WILEY-VCH

FULL PAPER

Heterocyclization and spirocyclization processes based on domino reactions of *N*-tosylhydrazones and boronic acids involving intramolecular allylborylations of nitriles

Manuel Plaza, Stefano Parisotto and Carlos Valdés*[a]

Abstract: Polycyclic molecules featuring all-carbon quaternary bridgehead centers are synthesized through domino cyclizations between *N*-tosylhydrazones and boronic acids. Variations of the general cascade have been applied for the preparation of 3-quinuclidinones and related alkaloid-like scaffolds through transannular heterocyclizations. Moreover, the employment of 3-cyanopropyl and 4-cyanobutylboronic acids and α,β-unsaturated *N*-tosylhydrazones led to spirocycles through unprecedented formal [n+1] cyclizations, including the steroselective spirocyclization of the Hajos-Parrish ketone. The common feature of all the new reactions described is the creation of an all-carbon quaternary center by formation of two Csp^3-C bonds on the hydrazonic carbon atom. DFT-based calculations suggest cascade processes that involve a diazo compound carboborylation followed by a 1,3-borotropic rearrangement on an intermediate allylboronic acid and a novel bora-aza-ene cyclization.

Introduction

The synthesis of polycyclic molecules with novel "sp^3 rich" three dimensional scaffolds is a subject of great interest in organic synthesis, as they allow the exploration of unknown areas of the chemical space in the search of new biologically active molecular structures.[1,2] In this regard, polycyclic molecules featuring all-carbon quaternary centers at bridgehead positions are particularly attractive.[3] The rigidity imposed by the quaternary center enforces specific three dimensional structures that display the functional groups of the molecules into particular arrangements that might be determining for potential interactions with biological receptors. Examples of these classes of structures are fused bicyclic structures **I**, [a.b.c] bicyclic structures **II**, and spirocyclic structures[4] **III** (Figure 1). Therefore, the development of efficient and flexible methods for the preparation of these types of molecules is highly demanded.

Very appealing approaches towards these scaffolds would be the formation of two C-C bonds on the same carbon atom in a single step. While these transformations are relatively frequent when heteroatoms are involved, they are really challenging if an all-carbon quaternary center is to be formed. Moreover, these classes of cyclizations normally require a transition-metal catalyst that acts as a molecular assembler of the starting materials.[5,6]

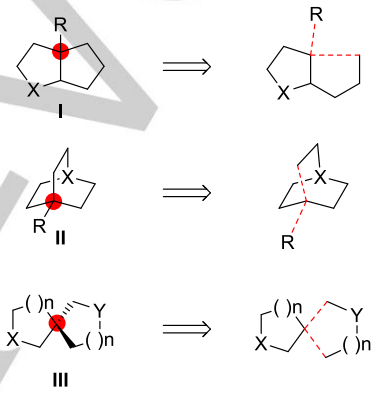


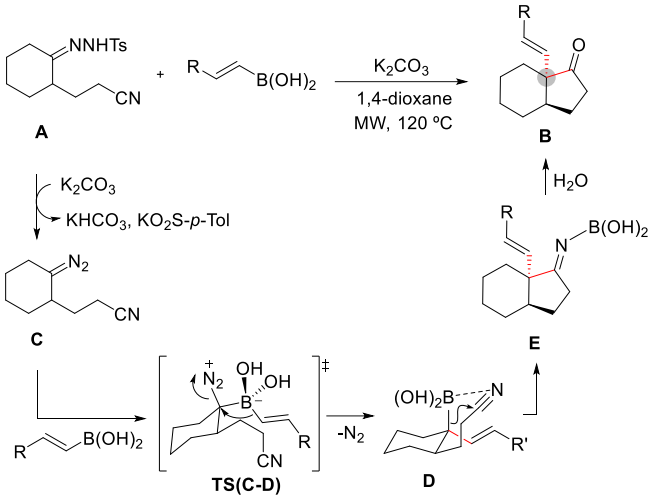
Figure 1. Molecular scaffolds featuring quaternary centers at bridgehead positions and the strategies for their synthesis discussed in this paper.

In the context of our interest on the metal-free reactions between sulfonylhydrazones and boronic acids,[7] we have recently reported a transition-metal free cascade carbocyclization involving γ- and δ-cyano-*N*-tosylhydrazones and alkenylboronic acids, which led to fused carbocyclic structures of type **I** featuring an all-carbon quaternary stereocenter (Scheme 1).[8] In those reactions, two Csp^3-Csp^2 bonds are formed on the same carbon, representing a novel type of cascade carbocyclization with concomitant incorporation of a side chain.

The mechanism initially proposed for this transformation (Scheme 1) is based on the reductive couplings of *N*-tosylhydrazones with boronic acids,[7] and involves the following steps: 1) base promoted decomposition of the *N*-tosylhydrazone **A** to generate diazo compound **C**, 2) reaction of the diazo compound with the alkenylboronic acid, that forms an intermediate allylboronic acid **D**, 3) intramolecular carboborylation of the cyano group to give intermediate *N*-boroimine **E**, 4) hydrolysis of the imine to give the final ketone **B**.

[a] M. Plaza, S. Parisotto, Prof. Dr. Carlos Valdés*
Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica "Enrique Moles".
Universidad de Oviedo.
c/ Julián Clavería 8. Oviedo 33006. Spain.
E-mail: acvg@uniovi.es

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))



Scheme 1. Synthesis of fused bicyclic structures of type I by reaction of γ- and δ-cyano-N-tosylhydrazones and alkenylboronic acids and mechanism proposed.

In our previous publication, we have already shown the versatility of the reaction on carbocyclization processes, allowing for the synthesis of an ample variety of fused bicyclic structures of type I with very high diastereoselectivity (Figure 2). Importantly, the reaction could be even applied for the modification of steroids through a completely new and original approach.

