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Construction of NH-Unprotected Spiropyrrolidines and Spiroisoindolines by [4+1] Cyclizations of γ-Azidoboronic Acids with Cyclic *N*-Sulfonylhydrazones

*Lucía López, María-Paz Cabal, and Carlos Valdés**

Abstract: *The reactions of N-sulfonylhydrazones derived from cyclic ketones with γ-azidopropylboronic acid and 2-(azidomethyl)phenylboronic acid give rise to spirocyclic pyrrolidines and spiroisoindolines, respectively. The reactions proceed without the need of any transition-metal catalyst through a domino process that comprises the formation of a Csp^3-C and a Csp^3-N bond of the former hydrazonic carbon. The scope of the reaction has been explored by the preparation of over 50 examples of NH-unprotected spirocyclic derivatives. Importantly, this methodology could be applied for the preparation of alkaloid steroids from steroid N-tosylhydrazones.*

Introduction

Spirocycles are widely present in both natural and synthetic biological active products.[1,2] Indeed, molecules containing spirocyclic moieties are very appealing in medicinal chemistry, as the rigid three-dimensional structure of the sp^3-rich scaffold orients the substituents towards different directions, allowing the exploration of new areas of the chemical space in drug discovery programs.[3–6] In particular, spiropyrrolidines constitute a class of spirocycles which can be found in natural alkaloids[7] as well as in biologically active molecules (Figure 1).[8] Furthermore, small molecules containing the spiropyrrolidine fragment are being used as elements that provide three-dimensional diversity in fragment based drug discovery.[9] For these reasons, the development of flexible methods for the synthesis of structurally diverse spiropyrrolidines have concentrated great interest in the recent years.[10–18]

N-Sulfonylhydrazones are very attractive derivatives of carbonyl compounds, that have been extensively employed as precursors of diazo compounds in a variety of metal-catalyzed as well as non-catalytic transformations.[19–23] In particular, the transition-metal free reaction between *N*-sulfonylhydrazones and boronic acids, first reported by our group,[24] is a very useful C–C bond forming reaction that has found ample application in organic synthesis as a method to generate molecular diversity from carbonyl compounds.[25–31] These reactions proceed through the carboborylation of the *N*-sulfonylhydrazone which leads to a homologated boronic acid that can undergo protodeboronation or alternatively be trapped in a subsequent reaction.[24,32–34]

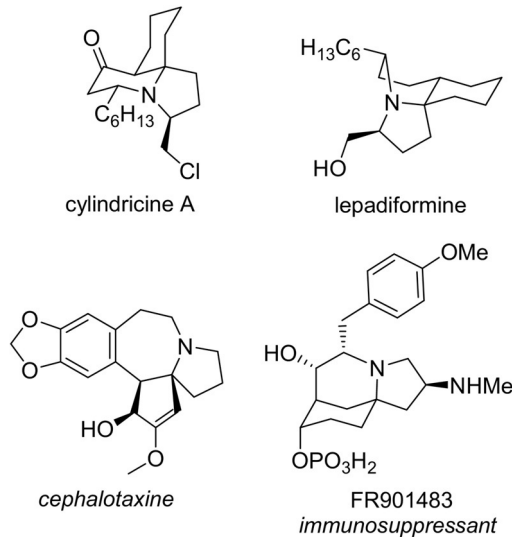

Figure 1. Examples of biorelevant spiropyrrolidines.

In the last years, we have concentrated on the development of cascade processes based on the ability of sulfonylhydrazones to form two bonds on the hydrazonic carbon[35,36] and designed several methods for the construction of spirocarbocyclic compounds through Pd- catalyzed[37,38] as well as transition metal-free transformations.[39] In this context, we reported recently a new approach for the construction of pyrrolidines **C** by reaction of boronic acids with γ-azido-*N*-sulfonylhydrazones **A**.[40] In this transformation, the homologated boronic acid **B** generated upon carboborylation of the *N*-sulfonylhydrazone undergoes the intramolecular carboborylation of the azide, to build the pyrrolidine ring with formation of a Csp^3-Csp^3 and a Csp^3-N bonds on the hydrazonic carbon (Figure 2a). In light of these results, we envisioned that the access to spirocyclic pyrrolidines **F** could be achieved through a similar approach by changing the arrangement of the reactive functional groups, employing γ-

