]^+$, found 310.04403. Calcd. for $C_{14}H_{16}{}^{79}BrNNaO_2$ $[M+Na]^+$ 332.02566, found 332.02600. *Anal.* Calcd. for $C_{14}H_{16}BrNO_2$ (310.19) C, 54.21; H, 5.20; N, 4.52%. Found: C, 54.40; H, 5.15; N, 4.51%.

Methyl 3-(2-bromophenyl)-2-(piperidin-2-ylidene)propanoate (9b). Prepared from **4b**, the residue was recrystallized from ethanol to give 43% of light beige solid with mp 132–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (br s, 1H); 7.51 (dd, *J* 7.9, 1.2 Hz, 1H); 7.20 (td, *J* 7.7, 1.2 Hz, 1H); 7.10–7.07 (m, 1H); 7.04–7.00 (m, 1H); 3.60 (br s, 2H); 3.59 (s, 3H); 3.35 (td, *J* 6.0, 2.5 Hz, 2H); 2.24 (t, *J* 6.5 Hz, 2H); 1.74–1.68 (m, 2H); 1.66–1.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 162.4, 141.6, 132.4, 128.6, 127.5, 127.2, 125.0, 86.6, 50.6, 41.7, 32.5, 26.1, 22.4, 20.1. HRMS-MALDI (*m/z*): Calcd. for $C_{15}H_{19}{}^{79}BrNO_2$ 324.05937 $[M+H]^+$, found 324.05955. Calcd. for $C_{15}H_{18}{}^{79}BrNNaO_2$ $[M+Na]^+$ 346.04131, found 346.04163. *Anal.* Calcd. for $C_{15}H_{18}BrNO_2$ (324.21) C, 55.57; H, 5.60; N, 4.32%. Found: C, 55.65; H, 5.58; N, 4.31%.

Methyl 2-(azepan-2-ylidene)-3-(2-bromophenyl)propanoate (9c). Prepared from **4c**, the residue was subjected to column chromatography (DCM:AcOEt 10:1, R_f 0.74) followed by recrystallization from *n*-hexane. Yield 26% of white crystalline solid, mp 80–81.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (br s, 1H); 7.51 (dd, *J* 7.9, 1.2 Hz, 1H); 7.19 (td, *J* 7.6, 1.2 Hz, 1H); 7.11–7.08 (m, 1H); 7.04–6.99 (m, 1H); 3.70 (s, 2H); 3.60 (s, 3H); 3.38–3.34 (m, 2H); 2.32–2.27 (m, 2H); 1.70–1.56 (m, 4H); 1.50–1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 168.7, 142.2, 132.4, 129.3, 127.3, 127.2, 124.7, 87.1, 50.7, 44.3, 33.4, 30.5, 30.2, 29.3, 25.4. HRMS-MALDI (*m/z*): Calcd. for $C_{16}H_{21}{}^{79}BrNO_2$ 338.07502 $[M+H]^+$, found 338.07528. Calcd. for $C_{16}H_{23}{}^{79}BrNO_3$ $[M+H_2O+H]^+$ 356.08558, found 356.08598. Calcd. for $C_{16}H_{22}{}^{79}BrNNaO_3$ $[M+H_2O+Na]^+$ 378.06753, found 378.06795. *Anal.* Calcd. for $C_{16}H_{20}BrNO_2$ (338.24) C, 56.82; H, 5.96; N, 4.14%. Found C, 56.91; H, 5.95; N, 4.15%.

4-(2-Bromophenyl)-3-(pyrrolidin-2-ylidene)butan-2-one (9d). Prepared from **6a**, the residue was subjected to column chromatography (DCM:AcOEt 10:1, R_f 0.44). Yield 42% of sandy solid, mp 109–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (br s, 1H); 7.48 (dd, *J* 7.8, 1.2 Hz, 1H); 7.17–7.12 (m, 1H); 7.03–6.97 (m, 2H); 3.60–3.54 (m, 4H); 2.45 (t, *J* 7.8 Hz, 2H); 1.93–1.87 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 168.2, 140.7, 132.7, 128.6, 127.73, 127.72, 125.1, 97.5,

48.2, 35.9, 31.7, 27.0, 21.4. HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{17}{}^{79}BrNO$ 294.04880 $[M+H]^+$, found 294.04904. Calcd. for $C_{14}H_{16}{}^{79}BrNNaO$ $[M+Na]^+$ 316.03075, found 316.03103. *Anal.* Calcd. for $C_{14}H_{16}BrNO$ (294.19) C, 57.16; H, 5.48; N, 4.76%. Found C, 57.29; H, 5.32; N, 4.61%.

