A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Synthesis of Pyrrolidines by a Csp3-Csp3/Csp3-N Transition Metal-free Domino Reaction of Boronic Acids with γ-Azido-N-Tosylhydrazones

Authors: Lucía Florentino, Lucía López, Raquel Barroso, María P. Cabal, and Carlos Valdés

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202010528

Link to VoR: https://doi.org/10.1002/anie.202010528

WILEY-VCH

10.1002/anie.202010528

RESEARCH ARTICLE

WILEY-VCH

Synthesis of Pyrrolidines by a Csp^3-Csp^3/Csp^3-*N* Transition Metal-Free Domino Reaction of Boronic Acids with γ-Azido-*N*-Tosylhydrazones

Lucía Florentino, Lucía López, Raquel Barroso, María-Paz Cabal and Carlos Valdés*[a]

To the memory of Prof. Kilian Muñiz.

[a] Dr. L. Florentino, L. López, Dr. R. Barroso, Prof. Dr. M.-P. Cabal, Prof. Dr. C. Valdés[a]*
Departamento de Química Orgánica e Inorgánica. Instituto 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.

Abstract: The reaction between γ-azido-*N*-tosylhydrazones and boronic acids leads to the obtention of 2,2-disubstituted pyrrolidines in a domino process that includes 1) diazoalkane formation, 2) intermolecular carboborylation of the diazocompound and 3) intramolecular carborylation of the azide, and comprises the formation of a Csp^3-Csp^3 and a Csp^3-N bonds on the same carbon atom. The reaction proceeds without the need of any transition metal catalyst under microwave activation, and features wide scope in both reaction partners. In particular, it can be applied to both alkyl and arylboronic acids with equal efficiency. Importantly, with *N*-tosylhydrazones derived from 2-(2-azidoethyl)-cyclopentanone and cyclohexanone the reactions are highly diastereoselective leading to the *cis*-fused bicyclic systems as unique diastereoisomers. The scope of the process is illustrated by over sixty examples, including scaffolds present in natural alkaloids, and the mechanistic proposal is suppported by DFT-based computations.

Introduction

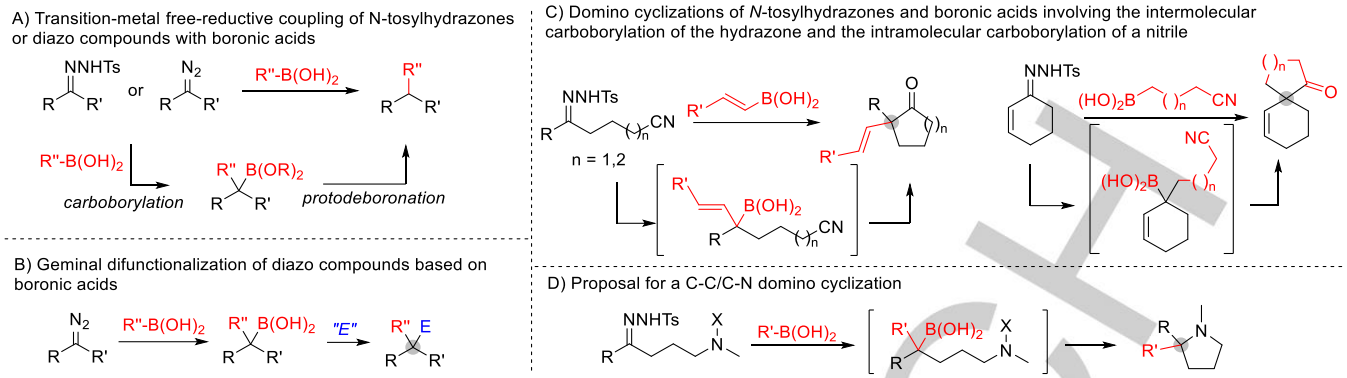
The transition metal-free reductive coupling of *N*-sulfonylhydrazones or diazo compounds with boronic acids[1-3] is a very useful C-C bond forming transformation that have found wide applications in the recent years.[4,5] The key step in these reactions is the geminal carboborylation of a diazo compound to generate a homologated boronic acid, which suffers a spontaneous protodeboronation under the reaction conditions to deliver the coupling product with formation of a Csp^3-C and a Csp^3-H bonds on the former hydrazonic carbon atom (scheme 1, A). Interestingly, if the protodeboronation is avoided, the intermediate boronic acid can be engaged in a subsequent reaction, and therefore, a double functionalization on the same center can be accomplished in a straightforward manner (scheme 1, B). This approach has been pioneered by Ley's group employing diazo compounds generated under mild conditions through continuous flow methodologies.[6] In an alternative approach, we have recently developed various C-C/C-C domino processes in which the allylboronic acid intermediate generated by reactions of appropriate *N*-tosylhydrazones and boronic acids are trapped in an intramolecular fashion by a cyano group placed in a strategic position (scheme 1, C).[7] These reactions lead to cyclopentanones and cyclohexanones featuring an all-carbon quaternary sterocenter. Interestingly, the carbocyclization and the incorporation of a side chain occur during the domino reaction giving remarkable versatility to these processes. To expand the concept of these domino cyclizations with incorporation of a side chain, we decided to explore the possibility of achieving a C-C/C-N bond forming sequence. Such a reaction might allow the synthesis of saturated nitrogenated heterocycles through a geminal carboamination reaction.[8] To that purpose, a molecule featuring the *N*-tosylhydrazone and an electrophilic aminating group[9] compatible with the reaction conditions, should be designed (scheme 1, D).