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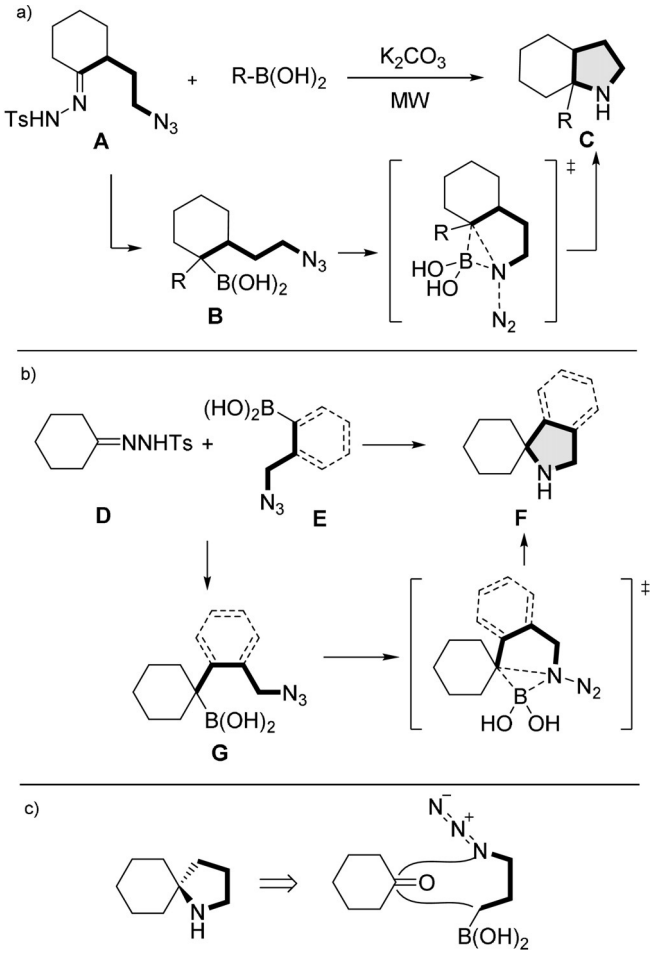
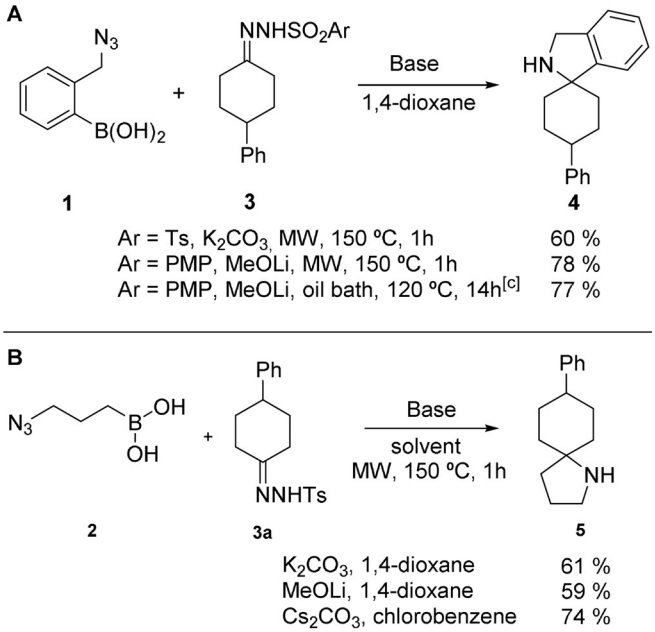


Figure 2. a) Synthesis of pyrrolidines through a Csp^3-C and a Csp^3-N bond forming cascade from boronic acids and γ-azido-*N*-sulfonylhydrazone. b) This work: spiropyrrolidines from *N*-sulfonylhydrazones and γ-azidoboronic acids. c) Novel [4+1] disconnection for the synthesis of pyrrolidines from ketones.

azidopropylboronic acids **E** and *N*-sulfonylhydrazones **D** derived from cyclic ketones (Figure 2b). We expected that the δ-azidoboronic acid **G** formed by carboborylation of the *N*-sulfonylhydrazone might undergo the spirocyclization through the intramolecular carboborylation of the azide. Since *N*-sulfonylhydrazones are readily prepared from ketones, this [4+1] cyclization would consist of a new disconnection for the synthesis of pyrrolidines by connecting the carbonylic carbon[16,41,42] of a cyclic ketone with both ends of the azidoboronic acid (Figure 2c).[43] In this paper we report the development of this concept, which has resulted in a new method for the construction of structurally diverse spirocyclic pyrrolidines and isoindolines.