4-(2-Bromophenyl)-3-(piperidin-2-ylidene)butan-2-one (9e). Prepared from **6b**, the residue was subjected to column chromatography (DCM:AcOEt 10:1, R_f 0.44). Yield 51% of yellowish solid, mp 64–68 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H); 7.55 (dd, *J* 7.9, 1.2 Hz, 1H); 7.23 (td, *J* 7.7, 1.2 Hz, 1H); 7.14–7.11 (m, 1H); 7.09–7.04 (m, 1H); 3.59 (s, 2H); 3.39 (td, *J* 5.9, 2.5 Hz, 2H); 2.24 (t, *J* 6.4 Hz, 2H); 1.99 (s, 3H); 1.77–1.70 (m, 2H); 1.69–1.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 164.5, 140.6, 132.7, 128.4, 127.74, 127.70, 125.1, 98.8, 41.5, 34.5, 27.5, 26.0, 21.8, 19.8. HRMS-MALDI (*m/z*) Calcd. for $C_{15}H_{19}{}^{79}BrNO$ $[M+H]^+$ 308.06445, found 308.06433. Calcd. for $C_{15}H_{18}{}^{79}BrNNaO$ 330.04640 $[M+Na]^+$, found 330.04648. Calcd. for $C_{15}H_{18}NO$ 228.13829 $[M–Br]^+$, found 228.13831. *Anal.* Calcd. for $C_{15}H_{18}BrNO$ (308.21) C, 58.45; H, 5.89; N, 4.54%. Found C, 58.52; H, 5.96; N, 4.50%.

2-Bromobenzyl-1,5-bis(2-bromophenyl)-4-(piperidine-2-ylidene)pentan-3-one (10a). Obtained from **6b** as a by-product from the above-mentioned chromatography (R_f 0.78), mp 127–129 °C. Yield 10.5% of yellow crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 13.14 (br s, 1H); 7.47 (d, *J* 7.7 Hz, 1H); 7.36 (d, *J* 7.7 Hz, 2H); 7.14–7.11 (m, 4H); 7.03–6.97 (m, 2H); 6.94 (t, *J* 7.5 Hz, 1H); 6.80 (t, *J* 7.4 Hz, 1H); 6.28 (d, *J* 7.4 Hz, 1H); 3.42–3.39 (m, 2H); 3.36–3.29 (m, 1H); 3.25 (s, 2H); 3.03 (dd, *J* 13.1, 8.5 Hz, 2H); 2.79 (dd, *J* 12.9, 6.2 Hz, 2H); 2.07 (t, *J* 6.5 Hz, 2H); 1.73–1.68 (m, 2H); 1.61–1.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 165.7, 140.6, 139.8, 132.9, 132.3, 132.2, 128.2, 127.8, 127.7, 127.2, 127.0, 125.4, 124.9, 99.4, 44.9, 41.5, 39.1, 32.9, 26.2, 21.8, 19.7 ppm. HRMS-MALDI (*m/z*): Calcd. for $C_{29}H_{29}{}^{79}Br_3NO$ $[M+H]^+$ 643.97938, found 643.98068. Calcd. for $C_{29}H_{28}{}^{79}Br_2NO$ $[M–Br]^+$ 564.05322, found 564.05412. *Anal.* Calcd. for $C_{29}H_{28}Br_3NO$ (646.25) C, 53.90; H, 4.37; N, 2.17; Br, 37.09%. Found C, 53.93; H, 4.38; N, 2.17; Br, 37.01%.

3-(Azepan-2-ylidene)-4-(2-bromophenyl)butan-2-one (9f). Prepared from **6c**, the residue was subjected to column chromatography (DCM:AcOEt 6:1, R_f 0.55). Yield 36% of yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 12.39 (br s, 1H); 7.54 (dd, *J* 7.9, 1.2 Hz, 1H); 7.23 (t, *J* 7.5 Hz, 1H); 7.13 (d, *J* 7.8 Hz, 1H); 7.06 (t, *J* 7.7 Hz, 1H); 3.68 (s, 2H); 3.42–3.38 (m, 2H); 2.29–2.27 (m, 2H); 2.03 (s, 3H); 1.73–1.67 (m, 2H); 1.65–1.60 (m, 2H); 1.51–1.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 170.5, 141.0, 132.5, 129.2, 127.6, 127.5, 124.7, 98.8, 44.1, 35.5, 30.5, 29.4, 29.3, 28.1, 24.8. HRMS-MALDI (*m/z*): Calcd. for $C_{16}H_{21}{}^{79}BrNO$ 322.08010 $[M+H]^+$, found 322.07990. Calcd. for $C_{16}H_{20}{}^{79}BrNNaO$ 344.06205 $[M+Na]^+$, found 344.06218. *Anal.* Calcd. for $C_{16}H_{20}BrNO$ (322.24) C, 59.64; H, 6.26; N, 4.35%. Found: C, 59.60; H, 6.35; N, 4.32%.

3-(2-Bromophenyl)-2-(pyrrolidin-2-ylidene)propannitrile (9g). Prepared from **8a**, the crude oil was suspended in ether and immersed in an ultrasound bath for ca 10 min. Precipitated white solid was isolated by suction. Another portion of the product was obtained on concentrating the ether solution. Product can be recrystallized from cyclohexane to obtain white solid, mp 113–117 °C and 133–136 °C. Total yield 39%. Product is 3:1 mixture of *E/Z* isomers. ^1H NMR (500 MHz, $CDCl_3$) ***major isomer*** δ 7.54–7.52 (m, 1H); 7.35 (dd, *J* 7.7, 1.6 Hz, 1H); 7.29–7.25 (m, 1H); 7.11–