Diazoalkane precursors such as *N*-tosylhydrazones have found remarkable applications in the synthesis of pyrrolidines and other saturated nitrogen heterocycles through intramolecular metal catalyzed C-H insertion reactions.[10] Moreover, transition-metal catalyzed C-H aminations[11] based on azides[12] and other nitrene precursors[13] have been recently developed as efficient alternatives for the construction of pyrrolidines.

The metal-catalyzed amination of boronates is a very well known transformation.[14] However, transition-metal free methods are rare,[15] and are either restricted to arylboronic acids,[16] or require electrophilic aminating agents and reaction conditions incompatible with the carboborylation of *N*-tosylhydrazones.[17] Indeed, the real challenge of this approach would be to find a nitrogenated functionality that will not react with a boronic acid in an intermolecular fashion but still reactive to participate in an intramolecular process. For this reason, we turned our attention to azides. The amination of arylboronic acids with azides has been previously described, but shows limited scope.[18] Moreover, alkyl boronates have been transformed into amines by reaction with azides, but the processes involve the transformation of the boronate into an alkyltrifluoroborate salt, and then to a highly reactive alkyldichloroborane, and not the direct reaction of a boronic acid.[19,20]

This article is protected by copyright. All rights reserved.

Accepted Manuscript



Scheme 1. A) Reductive cross-couplings of *N*-tosylhydrazones with boronic acids. B) Geminal difunctionalization of diazoalkanes through sequential reactions involving carboborylation of the diazoalkane followed by a subsequent transformation. C) C-C/C-C bond forming domino cyclizations of *N*-tosylhydrazones and boronic acids involving the intermolecular carboborylation of the hydrazone and the intramolecular carboborylation of a nitrile. D) Synthetic plan for a C-C/C-N bond forming domino cyclization.

Nevertheless, we decided to study a possible intramolecular cascade reaction involving an azide as the electrophilic aminating agent. We expected that the relative high temperatures which can be employed for the reaction of *N*-tosylhydrazones with boronic acids might promote in first place the carboborylation of the *N*-tosylhydrazone, and subsequenly the intramolecular reaction of the azide with the transient tertiary alkyl boronic acid. Herein we wish to present our results that have led to a quite general synthesis of 2,2-disubstituted pyrrolidines through a C-C/C-N domino cyclization, via an experimentally very simple and catalyst-free process.

Results and Discussion

We selected γ-azido-*N*-tosylhydrazone **1a** as the template to study the domino reaction. The initial experiments were carried out with (*E*)-(3-phenylprop-1-en-1-yl)boronic acid and 4-methoxylphenylboronic acid, (scheme 2, A) (see SI for further details). The conditions were also similar to those employed in reductive cross-couplings with *N*-tosylhydrazones: K_2CO_3 as base, 1,4-dioxane as solvent, and microwave thermal activation. The reactions with the alkenylboronic acid were quite sluggish, although the expected pyrrolidine could be detected in very poor yield. However, the reaction with 4-methoxyphenylboronic acid took place nicely at 150 ºC in only 1h, giving rise to the pyrrolidine **3a** in 70 % yield (scheme 2, A). After some experimentation it was determined that microwave irradiation for 1h at 150 ºC were indeed optimum conditions for the reaction.