Results and Discussion

To develop the spirocyclization reaction, we selected *o*-(azidomethyl)phenylboronic acid **1** and 3-azidopropylboronic acid **2**, functionalized aryl and alkylboronic acids, respectively. In an initial set of experiments, we studied the reactions with the *N*-tosylhydrazone of 4-phenylcyclohexanone **3a** under the conditions we had previously established for the domino synthesis of pyrrolidines (K_2CO_3, 1,4-dioxane, MW 150 °C, 1 h) (Scheme 1). The reaction with **1** led to spiro-

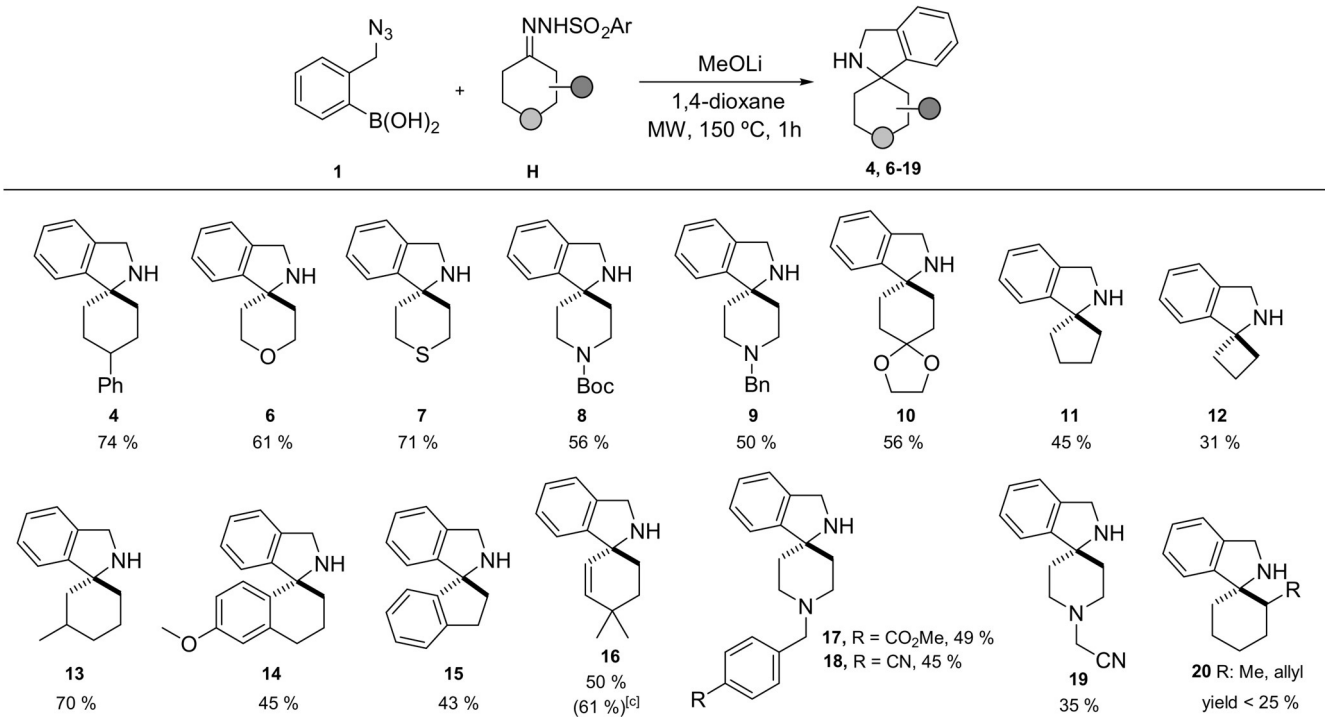


Scheme 1. [a,b] Selected preliminary experiments on the spirocyclization of *N*-sulfonylhydrazones with 2-azidomethylphenylboronic acid **1** (A) and 3-azidoproylboronic acid **2** (B). [a] Reaction conditions: Hydrazone **3**, 0.15 mmol, boronic acid **1** (3 equiv), base (3 equiv). 1,4-dioxane (1.2 mL). [b] Combined yield for the mixture of diastereoisomers. [c] Slow addition of the sulfonyl hydrazone. PMP: *p*-methoxyphenyl.

isoindoline **4** as 1:1 mixture of diastereoisomers in a 60% yield (Scheme 1A). To improve this initial result a set of experiments were carried out with variation of solvent, base, temperature and substitution on the aromatic ring of the hydrazide fragment (see SI for details). Indeed, the formation of the spiroisoindoline takes place employing K_2CO_3 or MeOLi as base, and both under MW activation (150 °C, 1 h) or oil bath heating (120 °C) with slow addition of the *N*-sulfonylhydrazone. Nevertheless, the employment of the 4-methoxyphenylsulfonylhydrazone **3b** gave slightly better yield than the *N*-tosylhydrazone,[25,31] and the use of LiOMe turned out to be the best base to achieve this transformation.