7.06 (m, 1H); 4.94 (br s, 1H); 3.49–3.42 (m, 4H); 2.81 (t, *J* 7.8 Hz, 2H); 2.07–2.00 (m, 2H). ***Minor isomer*** δ 7.54–7.52 (m, 1H); 7.33–7.31 (m, 1H); 7.29–7.25 (m, 1H); 7.11–7.06 (m, 1H); 5.15 (br s, 1H); 3.49–3.42 (m, 4H); 2.59 (t, *J* 7.7 Hz, 2H); 2.07–2.00 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) ***major isomer*** δ 163.3, 138.0, 132.8, 130.0, 128.5, 128.0, 124.3, 124.1, 67.9, 47.9, 34.2, 31.8, 23.0. ***Minor isomer*** δ 165.3, 139.1, 132.9, 129.9, 128.2, 127.8, 124.4, 122.5, 65.9, 46.8, 34.8, 29.7, 23.2. HRMS-MALDI (*m/z*): Calcd. for $C_{13}H_{16}{}^{79}BrN_2$ 279.04914 $[M+2H+H]^+$, found 279.04887. Calcd. for $C_{13}H_{14}{}^{79}BrN_2$ 277.03349 $[M+H]^+$, found 277.03367. Calcd. for $C_{13}H_{13}{}^{79}BrN_2Na$ 299.01543 $[M+Na]^+$, found 299.01564. *Anal.* Calcd. for $C_{13}H_{13}BrN_2$ (277.16) C, 56.34; H, 4.73; N, 10.11; Br, 28.83%. Found: C, 56.42; H, 4.69; N, 10.09; Br, 28.99%.

3-(2-Bromophenyl)-2-(piperidin-2-ylidene)propannitrile (9h). Prepared from **8b**, the crude oil was suspended in *n*-heptane and immersed in an ultrasound bath for ca 20 min. Precipitated compound was isolated by suction to give 43% of yellowish solid. The product is ca 10:3 mixture of *E/Z* isomers. On recrystallization from cyclohexane, 17% of white crystals were obtained as 15:1 *E/Z* mixture with mp 112–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) ***major isomer*** δ 7.54–7.52 (m, 1H); 7.33–7.26 (m, 2H); 7.10 (td, *J* 7.9, 1.9 Hz, 1H); 4.74 (br s, 1H); 3.45 (s, 2H); 3.20–3.17 (m, 2H); 2.70–2.68 (m, 2H); 1.77–1.70 (m, 4H). ***Minor isomer*** δ 7.54–7.52 (m, 1H); 7.32–7.26 (m, 3H); 5.31 (br s, 1H); 3.47 (s, 2H); 3.27 (td, *J* 6.0, 2.2 Hz, 2H); 2.35 (t, *J* 6.5 Hz, 2H); 1.77–1.70 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) ***major isomer*** δ 158.0, 137.5, 132.9, 129.7, 128.5, 128.0, 124.5, 123.7, 72.1, 42.7, 33.0, 28.0, 23.0, 20.5. ***Minor isomer*** δ 160.0, 139.0, 128.2, 127.8, 123.4, 69.9, 42.8, 33.2, 25.4 (only some signals on the minor form were detected). HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{16}{}^{79}BrN_2$ 291.04914 $[M+H]^+$, found 291.04943. *Anal.* Calcd. for $C_{14}H_{15}BrN_2$ (291.19) C, 57.75; H, 5.19; N, 9.62%. Found: C, 57.96; H, 5.14; N, 9.60%.

2-(Azepan-2-ylidene)-3-(2-bromophenyl)propannitrile (9i). Prepared from **8c**. The crude yellow oil was subjected to repeated column chromate graphy (DCM:AcOEt 20:1, R_f 0.67 and AcOEt:*n*-hexane 6:1, R_f 0.92) and subsequently purified by recrystallization from *n*-heptane to give 25% of white crystals with mp 76–97 °C. Product is then ca 7:1 mixture of *E/Z* isomers and still contains ca 20 mol.% of *N*-benzyl isomer. This almost inseparable by-product was finally removed by another column chromatography (silica gel, DCM, R_f 0.28) and the product was isolated in 7% yield. ^{1}H NMR (400 MHz, $CDCl_3$) ***major isomer*** δ 7.47–7.45 (m, 1H); 7.26–7.24 (m, 1H); 7.22–7.18 (m, 1H); 7.05–7.00 (m, 1H); 4.88 (br s, 1H); 3.36 (s, 2H); 3.16–3.12 (m, 2H); 2.66–2.64 (m, 2H); 1.64–1.57 (m, 4H); 1.46–1.41 (m, 2H). ***Minor isomer*** δ 7.47–7.44 (m, 1H); 7.22–7.18 (m, 3H); 5.48 (br t, 1H); 3.46 (s, 2H); 3.24–3.20 (m, 2H); 2.31–2.28 (m, 2H); 1.64–1.57 (m, 4H); 1.46–1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) ***major isomer*** δ 163.8, 137.2, 132.9, 129.5, 128.5, 128.0, 124.6, 124.2, 71.9, 45.0, 33.6, 32.1, 30.7, 30.2, 26.8. ***Minor isomer*** δ 165.9, 139.5, 129.9, 128.2, 44.8, 34.2, 30.6, 30.3, 28.1, 26.0. HRMS-MALDI (*m/z*) Calcd. for $C_{15}H_{18}{}^{79}BrN_2$ 305.06479 $[M+H]^+$, found 305.06536. *Anal.* Calcd. for $C_{15}H_{17}BrN_2$ (305.21) C, 59.03; H, 5.61; N, 9.18%. Found: C, 59.20; H, 5.60; N, 9.14%.