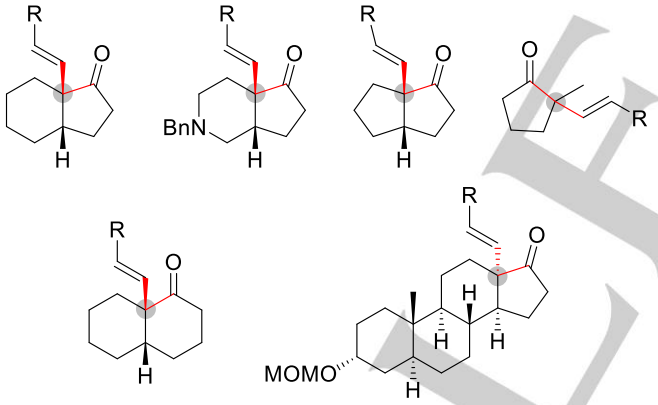


Figure 2. Fused cyclic structures synthesized through the domino cyclization

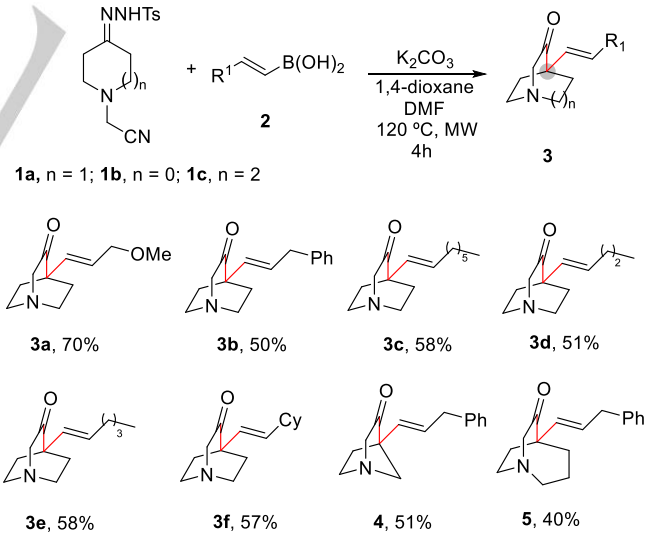
Based on this work, we considered that this new mode of reactivity may hold greater synthetic potential, as it could be applied for the construction of different classes of complex polycyclic structures featuring bridgehead quaternary centers by designing appropriate domino cyclizations.[9] Herein we wish to report our advances in this regard, that have led lead to development of synthetic methods for the structural motifs **II** and **III** through the innovative retrosynthetic disconnections represented in Figure 1. Additionally, mechanistic insights on these domino cyclizations are provided based on DFT-based calculations, which may help on the design and development of new cyclizations based on the same principle.

Results and Discussion

Transannular cyclizations for the synthesis of 1-aza[a.b.c] bicyclic structures **II**

In order to expand the applicability of the domino cyclization into heterocyclic systems, we chose the *N*-tosylhydrazone **1a**, bearing a cyanomethyl moiety attached to the nitrogen atom, as the platform to explore the construction of 1-aza[2.2.2]bicycles of type **II** through the transannular cyclization sketched in Figure 1.

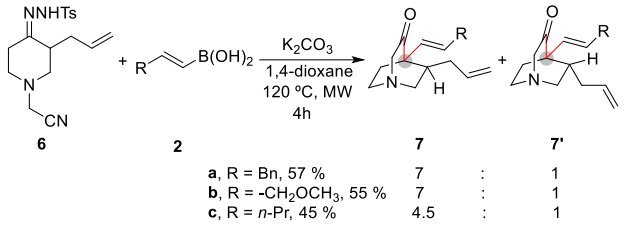
The initial reactions between tosylhydrazone **1a** and alkenylboronic acids **2**, carried out under the standard conditions for boronic couplings with tosylhydrazones[7] (K_2CO_3, 1,4-dioxane, 120 ºC, MW), led to the recovery of the starting tosylhydrazone **1**. However, the addition of a small amount of DMF increased the solubility of the highly polar *N*-tosylhydrazone salt allowing the reaction to proceed (Scheme 2). Under these conditions, the final quinuclidinones **3** were obtained in yields ranging from moderate to good through the planned transannular cyclization for a variety of alkyl substituted alkenylboronic acids (Scheme 2). Particularly attractive is compound **3a**, featuring a methoxy substituent that might allow for further derivatization of the side chain. From a synthetic point of view, this cascade reaction represents an unprecedented method to build the important 3-quinuclidinone core[10] by formation of two Csp^3-Csp^2 bonds (ring forming bond and side chain incorporation) on the hydrazonic carbon atom. Moreover, cyanomethylated 3-pyrrolidinone **1b** and 4-azepanone **1c** led also to the 1-aza[2.2.1] and [2.2.3] bicycles **4** and **5** respectively, increasing the versatility of the transformation.



Scheme 2. Synthesis of quinuclidinones and related systems by transannular domino cyclization of heterocyclic *N*-tosylhydrazones and alkenylboronic acids. Reaction conditions for the domino cyclization: Tosylhydrazone **1** (0.3 mMol), boronic acid **2** (0.6 mMol), K_2CO_3 (0.6 mMol), 1,4-dioxane (2.4 mL), MW (120 ºC).

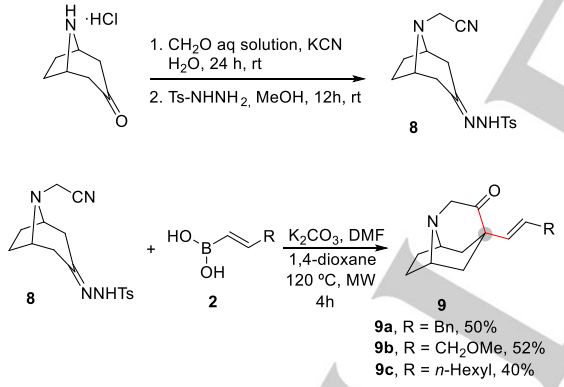
The stereoselectivity of the transannular cyclization was explored in the reaction with the α-allyl-*N*-tosylhydrazone **6**. The presence

of the substituent at the α-position was compatible with the reaction conditions, as the quinuclidinones **7** were isolated with moderate yields and with high but no total stereoselectivity (7:1 to 4.5:1 mixtures of isomers) (Scheme 3). As expected,[7f] the major isomer **7** corresponded to the incorporation of the alkenylboronic acid in a *trans* arrangement relative to the allyl substituent, which is determined in the first step of the cascade reaction. Thus, an all carbon bridgehead quaternary stereocenter is formed stereoselectively in this domino reaction.