On the other hand, the reaction with alkylboronic acid **2** under the standard conditions led the spiropyrrolidine **5** in 61% yield again as 1:1 mixture of diasteroisomers (Scheme 1B). Variations in solvent and base led only to small modifications in the reaction yield (see SI for details) and no improvement was observed upon the replacement of the tolyl group in the *N*-sulfonylhydrazone. After some experimentation it was found that for this specific example, the combination of the *N*-tosylhydrazone, Cs_2CO_3 as base and chlorobenzene as solvent provided the highest yield (Scheme 1B).

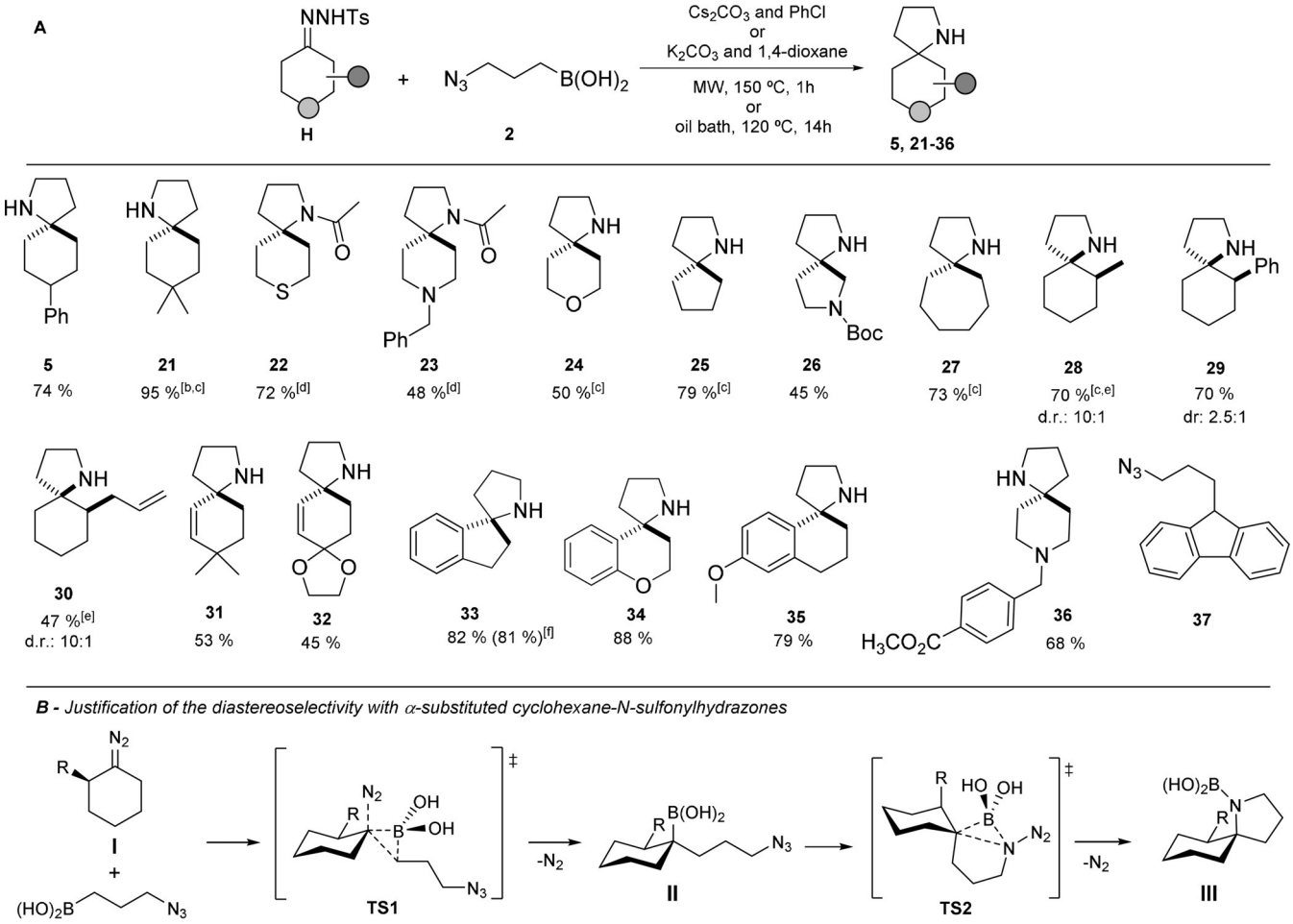
Then, the scope of the cascade reactions was studied employing a set of *N*-sulfonylhydrazones of cyclic ketones, leading to an array of NH-free spirocyclic isoindolines and pyrrolidines (Scheme 2 and Scheme 3 respectively). The