Methyl 3-(2-chlorophenyl)-2-(piperidin-2-ylidene)propanoate (9j). Prepared from **4b**, the residue was subjected to a column chromatography (DCM:AcOEt 4:1, R_f 0.76) to give 33% of white solid with mp 120–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (br s, 1H); 7.33–7.31 (m,

1H); 7.17–7.14 (m, 1H); 7.11–7.08 (m, 2H); 3.63 (s, 2H); 3.59 (s, 3H); 3.35 (td, *J* 6.0, 2.5 Hz, 2H); 2.25 (t, *J* 6.5 Hz, 2H); 1.74–1.69 (m, 2H); 1.66–1.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 162.4, 140.0, 134.1, 129.1, 128.4, 126.9, 126.8, 86.2, 50.6, 41.7, 29.5, 26.1, 22.4, 20.2. HRMS-MALDI (*m/z*): Calcd. for $C_{15}H_{19}{}^{35}ClNO_2$ 280.10988 $[M+H]^+$, found 280.10992. Calcd. for $C_{15}H_{18}{}^{35}ClNNaO_2$ $[M+Na]^+$ 302.09183, found 302.09195. *Anal.* Calcd. for $C_{15}H_{18}ClNO_2$ (279.76) C, 64.40; H, 6.49; N, 5.01%. Found: C, 64.49; H, 6.55; N, 4.99%.

4-(2-Chlorophenyl)-3-(pyrrolidin-2-ylidene)butan-2-one (9k). Prepared from **6a**, the residue was subjected to column chromatography (DCM:AcOEt 1:1, R_f 0.54). The product can be recrystallized from *n*-hexane. Yield 55% of yellowish solid, mp 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (br s, 1H); 7.36 (dd, *J* 7.3, 1.7 Hz, 1H); 7.19–7.10 (m, 3H); 3.67 (s, 3H); 3.64 (t, *J* 7.3 Hz, 2H); 2.52 (t, *J* 7.8 Hz, 2H); 2.00–1.92 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 168.0, 139.1, 134.2, 129.4, 128.4, 127.3, 127.0, 97.1, 48.1, 32.8, 31.6, 27.0, 21.4. HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{17}{}^{35}ClNO$ 250.09932 $[M+H]^+$, found 250.09931. Calcd. for $C_{14}H_{16}{}^{35}ClNNaO$ $[M+Na]^+$ 272.08126, found 272.08127. *Anal.* Calcd. for $C_{14}H_{16}ClNO$ (249.74) C, 67.33; H, 6.46; N, 5.61; found C, 67.29; H, 6.42; N, 5.59.

3-(Azepan-2-ylidene)-4-(2-chlorophenyl)butan-2-one (9l). Prepared from **6c**, the residue was subjected to a column chromatography (DCM:AcOEt 10:1, R_f 0.44). Yield 31% of yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (br s, 1H); 7.36–7.34 (m, 1H); 7.20–7.11 (m, 3H); 3.71 (s, 2H); 3.42–3.38 (m, 2H); 2.30–2.27 (m, 2H); 2.03 (s, 3H); 1.71–1.67 (m, 2H); 1.65–1.60 (m, 2H); 1.50–1.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 170.5, 139.5, 133.9, 129.2, 129.0, 127.3, 126.9, 98.4, 44.1, 32.5, 30.6, 29.4, 29.2, 28.1, 24.8. HRMS-MALDI (*m/z*): Calcd. for $C_{16}H_{21}{}^{35}ClNO$ 278.13062 $[M+H]^+$, found 278.13074. Calcd. for $C_{16}H_{20}{}^{35}ClNNaO$ 300.11256 $[M+Na]^+$, found 300.11272. *Anal.* Calcd. for $C_{16}H_{20}ClNO$ (277.79) C, 69.18; H, 7.26; N, 5.04%. Found C, 69.17; H, 7.29; N, 5.01%.

2-(Azepan-2-ylidene)-4-(2-chlorobenzyl)-1,5-bis(2-chlorphenyl)-pentan-3-one (10b). Obtained from **6c** as a by-product from the above-mentioned chromatography (R_f = 0.78), m.p. 124–126 °C. Yield 11% of yellowish crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.83 (br s, 1H); 7.27 (d, *J* = 9.1 Hz, 1H); 7.18–7.16 (m, 2H); 7.13–7.07 (m, 6H); 7.01 (t, *J* = 7.5 Hz, 1H); 6.76 (t, *J* = 7.5 Hz, 1H); 6.25 (d, *J* = 7.6 Hz, 1H); 3.41–3.39 (m, 2H); 3.37–3.34 (m, 1H); 3.32 (s, 2H); 3.02 (dd, *J* = 13.1, 8.6 Hz, 2H); 2.81 (dd, *J* = 13.1, 6.1 Hz, 2H); 2.12–2.10 (m, 2H); 1.66–1.62 (m, 4H); 1.36–1.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.2, 171.6, 139.4, 138.0, 134.6, 133.7, 131.9, 129.6, 128.9, 128.8, 127.5, 126.9, 126.8, 126.4, 99.2, 45.2, 44.2, 36.9, 30.7, 30.6, 29.45, 29.40, 24.6 ppm. HRMS-MALDI (*m/z*): Calcd. for $C_{30}H_{31}{}^{35}Cl_3NO$ $[M+H]^+$ 526.14657, found 526.14551. Calcd. for $C_{30}H_{30}{}^{35}Cl_3NNaO$ $[M+Na]^+$ 548.12852, found 548.12729. *Anal.* Calcd. for $C_{30}H_{30}Cl_3NO$ (526.92) C, 68.38; H, 5.74; N, 2.66%. Found C, 68.41; H, 5.75; N, 2.66%.