Scheme 3. Stereoselectivity on the synthesis of quinuclidinones **7**. Reaction conditions as in Scheme 2. Diastereomeric ratios determined by ^{1}H NMR.

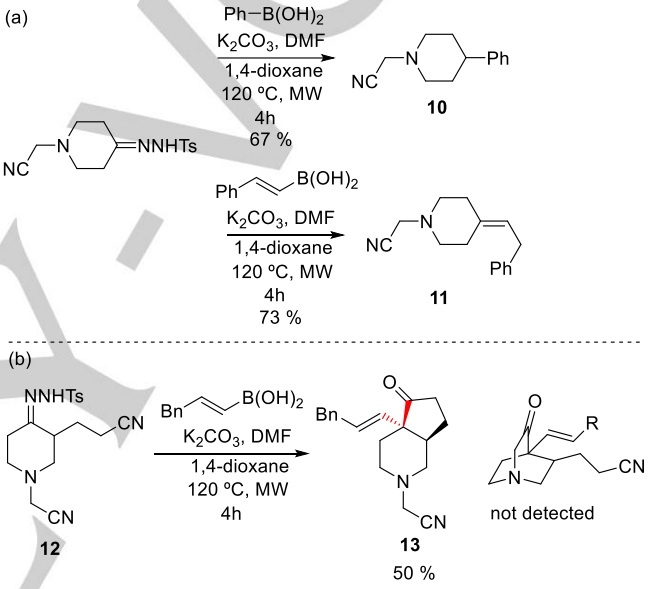
Then, we turned our attention to *N*-cyanomethylated tropinone, readily available from commercial tropinone, as starting material. Thus, treatment of tosylhydrazone **8** with the alkenylboronic acids **2** led to the tricyclic aminoketones **9** with moderate yields. It is noteworthy the high structural complexity achieved from readily available starting materials and through a very simple reaction, which only requires the presence of the coupling reagents and K_2CO_3 as a base (Scheme 4).



Scheme 4. Synthesis of quinuclidinones and related systems by transannular domino cyclization of heterocyclic *N*-tosylhydrazones and alkenylboronic acids.

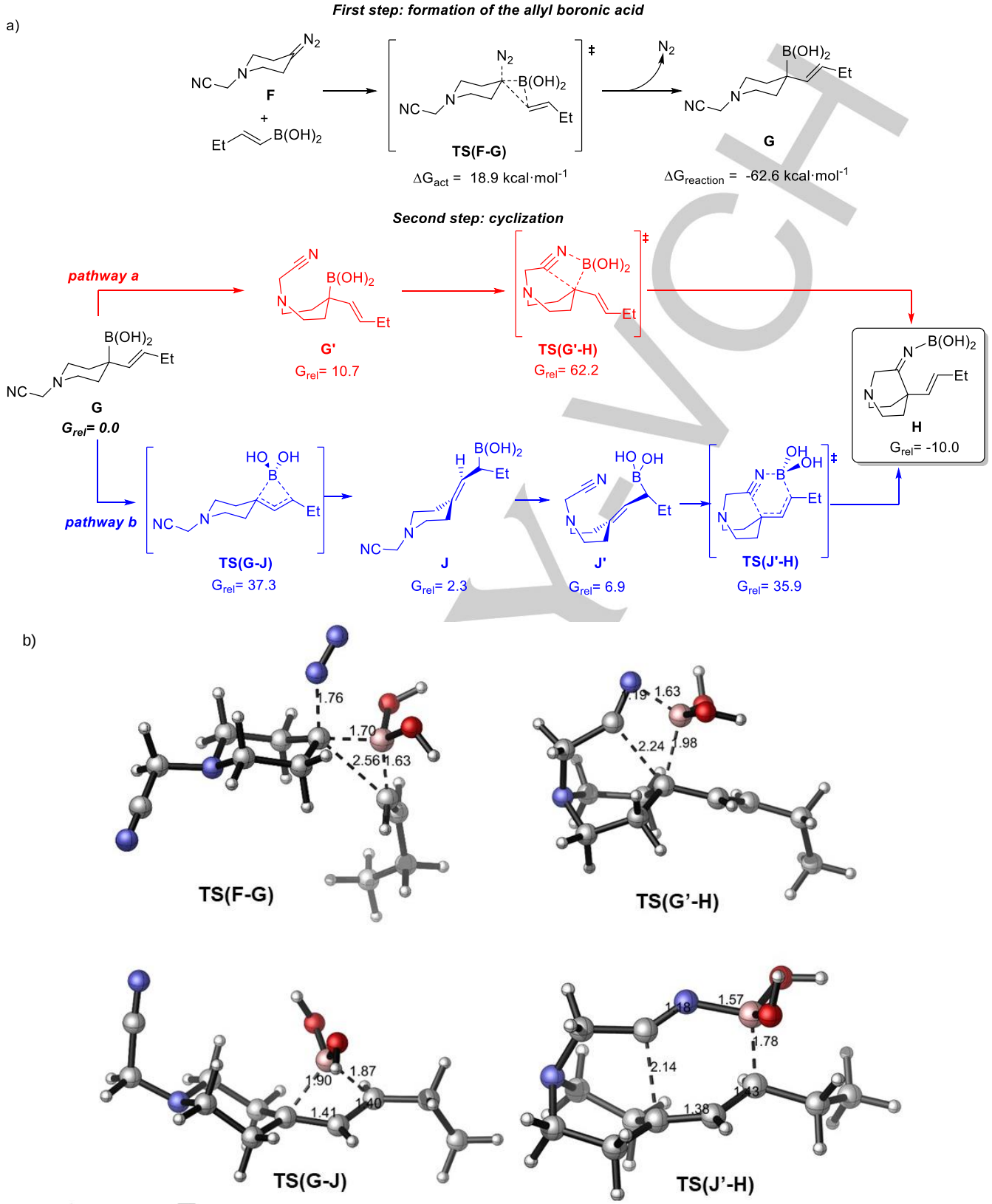
The limitations of the transannular cyclization must be indicated. When the reaction was attempted with arylboronic acids, no cyclization was observed, and the piperidine **10** derived from the reductive alkenylation was obtained (Scheme 5, a).[7a,d] Similarly, the reaction with styrylboronic acid led to the reductive alkenylation product **11**, with no cyclization product being detected. This latter result is not surprising, as we have previously reported the different behavior of alkyl and aryl substituted alkenylboronic acids in the reactions with *N*-tosylhydrazones.[7e] Thus, in both cases, the protodeboronation of the intermediate boronic acid is favoured towards the transannular cyclization. Finally, the reaction with *iso*-butylboronic acid, led to a complex reaction mixture, with no cyclization product being detected.