Scheme 2. [a,b] Synthesis of spiroisoindolines from cyclic *N*-sulfonylhydrazones **H** and arylboronic acid **1**. [a] Reaction conditions: Hydrazone **H**, 0.15 mmol, boronic acid **1** (3 equiv), base (3 equiv). 1,4-dioxane (1.2 mL). [b] Isolated yield after column chromatography. [c] Yield of the reaction at a 1 mmol scale.

reaction with arylboronic acid **1** (Scheme 2) is compatible with five- and six-membered ring carbo- and heterocyclic *N*-sulfonylhydrazones leading to the expected spiroisoindolines **4**, **6**–**11** and **13** with moderate to good yields. The reaction with the hydrazone derived from cyclobutanone also provided the product **12**, albeit in a modest 31 % yield. The reactions with *N*-sulfonylhydrazones derived from piperidones are noteworthy, as they furnish the interesting spirocycles **8**, **9**, **17**–**19** featuring two differently protected nitrogen atoms, that might be independently derivatized. Additionally, α-tetralone and α-indanone derived *N*-sulfonylhydrazones led to the isoindolines **14** and **15** which feature structures that have been reported as non-competitive NMDA antagonists.[44] Moreover the spirocyclization proceeded successfully also with *N*-sulfonylhydrazones derived from an α,β-unsaturated cyclic ketone, providing the corresponding spirocyclic isoindoline **16** featuring an endocyclic double bond. Regarding the functional group compatibility, the presence of ester and nitrile functional groups was tolerated as shown in the examples **17**–**19**. As a limitation of the method, the reactions with α-substituted *N*-tosylhydrazones were sluggish, providing very poor yields of the corresponding isoindolines **20**.

In the reactions with alkylboronic acid **2** it was observed that the conditions developed for *N*-sulfonylhydrazone **3a** (Cs_2CO_3, chlorobenzene) were not always optimal, and depending on the specific substrate had to be tuned by choosing the proper solvent (1,4-dioxane or chlorobenzene), the optimal base (Cs_2CO_3 or K_2CO_3), and the heating procedure (MW, 150 °C, 1 h or conventional heating, 120 °C, 14 h) (Scheme 3, **A**). Under the proper conditions, spiropyrrolidines containing five (**25**, **26**), six (**5**, **21**–**24**) and seven membered (**27**) carbo- and heterocycles could be prepared with moderate to good yields. As a general trend, the reactions with the alkylboronic acid **2** (Scheme 3) give higher yields than with the arylboronic acid **1** (Scheme 2). Again, the reactions with *N*-tosylhydrazones derived from nitrogen heterocycles are noteworthy, providing the diazaspirocycles (**23**, **26**, and **36**) featuring two differently protected nitrogen atoms. The reaction is also more general, as it could be applied to α-substituted cyclohexanone *N*-sulfonylhydrazones. Thus, methyl and phenyl substituents were well tolerated leading to the corresponding spiropyrrolidines **28** and **29** in good yield and high diastereoselectivity. Moreover, the reaction with 2-allylcyclohexanone *N*-tosylhydrazone led to the spirocyclic pyrrolidine **30** in an acceptable 47 % yield and as a 10:1 mixture of diastereoisomers. This is a particularly interesting example, as the double bond offers an additional handle for derivatization. Good results were also obtained for the reactions with α,β-unsaturated *N*-tosylhydrazones, which gave rise to spirocycles **31** and **32**, featuring the 1-azaspiro-[4.5]dec-6-ene structure, an important scaffold that has been employed in the construction of cephalotaxine analogues.[45] Finally, the transformation could be also applied to the *N*-sulfonylhydrazones derived from α-indanone chroma-4-one and α-tetralone, to provide the spirocyclic systems **33**, **34** and **35** respectively. However, the spirocyclization failed in the case of the reaction with the *N*-tosylhydrazone of 9-fluorenone, leading to the azide **37** derived from the conventional reductive coupling reaction. In this case, the protodeboronation of the intermediate dibenzylboronic acid is favoured towards the carboborylation of the azide.