3-(2-Chlorophenyl)-2-(pyrrolidin-2-ylidene)propannitrile (9m). Prepared from **8a**, the crude product was subjected to a column chromatography (DCM:EtOAc 4:1, R_f 0.72). The product was then recrystallized from *n*-heptane and subsequently from cyclohexane to give white solid, mp 91–107 °C. Total yield 34%. Product is 1.8:1 mixture of *E/Z* isomers. ^{1}H NMR (400 MHz, $CDCl_3$) ***major isomer*** δ 7.37–7.31 (m, 2H); 7.26–7.15 (m, 2H); 4.89 (br s, 1H); 3.49–3.41 (m, 4H); 2.81

(t, *J* 7.8 Hz, 2H); 2.08–1.99 (m, 2H). ***Minor isomer*** δ 7.37–7.31 (m, 2H); 7.26–7.15 (m, 2H); 5.10 (br s, 1H); 3.49–3.42 (m, 4H); 2.59 (t, *J* 7.7 Hz, 2H); 2.08–1.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) ***major isomer*** δ 163.1, 136.5, 133.6, 130.0, 129.6, 128.2, 127.4, 124.0, 68.1, 47.8, 31.8, 31.4, 23.1. ***Minor isomer*** δ 165.1, 137.5, 133.8, 129.9, 129.6, 127.9, 127.1, 122.4, 66.1, 46.8, 32.1, 29.6, 23.2. HRMS-MALDI (*m/z*): Calcd. for $C_{13}H_{16}{}^{35}ClN_2$ 235.09965 $[M+2H+H]^+$, found 235.09971. Calcd. for $C_{13}H_{14}{}^{35}ClN_2$ 233.08400 $[M+H]^+$, found 233.08429. Calcd. for $C_{13}H_{13}{}^{35}ClN_2Na$ 255.06595 $[M+Na]^+$, found 255.06618. *Anal.* Calcd. for $C_{13}H_{13}ClN_2$ (232.71) C, 67.10; H, 5.63; N, 12.04%. Found: C, 67.17; H, 5.59; N, 12.00%.

General procedure for intramolecular amination of enamines 9. Method A. A dried screw-cup vial, equipped with a magnetic stirring bar and septum was charged with substrate **9** (0.5 mmol), $Pd_2(dba)_3$ (3.5–5 mol.%), DPPP (7–10 mol.%) and *t*BuONa (0.6 mmol, 1.2 eq.). The vial was sealed and three-times evacuated and backfilled with argon. Dry toluene (2 mL) was then added via syringe and the mixture was heated to 100 °C for 24–36 h (for exact conditions see Table 3). The mixture was then cooled, diluted with AcOEt and filtered through a plug of Celite®. The filtrate was evaporated to dryness, the residue was suspended in ether (25 mL) and subjected to an ultrasound irradiation. The precipitated impurities were removed by a filtration through Celite®. Product **11** was obtained upon evaporation of the filtrate.

Method B. A dried screw-cup vial, equipped with a magnetic stirring bar and septum was charged with substrate **9** (0.5 mmol), precatalyst **L1** (1.5–2 mol.%) and K_3PO_4 (1 mmol, 2 eq.). The vial was sealed and three-times evacuated and backfilled with argon. Dry *t*BuOH (2 mL) was added via syringe and the mixture was heated to 80 °C for 16–24 h (for exact conditions see Table 3). The mixture was then cooled, diluted with AcOEt and filtered through a plug of Celite®. Product **11** was obtained upon evaporation of the filtrate.

Method C. A dried screw-cup vial (A) equipped with a magnetic stirring bar and septum was charged with substrate **9** (0.5 mmol) and Cs_2CO_3 (0.7 mmol, 1.4 eq.). Another vial (B) equipped with a magnetic stirring bar and septum was charged with $Pd_2(dba)_3$ (22.9 mg, 5 mol.%) and RuPhos (23.3 mg, 10 mol.%). Both the vials were sealed and three-times evacuated and backfilled with argon. Toluene (3 mL) was added via syringe into the vial B. The mixture was then heated to 100 °C for 30 minutes and subsequently transferred into the vial A via syringe. The mixture was then heated to 100 °C for 60 h. The mixture was then cooled, diluted with AcOEt and filtered through a plug of Celite®. The filtrate was evaporated to dryness to give product **11**.