The chemoselectivity of the cyclization was explored in the reaction with *N*-tosylhydrazone **12**, which features two different electrophilic positions susceptible to the attack of the allylboronic acid intermediate. Only the benzofused bicycle **13** was isolated, therefore, the transannular cyclization is outcompeted by the cyclization over the cyanide in the side chain (Scheme 5, b).[8] A justification for the chemoselectivity of this cyclization reaction by means of DFT computational modeling is discussed below and in the supporting information.



Scheme 5. (a) Limitations of the transannular cyclization. (b) Chemoselectivity in the cascade cyclization.

Mechanistic considerations: These results show that the domino cyclization takes place only when alkenylboronic acids are employed. Considering the mechanism proposed for the reactions of *N*-tosylhydrazones with boronic acids,[7] it suggests that the formation of an intermediate allylboronic acid is a requirement for the cyclization reaction to occur.[11] To explain the observed facts and get further understanding on the mechanism of the reaction, DFT-based computational studies were conducted.[12,13] We focused on the cyclization to afford the quinuclidone nucleus. Thus, we considered as the first step the formation of the allylboronic acid **G,** by the reaction of the diazo compound **F** generated from the *N*-tosylhydrazone, with the alkenylboronic acid.[7f,14] Afterwards, two possible cyclization pathways from **G** were found: *Pathway a*: direct cyclization to give **H**. *Pathway b*: stepwise reaction involving a 1,3-borotropic rearrangement[15] to give the new allylboronic acid **J**, followed by cyclization through the allylboration of the cyano group that furnishes **H**. A summary of the results of the computational study is presented in Scheme 6.



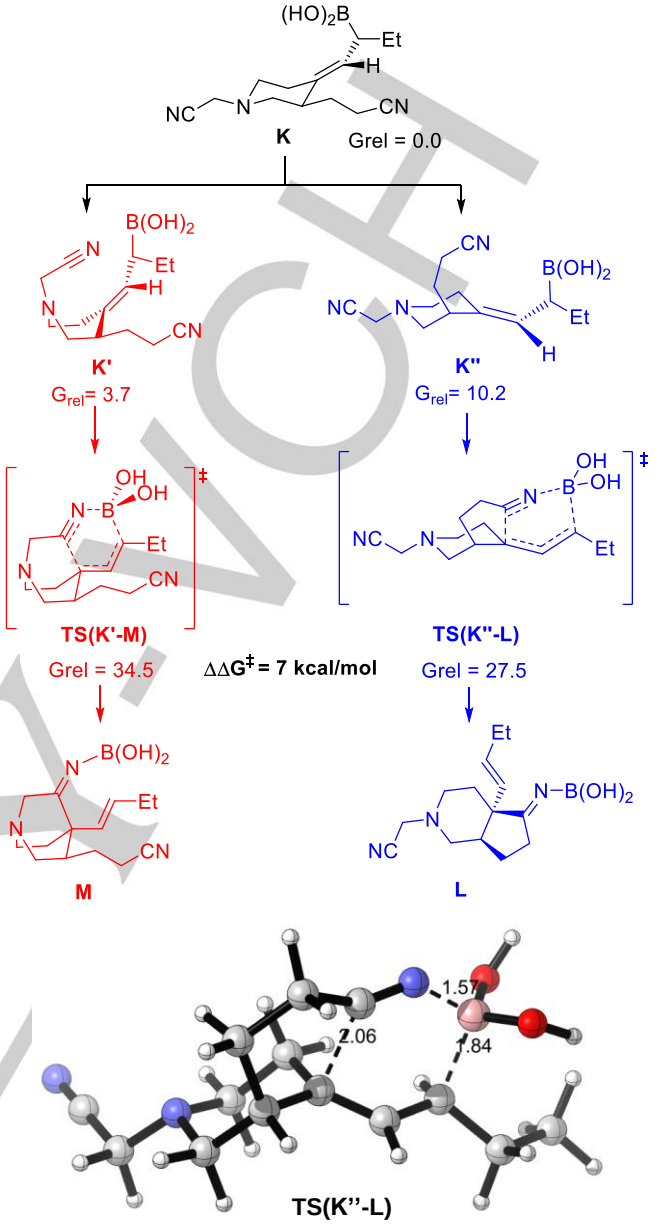
Scheme 6. a) Calculated pathways for the domino cyclization. b) Three-dimensional models for the different transition states located. The calculations were carried out at the M06-2X/6-311++G**(PCM, 1,4-dioxane) level. The relative Gibbs free energies are given in kcal·mol^{-1}. The three-dimensional structures of the transition states have been rendered with Cylview.[16]