***B -** Justification of the diastereoselectivity with α-substituted cyclohexane-N-sulfonylhydrazones*

Scheme 3. [a,b] A) Synthesis of spiropyrrolidines from cyclic *N*-sulfonylhydrazones **H** and arylboronic acid **2**. [a] Reaction conditions: Hydrazone **H**, 0.15 mmol, boronic acid **2** (3 equiv), base (3 equiv), solvent (1.2 mL). [b] Isolated yield after column chromatography; [c] Isolated as the hydrochloride. [d] Isolated yield after in situ acetylation. [e] Carried out in an oil bath (120 °C) with syringe pump slow addition of **2**. [f] Yield for the reaction at 1 mmol scale. B) Justification for the diastereoselectivity observed in the reactions with α-substituted cyclohexane-*N*-sulfonylhydrazones.

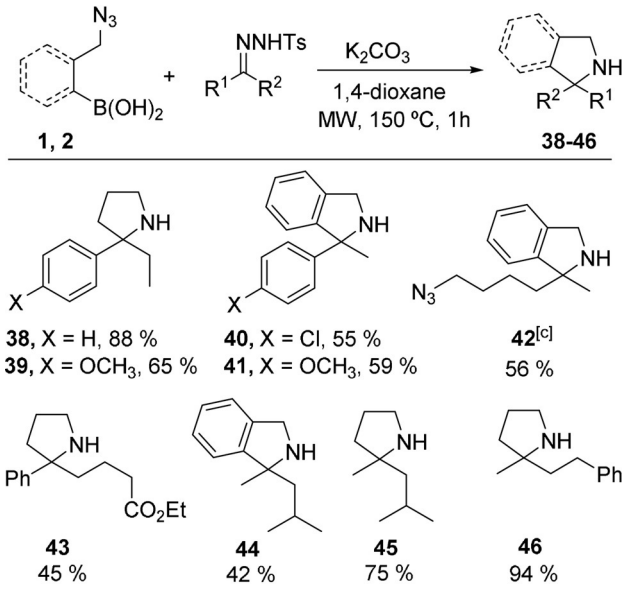
The results presented in Scheme 2 and Scheme 3 altogether clearly demonstrate the usefulness of this transformation in the straightforward construction of structurally diverse spirocyclic isoindolines and pyrrolidines, through a very simple experimental procedure. Importantly, the reactions directly deliver the N-H unprotected heterocycles, enabling their direct derivatization or employment in fragment-based drug discovery.[46]

The diastereoselectivity observed in the reactions with α-substituted cyclohexane-*N*-sulfonylhydrazones (entries **28**–**30**) can be explained based on our mechanistic proposal and our previous studies in the diastereoselective carboborylation of substituted cyclic *N*-sulfonylhydrazones (Scheme 3, **B**).[24,47] Thus, in a first step, the stereoselective carboborylation takes place by the approach of the boronic acid through the less hindered face of the diazocompound **I** through the transition state **TS1** to form the intermediate boronic acid **II**. Then, the stereoretentive carboborylation of the azide occurs through **TS2** to furnish the spirocycle **III** that features the α-substituent and the nitrogen atom in a *cis* arrangement (see SI for a discussion of the stereochemical assignment).

The pyrrolidine synthesis through the [4+1] approach can be also applied to acyclic *N*-tosylhydrazones as demonstrated in some representative examples presented in Scheme 4. The reaction leads to pyrrolidines and isoindolines featuring 2,2-dialkyl (**42**, **44**–**46**) as well as 2-alkyl-2-aryl substitution (**38**–**41**, **43**). The presence of a sensitive carboxylic ester (**43**) is tolerated, and moreover, an azide functionality, which is not in the proper position to undergo the cyclization also remains untouched in the reaction (**42**).

Application to biologically relevant scaffolds

The transformations carried out with *N*-sulfonylhydrazones are synthetically very appealing because they are readily prepared from ketones, and the supply of structurally diverse ketones is almost unlimited. Thus, we decided to explore the usefulness of this methodology in more complex and biologically relevant molecules featuring a carbonyl functionality, in the idea that those structures might be easily transformed into spirocyclic unnatural alkaloid-like mole-



Scheme 4. [a,b] Synthesis of 2,2-disubstituted pyrrolidines and isoindolines from acyclic *N*-sulfonylhydrazones and azidoboronic acids **1** and **2**. [a] Reaction conditions as in Scheme 3. [b] Isolated yields after column chromatography. [c] LiOMe as base.