Methyl 1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (11a). Prepared by method A, reaction time 24 h, 5% $Pd_2(dba)_3$, 10% DPPP, yield 65% of red-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.07 (m, 2H); 6.94 (td, *J* 7.4, 1.1 Hz, 1H); 6.65 (d, *J* 7.5 Hz, 1H); 3.79 (s, 2H); 3.72 (s, 3H); 3.60 (t, *J* 7.1 Hz, 2H); 3.14 (t, *J* 7.8 Hz, 2H); 2.12 (quint, *J* 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 156.1, 138.7, 129.2, 127.2, 124.1, 123.2, 112.8, 90.5, 51.0, 48.5, 32.3, 28.0, 21.9. HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{14}NO_2$ 228.10191 $[M–H]^+$, found 228.10216. Calcd. for $C_{12}H_{12}N$ 170.09643 $[M–COOCH_3]^+$, found 170.09664.

Methyl 1,2,3,4,6-pentahydropyrido[1,2-*a*]quinoline-5-carboxylate (11b). Prepared by method B, reaction time 16 h, 1.5% **L1**, yield 95% of yellow oil and method C, reaction time 66 h, yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.12 (m, 1H); 7.08 (dd, *J* 7.4, 1.2 Hz, 1H); 6.98 (td, *J* 7.4, 1.0 Hz, 1H); 6.87 (d, *J* 8.2 Hz, 1H); 3.71 (s, 3H); 3.65 (s, 2H); 3.63–3.60 (m, 2H); 3.21 (tt, *J* 7.0, 0.9 Hz, 2H); 1.95–1.88 (m, 2H); 1.74 (quint, *J* 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 154.1, 141.5, 128.3, 126.8, 125.1, 123.1, 112.6, 94.3, 51.0, 45.2, 28.1, 26.8, 22.8, 19.4. HRMS-MALDI (*m/z*): Calcd. for $C_{15}H_{16}NO_2$ 242.11756 $[M–H]^+$, found 242.11782. *Anal.* Calcd. for $C_{15}H_{17}NO_2$ (243.30) C, 74.05; H, 7.04; N, 5.76%. Found: C, 74.02; H, 7.00; N, 5.70%.

Methyl 5,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6-carboxylate (11c). Prepared by method B, reaction time 16 h, 1.5% **L1**, yield 97% of red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.12 (m, 1H); 7.08 (dd, *J* 7.4, 1.1 Hz, 1H); 6.96 (td, 1H, *J* 7.4, 1.0 Hz); 6.88 (d, 1H, *J* 8.2 Hz); 3.90–3.86 (m, 2H); 3.72 (s, 3H); 3.57 (s, 2H); 3.29 (br m, 2H); 1.85–1.77 (m, 2H); 1.73–1.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 158.2, 141.9, 128.1, 126.8, 125.5, 122.7, 112.8, 95.7, 51.2, 47.4, 29.1, 28.7, 28.6, 27.9, 26.6. HRMS-MALDI (*m/z*): Calcd. for $C_{16}H_{18}NO_2$ 256.13321 $[M–H]^+$, found 256.13364. *Anal.* Calcd. for $C_{16}H_{19}NO_2$ (257.33) C, 74.68; H, 7.44; N, 5.44%. Found: C, 74.71; H, 7.46; N, 5.43%.

4-Acetyl-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline (11d). Prepared by method A, reaction time 36 h, 3.5% $Pd_2(dba)_3$, 7% DPPP, yield 87% of yellow-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.10 (m, 1H); 6.96 (t, *J* 7.4 Hz, 1H); 6.68 (d, *J* 7.9 Hz, 1H); 3.86 (s, 2H); 3.62 (t, *J* 7.1 Hz, 2H); 3.16 (t, *J* =7.7 Hz, 2H); 2.23 (s, 3H); 2.14 (quint, *J* 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 156.0, 138.2, 129.0, 127.3, 124.5, 123.4, 112.9, 101.4, 48.2, 33.1, 29.4, 29.1, 21.9. HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{14}NO$ 212.10699 $[M–H]^+$, found 212.10725. Calcd. for $C_{12}H_{12}N$ 170.09643 $[M–CH_3CO]^+$, found 170.09660.

5-Acetyl-1,2,3,4,6-pentahydropyrido[1,2-*a*]quinoline (11e). Prepared by method B, reaction time 24 h, 2% **L1**, yield 98% of yellow-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* 7.7 Hz, 1H); 7.10 (d, *J* 7.4 Hz, 1H); 7.00 (td, *J* 7.4, 1.0 Hz, 1H); 6.89 (d, *J* 8.0 Hz, 1H); 3.67 (s, 2H); 3.64 (t, *J* 6.0 Hz, 2H); 3.19 (t, *J* 7.0 Hz, 2H); 2.26 (s, 3H); 1.95–1.88 (m, 2H); 1.73 (quint, *J* 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 154.1, 141.3, 128.2, 126.9, 125.3, 123.4, 112.9, 104.1, 45.4, 30.6, 29.8, 27.6, 22.6, 19.3. HRMS-MALDI (*m/z*): Calcd. for $C_{15}H_{16}NO$ 226.12264 $[M–H]^+$, found 226.12213. Calcd. for $C_{15}H_{18}NO$ 228.13829 $[M+H]^+$, found 228.13772. *Anal.* Calcd. for $C_{15}H_{17}NO$ (227.30) C, 79.26; H, 7.54; N, 6.16%. Found C, 79.26; H, 7.55; N, 6.16%.

