Intramolecular Buchwald-Hartwig *N*-Arylation of Bicyclic Hydrazines: Practical Access to Spiro[indoline-2,3'-piperidines]

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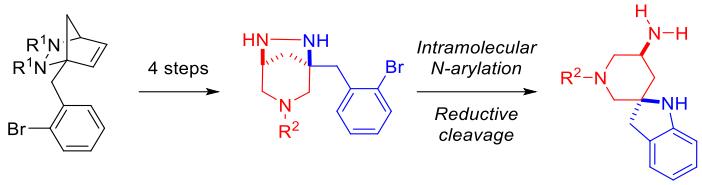
Supporting Information Placeholder



ABSTRACT: In recent years, spirocycles have been the focus of medicinal chemistry, and several drugs or drug candidates incorporating these "non-planar" chemical motifs have been developed. New advancements in this field, however, are greatly limited by the lack of innovative methods enabling the preparation of original spirocyclic cores. Herein, an unprecedented intramolecular Buchwald-Hartwig *N*-arylation of bicyclic hydrazines is described. This key reaction gives access to unique spiro[indoline-2,3'-piperidine] derivatives after reductive cleavage of the nitrogen–nitrogen bond. This approach widens the chemical space of spirocycles and may reveal useful to explore new avenues of research in drug discovery.

Spirocycles are a fascinating class of compounds which incorporate two or more rings linked together only by one common atom, usually a quaternary carbon.[1] These original scaffolds can be found in numerous natural and non-natural products.[2,3] Since the early 2000s, spirocycles have emerged as privileged chemical motifs in medicinal chemistry due to their inherent three-dimensionality. The presence of quaternary carbons in their structures has indeed been associated with more effective and selective binding to biological targets with improved physicochemical properties compared to structurally more simple flat molecules.[4] As a consequence, several drugs or drug candidates incorporating these "non-planar" frameworks have been developed.[3] However, the construction of spiro ring systems is often a task that requires considerable synthetic efforts. As of today, the lack of methods enabling the preparation of original spirocyclic cores still greatly limits the potential applications of these molecules in modern drug discovery. The development of innovative procedures allowing to widen the chemical space of spirocycles is therefore highly desirable.

Among other scaffolds, spirocyclic piperidines are nowadays considered as privileged building blocks for the development of drug-like small molecules,[5] and a few active substances containing these motifs have been authorized for market access (Figure 1).[3] A variety of strategies involving different key reactions have been reported in the literature to prepare this type of compounds. For example, several intermolecular processes have been developed, including mono- and bis-alkylations,[6,7] Pictet–Spengler cyclizations,[8-10] or

other condensation reactions.[11-14] As well intramolecular transformations have been described that mainly rely on reductive aminations,[15] *N*-acylations,[16] Friedel-Crafts alkylations,[17] ring-closing metathesis,[18,19] Robinson-type spiroannulations,[20] ene-type[21] or dearomative cyclizations.[22-24]

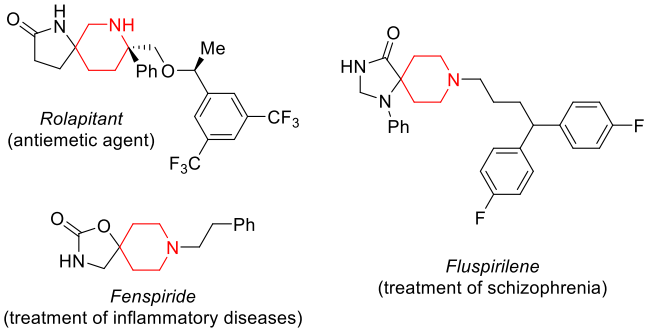


Figure 1. Approved drugs containing spirocyclic piperidine cores

Spiroindoles and spiroindolines constitute another class of compounds present in a wide range of pharmaceuticals and biologically relevant natural products.[25] Among these molecules, two main families can be distinguished based on the position of the spiro quaternary carbon: C2-spirocyclicindolines and C3-spirocyclicindoles or C3-spirocyclicindolines. Despite their important biological properties and pharmacological potential (Figure 2), molecules belonging to the first family have scarcely been explored compared to the latter.[26] This is possibly due to a lack of synthetic strategies leading to C2-spirocyclicindolines. Up to now, such spirocycles have for example been prepared though oxidative dearomatization of indoles,[27] ring contractions,[28] and [3+2] cycloaddition reactions.[29]