The stationary points for both cyclization pathways were characterized. *Pathway a* involves i) chair/twist-boat isomerization (**G** to **G'**), ii) the α-attack of the alkenylboronic acid to the nitrile carbon atom through the transition state **TS(G'-H)**. This step featured an unreachable very high energy barrier of 62.2 kcal·mol^{-1}, and therefore it was discarded.[17] *Pathway b* consists on: i) 1,3-borotropic rearrangement to give allylboronic acid **J**, ii) chair to twist-boat isomerization to **J'** and iii) intramolecular allylborylation of the cyano group through the six-centered cyclic transition state **TS(J'-H)**. The transition state for the 1,3-borotropic rearrangement **TS(G-J)** featured the highest energy of this reaction profile, and therefore could be considered the rate determining step for the cyclization reaction. The activation barrier for this step (ΔG_{act} = 37.3 kcal·mol^{-1}) is very high, and this might explain why these reactions proceed only at 120 ºC and under microwave irradiation. Then, after the **J** to **J'** interconversion, **J'** undergoes cyclization to form **H** through the concerted transition state **TS(J'-H)** that could be seen as a bora-aza-ene reaction. An activation free energy of 29.0 kcal·mol^{-1} was obtained for the intramolecular allylboration step. Thus, the calculations point to the stepwise *pathway b* as the more likely reaction mechanism. Additionally, the requirement of a cyclic six-centered transition state explains nicely why the cyclization is observed exclusively with alkenylboronic acids, and not observed for the reactions with arylboronic acids.

The cyclization through the six-centered transition state was also studied for the allylboronic acid derived from *N*-tosylhydrazone **12** to account for the regioselectivity observed (Scheme 5, b). Assuming the 1,3-borotropic rearrangement step, the allylboronic acid intermediate **K** could evolve through the carboborylations of either of the cyano groups to boroimines **M** or **L** through the transition states **TS(K'-M)** and **TS(K''-L)** respectively (Scheme 7). The calculations are in agreement with the experimental observations, and indicate that the formation of the fused bicycle **L** is clearly favoured over the product of the transannular cyclization. Thus, the combination of theoretical and experimental results give further support to the proposed concerted bora-aza-ene mechanism.

It must be pointed the novelty of this cyclization mode: while the allylborations of carbonyl compounds and imines are very well known reactions,[18] there are very few examples of the analogous reaction with nitriles, and to the best of our knowledge, no intramolecular process had been previously reported.[19,20]

The reaction mechanism described above prompted us to consider other possible combinations that would generate an intermediate allylboronic acid able to participate in a bora-aza-ene reaction. We envisioned that the coupling of *N*-tosylhydrazones derived from α,β-unsaturated ketones with alkylboronic acids featuring a cyano substituent in the proper position might meet those requirements (Figure 3). Such a reaction would represent a conceptually new [n+1] cyclization under extremely simple reaction conditions.



Scheme 7. a) Representation of the DFT-calculated pathways that establish the preference of the fused towards the transannular cyclization in compound **12**. b) Three-dimensional model for the transition state **TS(K''-L)**. The calculations were carried out at the M06-2X/6-311++G**(PCM, 1,4-dioxane) level. The relative Gibbs free energies are given in kcal·mol^{-1}. The three-dimensional structures of the transition states have been rendered with Cylview.

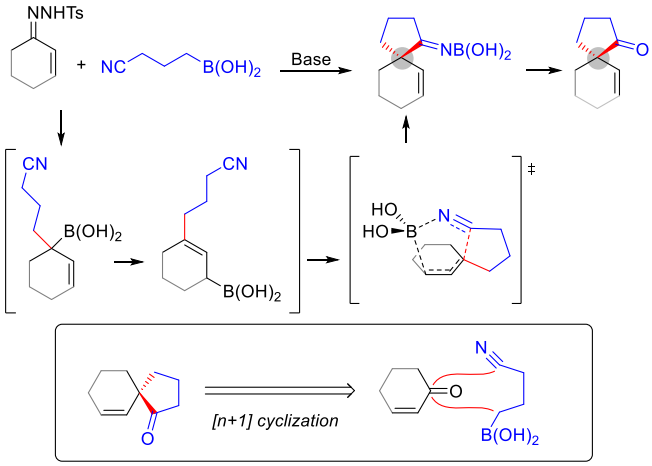
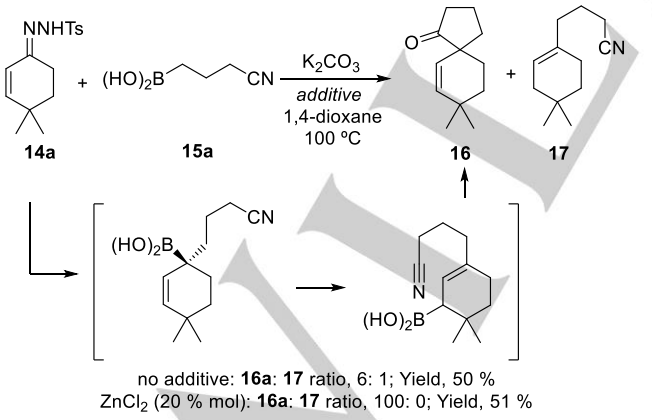


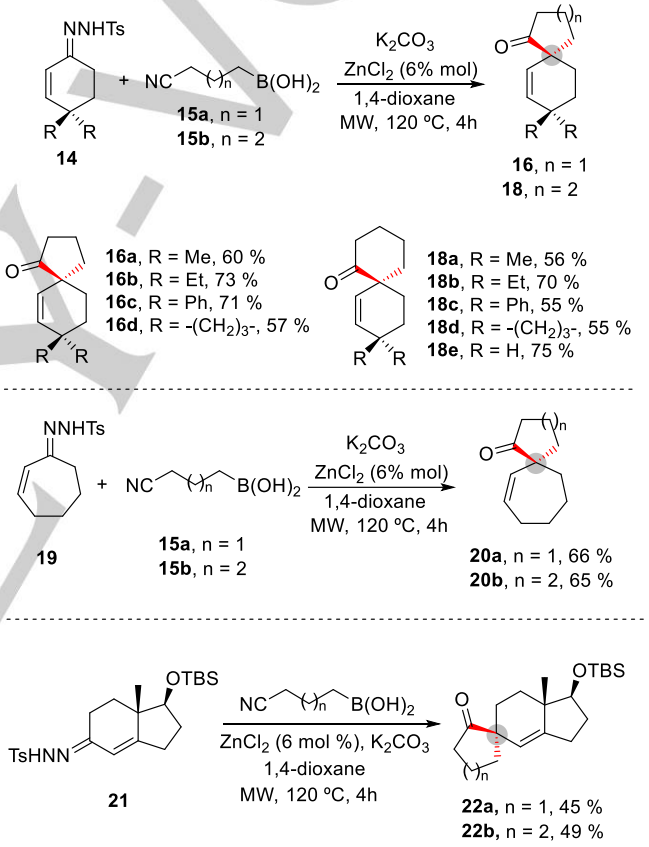
Figure 3. Proposal for a [n+1] cascade cyclization with α,β-unsaturated *N*-tosylhydrazones and cyanoalkylboronic acids.