We then started to study the scope of the reaction regarding the arylboronic acid. It was observed that the electronic properties of the boronic acid played a decisive role in the outcome of the process (scheme 2, A). The reactions with electron-rich arylboronic acids gave rise to the pyrrolidines **3** as unique reaction product, however, the absence of electron-donating groups or the presence of electron-withdrawing substituents provided a mixture of the pyrrolidine **3** and the open-chain product **4**. Noteworthy, an increasing ratio of **4** is obtained with the more electronwithdrawing character of the substituent: see the series **3a** to **3i**.

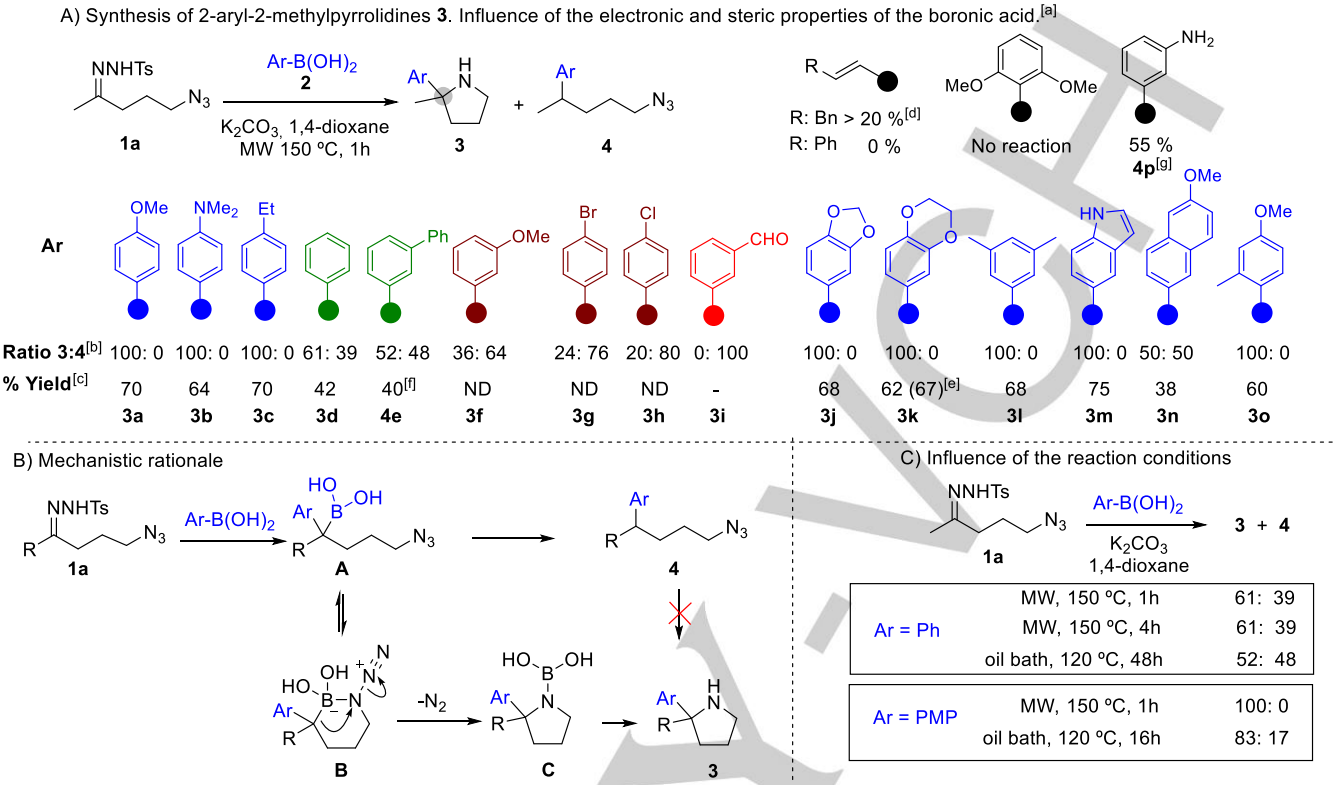
The azide **4** is the expected product of the reductive arylation of the *N*-tosylhydrazone **1a** with the boronic acid, which takes place through the formation of the benzylboronic acid **A**, followed by the spontaneous protodeboronation (scheme 2, B). Alternatively, after the generation of **A**, coordination of the azide to the boron center would form boronate **B**. Then, complex **B** could undergo 1,2-migration of the tertiary carbon substituent, with formation of the C-N bond and release of a molecule of nitrogen to form *N*-boropyrrolidine **C**, which will furnish pyrrolidine **3** upon hydrolysis. According to this mechanistic proposal, the ratio of the products **3** and **4** will be determined by the balance between the rates of the protodeboronation of **A** and the 1,2-migration reaction respectively. Therefore, with electronwithdrawing substituents on the aromatic ring, which are known to accelerate the protodeboronation of benzylboronic acids,[21] the formation of **4** increases, while with electron-donating substituents, that slow down the protodeboronation, formation of the pyrrolidines **3** will be favoured.