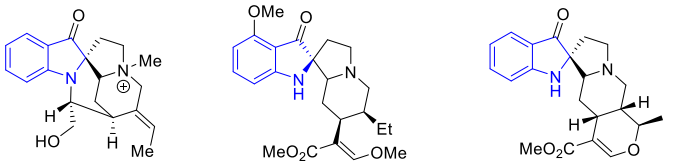
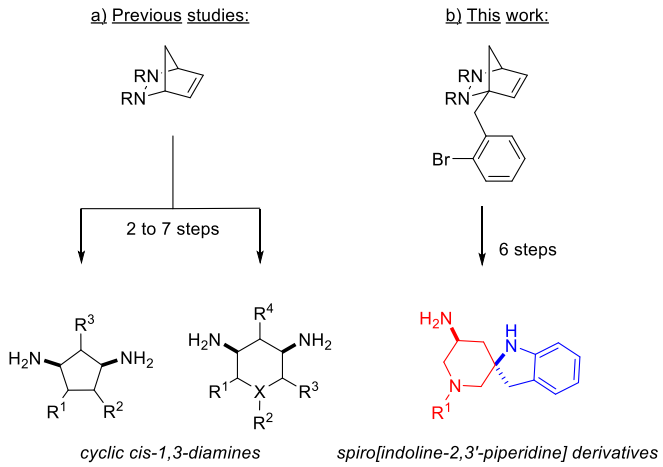


Figure 2. Natural alkaloids containing C2-spirocyclicindolines

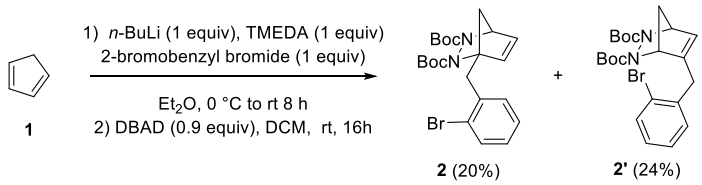
Aiming to further expand molecular diversity,[30] we recently envisaged to employ underexplored key reactions for preparing unprecedented spirocyclic compounds incorporating both piperidine and indoline moieties. More particularly, based on previous synthetic methodologies developed in our group (Scheme 1a), [31-39] we anticipated the possibility to access spiro[indoline-2,3'-piperidine] derivatives starting from 2,3-diazabicyclo[2.2.1]heptyl ring systems (Scheme 1b). To the best of our knowledge, the preparation of such original spiro scaffolds has not been reported in the literature to date, although spiro[indoline-3,4'-piperidine] or spiro[indoline-3,3'-piperidine] derivatives are known.[40-43] Herein, a versatile procedure to generate a new class of spiro compounds is described. This strategy involves an unprecedented intramolecular Buchwald-Hartwig *N*-arylation of bicyclic hydrazines as a key synthetic step.

Scheme 1. Previous studies and aim of this work



The investigations started with the preparation of a bicyclic hydrazine bearing a 2-bromobenzyl substituent on one of its bridgehead carbon atoms (**2**, Scheme 2). This crucial synthetic intermediate was obtained in two steps starting from cyclopentadiene. The functionalization of this commercially available and cheap precursor was first achieved through a deprotonation- alkylation sequence, following a protocol previously described in the literature.[44,45] The two expected inseparable and instable products of this reaction[46] were then directly engaged in a Diels-Alder cycloaddition in the presence of di-tert-butyl azodicarboxylate (DBAD, Scheme 2). After purification, the desired regioisomer **2** was isolated in 20% overall yield on a multi-gram scale.

Scheme 2. Synthesis of substituted bicyclic hydrazines



Compound **2** was submitted to a series of derivatization reactions to access differently substituted triazabicyclo[3.2.1]octanes **5a-h** (Scheme 3). Dihydroxylation of the double bond[38] proceeded smoothly to deliver product **3** in 88% yield. An oxidative cleavage of the vicinal diol was then conducted to quantitatively form dialdehyde **4**. This unstable intermediate was directly engaged in a double reductive amination.[38] The reaction was realized under acidic conditions, in the presence of various primary amines and tetra-*n*-butylammonium borohydride as the reducing agent (Scheme 3). After purification, products **5a-h** were isolated in up to 91% yield. The reaction tolerated several substituents at the nitrogen atom, including benzyl groups (**5a** and **5b**, Table 1, entries 1 and 2), side chains incorporating electron poor or electron rich aromatic rings (**5c** and **5d** respectively, Table 1, entries 3 and 4), fully saturated motifs (**5e** and **5h**, Table 1, entries 5 and 8), heterocycle containing moieties (**5g**, Table 1, entry 7), and even an aliphatic chain with a free hydroxyl group (**5f**, Table 1, entry 6).