The initial experiments were conducted with the *N*-tosylhydrazone of 4,4,-dimethylcyclohexenone **14a** and (3-cyanopropyl)boronic acid **15a,** and led to a mixture of the expected spirocyclic ketone **16a** and the alkene derived from the protodeboronation of the intermediate allylboronic acid **17** (scheme 8). Then, we tried the introduction of a Lewis acid with the idea of enhancing the electrophilicity of the nitrile group. Delightfully, when $ZnCl_2$ (0.1 M in 1,4-dioxane solution) was introduced, the formation of the protodeboronation product **17** was totally avoided and the spirocyclic ketone **16a** was exclusively obtained (Scheme 8). At this point the role of the $ZnCl_2$ is not clear,[21] but it should be pointed that it enhances the selectivity of the reaction, but *is not essential* for the cyclization to occur. Thus, an unprecedented [4+1] spirocyclization has occurred by formation of both a Csp^3-Csp^3 and a Csp^3-Csp^2 bonds on the hydrazonic carbon atom.



Scheme 8. Initial experiments on spirocyclization reactions between α,β-unsaturated *N*-tosylhydrazone **14a** and (3-cyanopropyl)boronic acid **15a** .

These reaction conditions were applied to a set of *N*-tosylhydrazones **14** derived from 4,4,-disubstituted cyclohexenones (Scheme 9). The cascade processes occurred successfully for the formation of the spirocyclic ketones **16** upon construction of a new five-membered ring in the reactions with (3-cyanopropyl)boronic acid **15a**, and to the spirocyclic ketones **18** featuring a new six-membered ring upon the employment of (4-cyanobutyl)boronic acid **13b**. Additionally, the cyclization proceeded successfully also with the cyclohepten-2-one *N*-tosylhydrazone **19**, giving rise to spiro[4.6]undec-6-en-1-one **20a** and spiro[5.6]dodec-7-en-1-one **20b** respectively (Scheme 9). These new spirocyclic scaffolds are very promising synthetic intermediates, as they present two points for orthogonal diversification, the carbonyl group and the unsaturation.



Scheme 9. Synthesis of spirocyclic ketones **16**, **18**, **20** and **22** through the [4+1] and [5+1] cyclizations. Reaction conditions for the domino spirocyclization: *N*-Tosylhydrazone **14, 19** (0.15 mMol), boronic acid **15** (0.3 mMol), K_2CO_3 (0.3 mMol), 1,4-dioxane (1.2 mL), $ZnCl_2$ (0.1 M in 1,4-dioxane ,100 μL), MW (120 ℃), 4h.

To test the applicability of the spirocyclization to more challenging substrates, we focused on trisubstituted α,β-unsaturated ketones. We found the venerable Hajos-Parrish ketone[22] a very appealing platform, which might also allow to study the diastereoselectivity of the reaction. Thus, the *N*-tosylhydrazone **21**, easily accessible from the Hajos-Parrish ketone,[23] was examined in the domino spirocyclization.[24] After some experimentation we found that the reactions with (4-

cyanoalkyl)boronic acids **15a** and **15b** proceeded successfully to give the spirocyclic ketones **22a** and **22b** respectively, and importantly, as a single stereoisomers (Scheme 9).[25] These are remarkable results, as the all-carbon quaternary stereocenters have been created in a diastereoselective manner on the optically pure material.

Conclussions

As summary, we have presented herein new heterocyclization and spirocyclization reactions based on the coupling between *N*-tosylhydrazones and boronic acids. The key of the domino cyclizations, as established by experiments and computational calculations, is the generation of an allylboronic acid intermediate that can undergo an intramolecular allylboration with a cyano group in a proper position through a bora-aza-ene reaction. Unprecedented functionalized alkaloid-like nitrogenated bicyclic structures featuring an all-carbon quaternary center can be constructed through this method. Additionally, a conceptually new [4+1] cascade spirocyclization reaction has been devised, which furnishes functionalized spirocycles, and that has been applied to the modification cyclohexenones, including the stereoselective spirocyclization of the Hajos-Parrish ketone. Undoubtfully, these new domino "diazo compound carboborylation / borotropic rearrangement / intramolecular allylborylation" reactions hold great potential in synthetic organic chemistry, and new applications will be reported in due course.

Experimental Section

General procedure for the reaction of *N*-tosylhydrazones with alkenylboronic acids under microwave irradiation to form compounds 3, 4, 5, 9, 10, 11 and 13

A microwave vial provided with a triangular stir bar was charged with the corresponding tosylhydrazone (0.15 mmol), the alkenyl boronic acid (0.30 mmol), K_2CO_3 (41.4 mg, 0.30 mmol) in 1.2 mL of dry 1,4-dioxane and 200 µL of dry DMF. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) were added and the layers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

General procedure for the spirocyclization reaction of *N*-tosylhydrazones with alkylboronic acids under microwave irradiation to form compounds 16, 18, 20 and 22

A microwave vial provided with a triangular stir bar was charged with the corresponding tosylhydrazone (0.15 mmol), the alkylboronic acid (0.30 mmol), K_2CO_3 (41.4 mg, 0.30 mmol) in 1.2 mL of dry 1,4-dioxane. To this vial was also added 100 µL of a commercial 0.1 M solution of $ZnCl_2$ in dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) were added and the layers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

Acknowledgements

Financial support of this work by Ministerio de Economía y Competitividad (MINECO) of Spain: Grant CTQ2016-76794-P (AEI/FEDER, UE). A FPU predoctoral fellowship (MECD) to MP and an Erasmus+ Traineeship (EU) to SP are gratefully acknowledged. We wish to thank Dr. Isabel Merino for her assistance on the NMR stereochemical studies.