Interestingly, the reaction with phenylboronic acid gives exactly the same ratio of products **3d** and **4d** after 1h and after 4h at 150 °C (scheme 2, C), indicating that once azide **4d** is formed, it does not undergo cyclization, ruling out a possible **4** to **3** conversion through a C-H insertion reaction as an alternative mechanism. Finally, the formation of the pyrrolidines takes place also under conventional heating (sealed tube,1,4-dioxane, oil bath, 120 ºC, overnight), as demonstrated in the reactions with phenylboronic acid and *p*-methoxyphenylboronic acid, however, a slight increase in the formation of non-cyclized azides **4d** and **4a** was observed (scheme 2, C). For this reason, we kept the MW heating method as the experimental conditions of choice over this work. Noteworthy, even with the limitations described, the reaction features remarkable synthetic interest provided that electron-neutral or electron-rich aryl boronic acids are employed, as demonstrated by some further examples (scheme 2, A) which include several substituted phenylboronic acids (**3j**-**3l**) and also condensed (**3n**) derivatives. Interestingly, the presence of an NH- unprotected indole (**3m**) is well tolerated in the reaction. However, the reaction with 3-aminophenylboronic acid, featuring a free NH_2 provided exclusively the open chain azide **4p** with moderate yield. The process is compatible with ortho substitution in the aromatic ring, as an electron-rich *o*-substituted boronic acid provided the expected pyrrolidine with acceptable

This article is protected by copyright. All rights reserved.

Accepted Manuscript

yield (**3o**), however in the reaction with 2,6-dimethoxyphenylboronic acid no pyrrolidine **3** was detected.



Scheme 2. A) Synthesis of 2-aryl-2-methylpyrrolidines **3** from γ-azido-*N*-tosylhydrazone **1a** and arylboronic acids: Influence of the electronic and steric properties of the arylboronic acids. B) Mechanistic proposal to justify the formation of compounds **3** and **4**. C) Influence of the reaction conditions on the **3**: **4** ratio. [a] Reaction conditions: *N*-tosylhydrazone **1a** (0.3 mmol), boronic acid **2** (0.6 mmol), K_2CO_3 (0.9 mmol), 1,4-dioxane (2.5 mL), 150 ºC (MW), 1h. [b] Determined by ^{1}H NMR of the reaction crude. [c] Isolated yield of pure **3** after acid-base extraction or column chromatography. [d] The pyrrolidine could be detected by ^{1}H NMR and GC/MS in small amount. [e] Isolated yield after in situ acetylation. [f] Isolated yield of the azide **4e**. [g] No pyrrolidine **3** was formed.