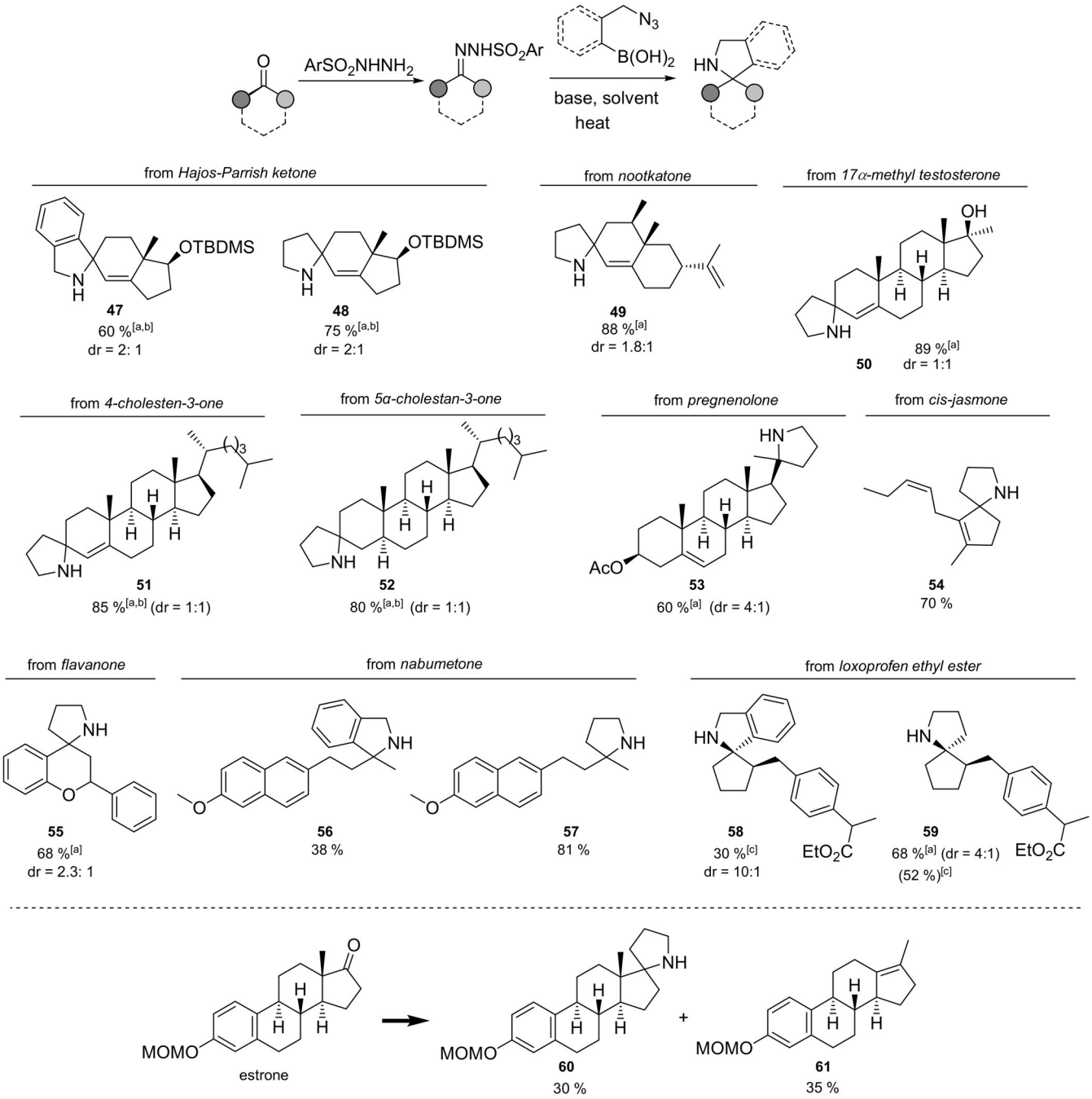
cules (Scheme 5). Firstly, the reactions of boronic acids **1** and **2** with a bicyclic *N*-tosylhydrazone obtained from Hajos-Parrish ketone led to the expected spiroisoindoline **47** and the spiropyrrolidine **48** respectively with good yields as separable mixtures of distereoisomers. Similarly, the carbonyl in the natural sesquiterpene *Nootkatone* could be trapped by reaction with **2** to obtain the terpenoid alkaloid **49** in very good 88% yield.