Keywords: Boronic acids · *N*-tosylhydrazones · spiro compounds · domino reactions · diazo compounds.

[1] a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752. b) C. M. Marson, *Chem. Soc. Rev.* **2011**, *40*, 5514.

[2] a) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80. b) M. Garcia-Castro, L. Kremer, C. D. Reinkemeier, C. Unkelbach, C. Strohmann, S. Ziegler, C. Ostermann, K. Kumar, *Nat. Commun.* **2015**, *6*, 6516.

[3] For some recent reviews on all-carbon quaternary stereocenters: a) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181. b) T. Ling, F. Rivas, *Tetrahedron* **2016**, *72*, 6729.

[4] a) Y. Zheng, C. M. Tice, S. B. Singh, *Bioor. Med. Chem. Lett.* **2014**, *24*, 3673. b) F. Voss, S. Schunk, H. Steinhagen, in *Privileged Scaffolds in Medicinal Chemistry*; (Ed: S. Bräse), RSC, Cambridge, UK, **2016**, pp 439-458. c) G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe, J. Bajorath, *Chem. Eur. J.* **2017**, *23*, 703.

[5] Selected examples of transition-metal catalyzed cascade carbocyclizations by formation of two bonds on the same C atom: a) A. Yada, S. Fujita, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 7217. b) Y. Xia, Z. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 3013. c) M. Paraja, M. C. Pérez-Aguilar, C. Valdés, *Chem. Commun.* **2015**, *51*, 16241. d) M. Paraja, C. Valdés, *Chem. Commun.* **2016**, *52*, 6312. e) S.-S. Li, H. Lin, C.- F. Liu, Y.-Q. Xia, X.-M. Zhang, L. Dong, *Adv. Synth. Catal.* **2016**, 358, 1595. f) Á. Gutiérrez-Bonet, F. Juliá-Hernández, B. de Luis, R. Martin, *J. Am. Chem. Soc.* **2016**, 138, 6384. g) G.-W. Wang, N. G. McCreanor, M. H. Shaw, W. G. Whittingham, J. F. Bower, *J. Am. Chem. Soc.* **2016**, *138*, 13501. h) S. Xu, R. Chen, Z. Fu, Q. Zhou, Y. Zhang, J. Wang, *ACS Catalysis* **2017**, *7*, 1993.

[6] Selected examples of metal catalyzed cascade spirocyclizations by formation of two bonds on the same C atom: a) R. Barroso, M.-P. Cabal, R. Badia-Laino, C. Valdés, *Chem. - Eur. J.* **2015**, *21*, 16463. b) L. Bai, Y. Yuan, J. Liu, J. Wu, L. Han, H. Wang, Y. Wang, X. Luan, *Angew. Chem.* **2016**, *128*, 7060; *Angew. Chem. Int. Ed.* **2016**, *55*, 6946. c) Y. Liu, R.-J. Song, J.-H. Li, *Chem. Commun.* **2017**, *53*, 8600. d) Z. Zuo, H. Wang, L. Fan, J. Liu, Y. Wang, X. Luan, *Angew. Chem.* **2017**, *129*, 2811; *Angew.*

Chem. Int. Ed. **2017**, *56*, 2767. e) M. Pérez-Gómez, S. Hernández-Ponte, D. Bautista, J.-A. García-López, *Chem. Commun.* **2017**, *53*, 2842.

[7] a) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat. Chem.* **2009**, *1*, 494. b) C. Peng, W. Zhang, G. Yan, J. Wang, *Org. Lett.* **2009**, *11*, 1667. c) S. Nakagawa, K. A. Bainbridge, K. Butcher, D. Ellis, W. Klute, T. Ryckmans, *ChemMedChem* **2012**, *7*, 233. d) D. M. Allwood, D. C. Blakemore, A. D. Brown, S. V. Ley, *J. Org. Chem.* **2014**, *79*, 328. e) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem.* **2012**, *124*, 6055; *Angew. Chem., Int. Ed.* **2012**, *51*, 5953. f) M. Plaza, M. C. Pérez-Aguilar, C. Valdés, *Chem. - Eur. J.* **2016**, *22*, 6253. g) M. Paraja, M. Plaza, C. Valdés, *Synlett* **2017**, *28*, 2373.

[8] M. Plaza, C. Valdés, *J. Am. Chem. Soc.* **2016**, *138*, 12061.

[9] For the definition and synthetic applications of domino reactions see: a) L. F. Tietze, Chem Rev. 1996, 96, 115. b*) Domino reactions, Concepts for efficient organic synthesis*. Ed: L. F. Tietze, Wiley-VCH, Weinheim, Germany, **2014**.