6-Acetyl-5,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline (11f). Prepared by method B, reaction time 24 h, 2% **L1**, yield 96% of yellow oil and method C, reaction time 60 h, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.14 (m, 1H); 7.10 (d, *J* 7.3 Hz, 1H); 6.99 (td, *J* 7.4, 0.9 Hz, 1H); 6.91 (d, *J* 8.2 Hz, 1H); 3.92–3.88 (m, 2H); 3.54 (s, 2H); 3.18–3.14 (br m, 2H); 2.30 (s, 3H); 1.85–1.79 (m, 2H); 1.73–1.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 157.3, 141.6, 128.0, 126.8, 125.6, 122.9, 112.9, 106.3, 47.3, 30.5, 29.7, 29.1, 28.9, 27.7, 26.6. HRMS-MALDI (*m/z*): Calcd. for $C_{16}H_{18}NO$ $[M–H]^+$ 240.13829, found 240.13849. *Anal.* Calcd. for $C_{16}H_{19}NO$ (241.33) C, 79.63; H, 7.94; N, 5.80%. Found: C, 79.55; H, 7.97; N, 5.77%.

1,2,3,5-Tetrahydropyrrolo[1,2-*a*]quinoline-4-carbonitrile (11g). Prepared by method A, reaction time 36 h, 5% $Pd_2(dba)_3$, 10% DPPP, yield 67% of red-brown oil and method C, reaction time 60 h, yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.11 (m, 1H); 7.02–6.99 (m, 1H); 6.94 (td, *J* 7.4, 1.1 Hz, 1H); 6.63 (dd, *J* 8.0, 0.9 Hz, 1H); 3.72 (s, 2H); 3.63 (t, *J* 6.9 Hz, 2H); 2.83 (t, *J* 7.8 Hz, 2H); 2.15 (quint, *J* 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 137.7, 128.9, 127.7, 123.4, 121.8, 120.9, 113.1, 69.3, 49.0, 30.6, 28.0, 21.4. HRMS-MALDI (*m/z*): Calcd. for $C_{13}H_{11}N_2$ 195.09167 $[M–H]^+$, found 195.09248. Calcd. for $C_{26}H_{23}N_4$ 391.19172 $[2M–H]^+$, found 391.19065. *Anal.* Calcd. for $C_{13}H_{12}N_2$ (196.25) C, 79.56; H, 6.16; N, 14.27%. Found: C, 79.49; H, 6.21; N, 14.17%.

1,2,3,4,6-Pentahydropyrido[1,2-*a*]quinoline-5-carbonitrile (11h). Prepared by method B, reaction time 24 h, 2% **L1**, yield 97% of yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.16 (m, 1H); 7.01–6.97 (m, 2H); 6.90 (d, *J* 8.3 Hz, 1H); 3.63 (s, 2H); 3.53 (t, *J* 6.1 Hz, 2H); 2.78 (t, *J* 6.8 Hz, 2H); 1.95 (quint, *J* 6.3 Hz, 2H); 1.76–1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 152.4, 140.1, 128.9, 127.5, 123.7, 121.9, 121.7, 113.0, 74.3, 45.1, 28.4, 28.1, 23.4, 19.3. HRMS-MALDI (*m/z*): Calcd. for $C_{14}H_{13}N_2$ 209.10732 $[M–H]^+$, found 209.10774. Calcd. for $C_{14}H_{15}N_2O$ 227.11789 $[M–H+H_2O]^+$, found 227.11841. *Anal.* Calcd for $C_{14}H_{14}N_2$ (210.27) C, 79.97; H, 6.71; N, 13.32%. Found: C, 79.92; H, 6.84; N, 13.31%.

5,7,8,9,10,11-Hexahydroazepino[1,2-*a*]quinoline-6-carbonitrile (11i). Prepared by method B, reaction time 24 h, 2% **L1**, yield 98% of yellow-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.16 (m, 1 H); 7.05–7.03 (m, 1H); 7.01–6.97 (m, 1H); 6.88 (d, *J* 8.3 Hz, 1H); 3.82–3.79 (m, 2H); 3.52 (s, 2H); 2.85–2.83 (m, 2H); 1.77–1.70 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 140.8, 128.6, 127.5, 123.2, 122.3, 122.0, 113.1, 76.0, 47.8, 32.9, 29.3, 28.9, 27.8, 27.0. HRMS-MALDI (*m/z*): Calcd. for $C_{15}H_{15}N_2$ 223.12298 $[M–H]^+$, found 223.12315. *Anal.* Calcd. for $C_{15}H_{16}N_2$ (224.30) C, 80.32; H, 7.19; N, 12.49%. Found: C, 80.06; H, 7.39; N, 12.33%.

General procedure for the synthesis of fused quinolinium perchlorates 12. CAUTION: Although we have not observed any problems, mixtures of perchloric acid with organic compounds are potentially explosive and must be handled with care. To the solution of **11** in dry dioxane (ca 1.5 mL per 0.1 mmol of **11**) was added ca 11.6 M perchloric acid (ca 2–5 eq.). The mixture was left to stand at laboratory temperature until the product precipitated (1–24 h). The product was isolated by suction, washed with ether (6 × 2 mL) and left to dry under vacuum in a desiccator.