The spirocyclization reaction was also examined on steroid derivatives. Of note, the modification of steroids oriented to the discovery of new drugs, and in particular the introduction of nitrogenated functionalities, is a field of enormous interest in medicinal chemistry.[48–51] Delightfully, the application of the methodology to the *N*-tosylhydrazone of 17α-methyltestosterone provided the modified steroid **50** featuring the spirocyclic pyrolidine moiety in a remarkable 89% yield. Noteworthy, no protection of the hydroxy group was needed. The same transformation could be accomplished successfully to cholesterol derivatives 4-cholesten-3-one and 5-α-cholestan-3-one to provide the novel cholesterol-derived unnatural alkaloids **51** and **52** respectively with high yields. In these examples a 1:1 mixture of diasteroisomers was obtained, but interestingly, could be cleanly separated by conventional column chromatography on neutral Al_2O_3. Moreover, the NH-free pyrrolidine moiety could be also introduced in the methyl ketone of pregnenolone to give the novel unnatural steroid alkaloid **53**. Considering that the ketone functionality is present in a wide variety of natural terpenes and steroids, this method might be a powerful alternative for the transformation of these classes of natural products into unnatural spirocyclic terpenoid and steroid alkaloids. Finally, but not least important, the free NH derivatives are directly obtained, offering the possibility of immediate subsequent modification for the elaboration of novel classes of modified natural products.

The cyclization reaction could be applied also to other biologically relevant molecules. For instance, the reaction proceeded successfully with the *N*-tosylhydrazone of the natural scent *jasmone*, to obtain the expected spiropyrrolidine **54**. This interesting example expands the scope of the spirocyclization to 2-substituted cyclopentenones. The reaction was also applied for the introduction of the pyrrolidine moiety in *flavanone* to provide a 2:1 mixture of diastereoisomers of the new spiroheterocycle **55**. Finally, the usefulness of this chemistry was further illustrated by the modification of the anti-inflammatory drugs *nabumetone* and *loxoprofen* to give the new pyrrolidines **56**, **57**, **58** and **59** respectively. The reaction with the *loxoprofen* ethyl ester also illustrates the application of the spirocyclization reaction to a α-substituted cyclopentanone *N*-sulfonylhydrazone, which had not been explored in the study of the scope of the reactions included in Scheme 2 and Scheme 3. Importantly, like in the case of the reactions with α-substituted cyclohexanone derivatives, the process is diastereoselective giving rise to a separable 4:1 mixture of diastereoisomers for spiropyrrolidine **59**. Additionally, in spite of the observed higher sensitivity to steric hindrance of the reactions with boronic acid **1**, the spiroisoindoline **58** could be also obtained in 30% yield with very high diastereoselectivity. Moreover, the spirocyclization proceeded also, although in lower yield in the cyclopentanone ring of *estrone* to give the pentacyclic derivative **60**. For this example, an almost equimolar mixture of the spirocycle derivative **60** and the alkene **61** was obtained in the reaction. The formation of **61** can be explained considering an abnormal Bamford-Stevens decomposition of the *N*-tosylhydrazone with migration of the angular methyl group. Thus, in this case the unimolecular decomposition of the diazo compound generated from the *N*-tosylhydrazone competes with the addition of the boronic acid due to the steric congestion around the hydrazonic carbon.

Conclusion

As summary, we have reported herein a new approach for the preparation of spirocyclic pyrrolidines and isoindolines, which are interesting building blocks in drug discovery. The nitrogenated five membered ring is built by a formal [4+1] cyclization between a *N*-sulfonylhydrazone and a γ-azidoboronic acid. From a synthetic perspective, since *N*-sulfonylhydrazones are readily prepared from ketones, the pyrrolidine ring is formed by connecting the carbonyl carbon of a ketone with both ends of the azidoboronic acid, thus representing a novel disconnection for the formation of these important five membered rings. The reaction is quite versatile allowing for the preparation of a wide variety of spirocyclic scaffolds featuring a free NH, and therefore, amenable for further derivatization. Furthermore, it has been demonstrated the usefulness of the reaction in the transformation of a variety of biorelevant molecules bearing a ketone functionality, among them the conversion of steroids into unnatural steroidal alkaloids featuring the NH-spiropyrrolidine moiety.



Scheme 5. Modification of biorelevant ketones by application of the spirocyclization reaction: Synthesis of unnatural terpenoid and steroid alkaloids. See SI for the specific reaction conditions. [a] Combined yield for the mixture of diastereoisomers. [b] Diastereoisomers could be cleanly separated by flash chromatography. [c] Yield of the major isomer after flash chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: azides · boronic acids · *N*-tosylhydrazone · pyrrolidines · steroids

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