Scheme 3. Synthesis of triazabicyclo[3.2.1]octanes

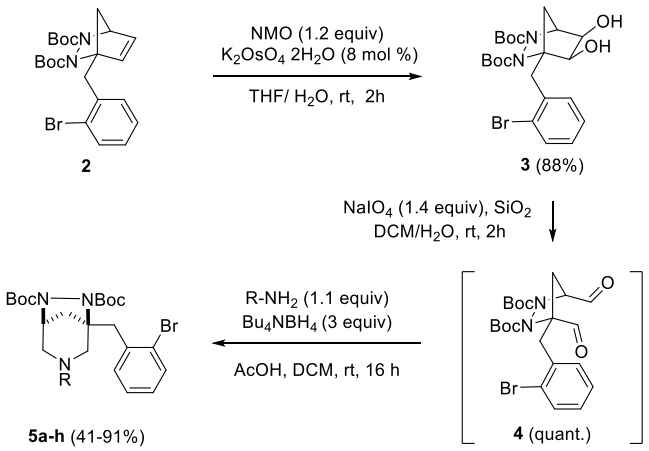
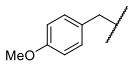
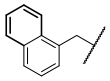
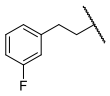
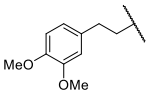
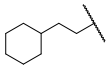
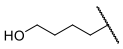
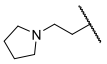


Table 1. Substrate scope of the reductive amination[a]

Entry	Product	R group	Yield (%)[c]
1	**5a**		63
2	**5b**		79
3[b]	**5c**		91
4	**5d**		61
5	**5e**		41
6	**5f**		78
7	**5g**		43
8	**5h**		43

[a] Reaction conditions: dialdehyde **4** (1 equiv.), R-NH_2 (1.1 equiv.), *n*-Bu_4NBH_4 (3.0 equiv.), and AcOH (1.8 equiv.) in DCM (0.5M) at rt overnight. [b] STAB (3.0 equiv.) was used as the reducing agent in this transformation. [c] Isolated yields after purification on silica gel column chromatography.

It is worth mentioning that few anilines were engaged in the reductive amination reaction but failed to react with dialdehyde **4**. This lack of reactivity, which was not observed on non-substituted bicyclic hydrazine, [37,38] is probably due to steric hindrance caused by the presence of the bromobenzyl group on compound **4**.

With compounds **5a-h** in hand, the possibility to achieve intramolecular Buchwald-Hartwig aminations was examined. To this end, the protecting groups installed on the nitrogen atoms of products **5a-h** were first removed by treatment with HCl in methanol (Scheme 4). In a first cyclization attempt, the reaction was performed in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %) and $CsCO_3$ (2 equiv.), starting from a model substrate (**5c**). However, under these conditions, the coupling failed to deliver the desired product. Buchwald-Hartwig arylations of hydrazines have rarely been reported in the literature.[47,48] The few successful examples all involve intermolecular transformations promoted by highly reactive palladium complexes or, as an alternative, copper- and nickel-based catalysts.[49-51] A palladacycle was therefore used to catalyze the reaction. Remarkably, RuPhos Pd G3 was found capable of delivering products **6a-h** when associated to sodium *tert*-butoxide (Scheme 4). The intramolecular amination proceeded smoothly with a low catalyst loading (2 mol %) in 1,4-dioxane at reflux. The amount of base (3.5 equiv.) played a crucial role in the reaction, as a higher quantity (5 equiv.) completely inhibited the *N*-arylation process.

Scheme 4. Boc-deprotection and intramolecular Buchwald-Hartwig aminations

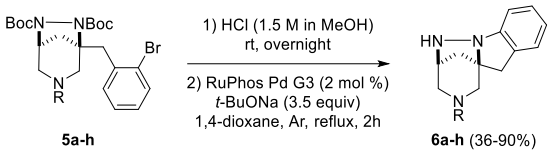
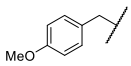
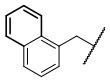
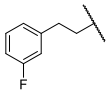
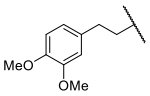
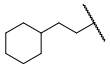
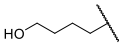
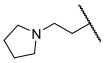


Table 2. Substrate scope of the intramolecular Buchwald-Hartwig *N*-arylation[a]

Entry	Product	R group	Yield (%)[b]
1	**6a**		83
2	**6b**		65
3	**6c**		87
4	**6d**		76
5	**6e**		73
6	**6f**		50
7	**6g**		36
8	**6h**		90

[a] Reaction conditions: Boc-deprotected substrate (1 equiv.), RuPhos Pd G3 (2 mol %) *t*-BuONa (3.5 equiv.), 1,4-dioxane (0.04 M), reflux, 2h. [b] Isolated yields.