4-Cyano-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]quinolinium perchlorate (12a). Prepared from from **11g**, reaction time 2 h, recrystallization from ethanol, mp 273–278 °C (dec.). Yield 31% of greyish solid. ^{1}H NMR (500 MHz, DMSO) δ 9.71 (s, 1H); 8.38 (d, *J* 8.1 Hz, 1H); 8.32 (s, 2H); 8.07–7.98 (m, 1H); 5.09 (t, *J* 7.4 Hz, 2H); 3.77 (t, *J* 7.4 Hz, 2H); 2.39 (br s, 2H). ^{13}C NMR (125 MHz, DMSO) δ 164.9, 151.4, 138.3, 137.1, 131.1, 130.7, 127.0, 119.7, 114.2, 105.0, 57.9, 34.6, 19.7. HRMS-MALDI (*m/z*): Calcd. for $C_{13}H_{11}N_2$ 195.09167 $[M]^+$, found 195.09170. Calcd. for ClO_4 98.94906 $[ClO_4]^–$, found 98.94906. *Anal.* Calcd. for $C_{13}H_{11}ClN_2O_4$ (294.69) C, 52.98; H, 3.76; N, 9.51%. Found: C, 53.04; H, 3.77; N, 9.49%.

6-Acetyl-8,9,10,11-tetrahydro-7*H*-azepino[1,2-*a*]quinolinium perchlorate (12b). Prepared from **11f**, reaction time 1 h, mp 225–229 °C, yield 25.5% of off-white solid. ^{1}H NMR (400MHz, DMSO) δ 9.60 (s, 1H); 8.72 (d, *J* 9.0 Hz, 1H); 8.47 (d, *J* 8.2 Hz, 1H); 8.33 (t, *J* 7.9 Hz, 1H); 8.08 (t, *J* 7.5 Hz, 1H); 5.24–5.26 (m, 2H); 3.63 (br, 2H); 2.81 (s, 3H); 1.98 (br, 2H); 1.84 (br, 4H). ^{13}C NMR (125 MHz, DMSO) δ 199.5, 163.7, 145.5, 139.3, 137.0, 134.2, 131.4, 130.0, 127.4, 119.1, 52.2, 30.7, 30.5, 26.6, 23.8, 22.7. HRMS-MALDI (*m/z*): Calcd. for $C_{16}H_{18}NO$ 240.13829 $[M]^+$, found 240.13799. Calcd. for ClO_4 98.94906 $[ClO_4]^-$, found 98.94904.

6-Cyano-8,9,10,11-tetrahydro-7*H*-azepino[1,2-*a*]quinolinium perchlorate (12c). Prepared from **11i**, reaction time 1 h, mp 254–258 °C (dec.). Yield 36% of off-white solid. ^{1}H NMR (400 MHz, DMSO) δ 9.88 (s, 1H); 8.79 (d, *J* 8.9 Hz, 1H); 8.49 (d, *J* 8.3 Hz, 1H); 8.43 (t, *J* 8.3 Hz, 1H); 8.14 (t, *J* 7.6 Hz, 1H); 5.26–5.24 (m, 2H); 3.80 (br, 2H); 1.97–1.92 (br, 6H). ^{13}C NMR (100 MHz, DMSO) δ 165.9, 152.0, 139.9, 138.8, 131.5, 130.5, 127.4, 119.2, 114.9, 108.9, 53.3, 33.7, 26.8, 23.5, 22.1. HRMS-MALDI (*m/z*): Calcd. for $C_{15}H_{15}N_2$ 223.12298 $[M]^+$, found 223.12262. Calcd. for ClO_4 98.94906 $[ClO_4]^-$, found 98.94905.

6-Methoxycarbonyl-8,9,10,11-tetrahydro-7*H*-azepino[1,2-*a*]quinolinium perchlorate (12d). Prepared from **4c**, reaction time 1 h, mp 213–216 °C. Yield 50% of off-white solid. ^{1}H NMR (400 MHz, DMSO) δ 9.61 (s, 1H); 8.74 (d, *J* 9.0 Hz, 1H); 8.57 (dd, *J* 8.1, 1.4 Hz, 1H); 8.35 (ddd, *J* 8.8, 7.0, 1.5 Hz, 1H); 8.08 (t, *J* 7.5 Hz, 1H); 5.28–5.25 (m, 2H); 4.02 (s, 3H); 3.82 (br, 2H); 1.99 (br, 2H); 1.86 (br, 4H). ^{13}C NMR (100 MHz, DMSO) δ 164.7, 164.4, 147.6, 139.8, 137.5, 131.7, 129.9, 127.4, 126.4, 119.0, 53.8, 52.4, 30.7, 26.6, 23.7, 22.6. HRMS-MALDI (m/z): Calcd. for $C_{16}H_{18}NO_2$ 256.13321 $[M]^+$, found 256.13277. Calcd. for ClO_4 98.94906 $[ClO_4]^-$, found 98.94904. *Anal.* Calcd. for $C_{16}H_{18}ClNO_6$ (355.77) C, 54.02; H, 5.10; N, 3.94%. Found: C, 53.79; H, 5.09; N, 3.85%.

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