[10] a) M. I. Rodríguez-Franco, I. Dorronsoro, A. Castro, Martínez, A. Badía, J. E. Baños, *Bioor. Med. Chem.* **2003**, *11*, 2263. b) T. C. Nugent, R. Seemayer, *Org. Process. Res. Dev.* **2006**, *10*, 142. c) A. A. Mazurov, D. C. Kombo, T. A. Hauser, L. Miao, G. Dull, J. F. Genus, N. B. Fedorov, L. Benson, S. Sidach, Y. Xiao, P. S. Hammond, J. W. James, C. H. Miller, D. Yohannes, *J. Med. Chem.* **2012**, *55*, 9793. d) J. Y. Soni, S. Sanghvi, R. V. Devkar, S. Thakore, *RSC Advances* **2015**, *5*, 82112. e) J. Cook, F. C. Zusi, I. M. McDonald, D. King, M. D. Hill, C. Iwuagwu, R. A. Mate, H. Fang, R. Zhao, B. Wang, J. Cutrone, B. Ma, Q. Gao, R. J. Knox, M. Matchett, L. Gallagher, M. Ferrante, D. Post-Munson, T. Molski, A. Easton, R. Miller, K. Jones, S. Digavalli, F. Healy, K. Lentz, Y. Benitex, W. Clarke, J. Natale, J. A. Siuciak, N. Lodge, R. Zaczek, R. Denton, D. Morgan, L. J. Bristow, J. E. Macor, R. E. Olson, *J. Med. Chem.* **2016**, *59*, 11171. f) M. D. Hill, H. Fang, S. V. Digavalli, F. L. Healy, L. Gallagher, D. Post-Munson, P. Chen, J. Natale, Y. Benitex, D. Morgan, N. Lodge, L. Bristow, J. E. Macor, R. E. Olson, *Bioor. Med. Chem. Lett.* **2017**, *27*, 578. g) M. Quadri, C. Matera, A. Silnović, M. C. Pismataro, N. A. Horenstein, C. Stokes, R. L. Papke, C. Dallanoce, *ChemMedChem* **2017**, *12*, 1335. h) D. O' Donovan, P Aillard, M. Berger, A. de la Torre, D. Petkova, C. Knittl-Frank, D. Geerdink, M. Kaiser, N. Maulide, *Angew. Chem. Int. Ed.* **2018**, doi:10.1002/anie.201804551.

[11] a) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore, S. V. Ley, *Nat. Chem.* **2016**, *8*, 360. b) J.-S. Poh, S.-H. Lau, I. G. Dykes, D. N.; Tran, C.; Battilocchio, S. V. Ley, *Chem. Sci.* **2016**, *7*, 6803. c) J. A. Forni, S.-H. Lau, J.-S. Poh, C. Battilocchio, S. V. Ley, J. C. Pastre, *Synlett*, **2018**, *29*, 825.

[12] See Suporting Information for computational details and a further discussion.

[13] The computational calculations were carried out with the Gaussian09 package of programs: Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.

[14] a) A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó, E. Fernández, *Org. Biomol. Chem.* **2015**, *13*, 9659. b) C. Bomio, M. A. Kabeshov, A. R. Lit, S. Lau, J. Ehlert, C. Battilocchio, S. V. Ley*, Chem. Sci.*, **2017**, *8*, 6071.

[15] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org)

[16] For some key references on 1,3-borotropic rearrangements: a) K. G. Hancock, J. D. Kramer, *J. Am. Chem. Soc.* **1973**, *95*, 6463. (b) H. Miyamoto, D. L. Silverio, A. H. Hoveyda, *Angew. Chem.* **2016**, *128*, 4779; *Angew. Chem. Int. Ed.* **2016**, *55*, 4701 and references cited therein.

[17] For the silver catalyzed addition of boronates to aromatic nitriles: W. Zhao, J. Montgomery, *Angew. Chem.* **2015**, *127*, 12683; *Angew. Chem. Int. Ed.* **2015**, *54*, 12683.

[18] a) P. V. Ramachandran, P. D. Gagare, D. R. Nicponski, in *Comprehensive Organic Synthesis* 2nd Ed. *Vol. 2.* (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, Netherlands, **2014**, pp 2-71. b) C. Diner, K. J. Szabó, *J. Am. Chem. Soc.* **2017**, *139*, 2.

[19] R. W. Hoffmann, I. Münster, *Tetrahedron Lett.* **1995**, 36, 1431.

[20] a) A. Meller, W. Gerger, *Monatsh. Chem.* **1974**, *105*, 684. b) L. I. Lavrinovich, A. V. Ignatenko, Y. N. Bubnov, *Russ. Chem. Bull.* **1992**, *41*, 2051.

[21] Zinc salts have been reported to increase the rate of 1,3-borotropic rearrangements by coordination with the oxygen or nitrogen atoms of boronates and aminoboranes respectively (ref 12).

[22] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

[23] a) R. C. A. Isaacs, M. J. Di Grandi, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 3938. b) S. Yamashita, K. Iso, M. Hirama, *Org. Lett.* **2008**, *10*, 3413.

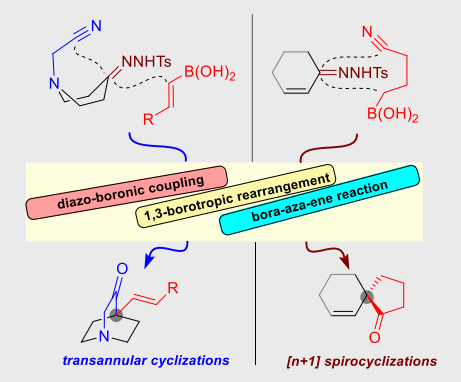
[24] For previous spirocyclization reactions of Hajos-Parrish ketone derivatives see: M. Asim, D. Klonowska, C. Choueiri, I. Korobkov, K. E. Carlson, J. A. Katzenellenbogen, T. Durst, *Bioor. Med. Chem. Lett.* **2012**, *22*, 3713.

[25] The stereochemistry of compounds **22a** and **22b** was assigned through two-dimensional NMR studies. See SI for details.

Entry for the Table of Contents (Please choose one layout)

FULL PAPER

Two bonds on the same carbon are formed in transannular cyclizations and [n+1] spirocyclizations involving properly designed *N*-tosylhydrazones and boronic acids, that lead to polycyclic structures featuring an all-carbon quaternary bridgehead center. The proposed mechanism for the domino processes involves carboborylation of a diazo compound a 1,3-borotropic rearrangement, and intramolecular bora-aza-ene reaction.



*Manuel Plaza, Stefano Parisotto and Carlos Valdés**

Page No. – Page No.

Heterocyclization and spirocyclization processes based on domino reactions of *N*-tosylhydrazones and boronic acids involving intramolecular allylborylations of nitriles