The different substituents on the starting materials **5a-h** were well tolerated in most cases (Table 2). The Buchwald-Hartwig *N*-arylations also proved successful in the presence of side chains showing a heterocyclic moiety or a free hydroxyl group. The corresponding products, however, were obtained only in moderate isolated yields (50% and 36% for compounds **6f** and **6g** respectively, Table 2, entries 6 and 7). Note that the tricyclic scaffolds isolated after this key transformation have never been reported. Intramolecular Buchwald-Hartwig *N*-arylations therefore grant access to a new class of molecules with an original three-dimensional structure. Parallel to spirocycles, these derivatives may also reveal useful in the future to explore new avenues of research in drug discovery.

The reductive cleavage of the nitrogen–nitrogen bond of compounds **6a-h** was finally studied to access the spiro[indoline-2,3'-piperidine] derivatives. Hydrogenolyses were conducted under flow conditions using an H-Cube® reactor equipped with adapted catalyst cartridges.

Scheme 5. Reductive cleavage of the tricyclic hydrazines and subsequent Boc-protection of the free amino groups

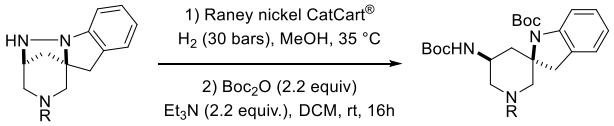
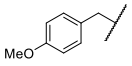
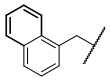
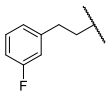
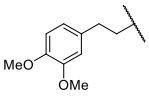
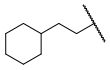
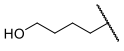
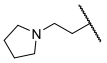


Table 3. Substrate scope of reductive N-N bond cleavage[a,b]

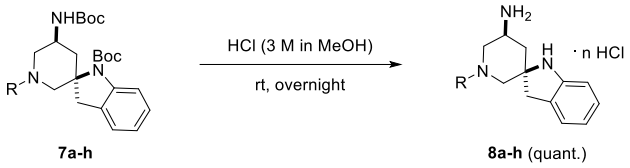
Entry	Product	R group	Yield (%)[c]
1	**7a**		45
2	**7b**		36
3	**7c**		49
4	**7d**		37
5	**7e**		26
6	**7f**		17
7	**7g**		15
8	**7h**		33

[a] Conditions: Substrates (1.0 eq.) in MeOH (0.0025 M). [b] H-Cube® parameters: Raney nickel CatCart®, flow rate: 1 mL/min, H_2 pressure: 30 bars, T: 35 °C. [c] Isolated yields after Boc-protection of the free amino groups and purification on silica gel column chromatography.

Compounds **6a-h** were eluted through the system at a flow rate of 1 mL/min. A first series of tests revealed that 10% Pd/C CatCart® was not able to deliver the desired products in an efficient fashion. More reactive Raney nickel CatCart® were therefore employed to promote the reaction. In the presence of these catalyst cartridges and H_2 (30 bars), the N-N bond of hydrazine **6a-h** was readily cleaved at 35 °C (Scheme 5). At this stage, protection of the resulting free amine groups as *tert*-butyl carbamates was required to purify the products which are otherwise highly hydrophilic and completely insoluble in common organic solvents (Scheme 5). Products **7a-h** were isolated in 15-49% overall yields after these transformations (Table 3). In general, better results were obtained starting from compounds incorporating an aromatic ring on their side chains in comparison with those bearing fully saturated substituents (Table 3, entries 1-4 vs entries 5 and 8). Spirocycles showing an additional heterocyclic moiety, or a free hydroxyl group were also obtained, albeit in low yields (Table 3, entries 6 and 7). Along with the challenging nature of the reported N-N bonds cleavages, technical difficulties encountered during the purification of the products can in part explain these results.

Removal of the carbamate groups with HCl in methanol (3 M) finally delivered the desired deprotected spiro[indoline-2,3'-piperidine] derivatives **8a-h** in quantitative yield (Scheme 6).

Scheme 6. Boc-deprotection of the spiro[indoline-2,3'-piperidine] derivatives



In conclusion, an original synthesis of C2-spirocyclicindolines incorporating differently substituted amino-piperidine moieties was developed. This previously unknown family of spirocycles was obtained starting from triazabicyclo[3.2.1]octanes bearing a 2-bromobenzyl substituent on one of its bridgehead carbon atoms. First, an unprecedented intramolecular Buchwald-Hartwig *N*-arylation of hydrazines was employed as a key step to access tricyclic key intermediates **6a-h**. These derivatives, which display a unique tridimensional core, were then submitted to hydrogenolysis under flow conditions. N-N bond cleavage reactions finally gave access to the desired spiro[indoline-2,3'-piperidines] **8a-h** in up to 42% over 5 steps. This study significantly widens the chemical space of spirocycles. In the future, this approach may open up new horizons in medicinal chemistry and drug discovery.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures for the preparation of all products; characterization data; copies of ^{1}H NMR and ^{13}C NMR spectra (PDF).

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Author Contributions

The manuscript was written through contributions of all authors.

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