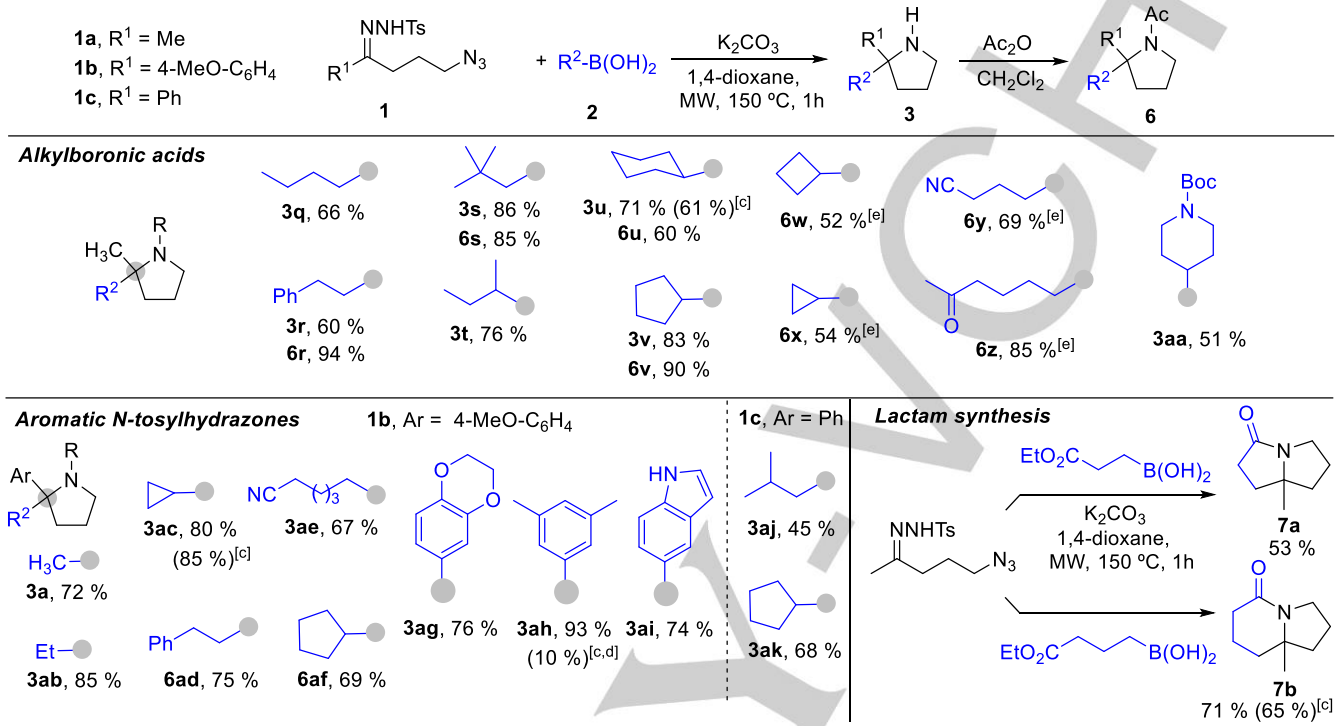
The domino process was then studied with alkylboronic acids (scheme 3). Interestingly, the pyrrolidines **3** were obtained as the only reaction product, which could be isolated upon acid-base extraction, or as the acetamides **6** after in situ acetylation to enable easier isolation. The reaction is compatible with primary boronic acids (*n*-butyl **3q**, phenethyl **3r**, neopentyl, **3s**) as well as secondary, both linear (*sec*-butyl **3t**), and cyclic (cyclohexyl **3u**, cyclopentyl **3v**, cyclobutyl **6w,** cyclopropyl **6x**) with good yields. Clearly, the protodeboronation of the intermediate tertiary boronic acid **A** substituted only with alkyl groups is slower than for the benzylboronic acids, favouring the cyclization process. The functional group tolerance of the reaction is also remarkable, as functionalized boronic acids, such as 4-cyanobutylboronic acid and 5-oxohexylboronic acid featuring an unprotected carbonyl and a nitrile functionalities respectively, were both competent coupling partners for the reaction (**6y** and **6z** respectively). To further illustrate the synthetic versatility of the reaction, the important 4-piperidyl heterocyclic moiety was also introduced efficiently (**3aa**). It must be pointed that in these reactions, due to the instability of some alkylboronic acids under the reaction conditions, a 3:1, boronic acid: hydrazone ratio was required to achieve high isolated yields.

Regarding the structure of the *N*-tosylhydrazone, the reaction is not restricted to alkyl substituted systems. In fact, hydrazones derived from arylketones are also compatible with the cyclization reaction (scheme 3). As expected, *N*-tosylhydrazone **1b** (Ar = 4-$MeOC_6H_4$) with an electron-donating substitutent in the aryl ring provided higher yields of the pyrrolidines than *N*-tosylhydrazone **1c** (Ar = Ph). This observation is in agreement with the mechanistic model. The same type of intermediate benzylboronic acid **A** (scheme 2, B) can be obtained combining an alkylboronic acid and an aryl substituted *N*-tosylhydrazone, or an arylboronic acid with the alkyl substituted *N*-tosylhydrazone. Therefore, the same evolution of intermediate **A** should be expected regardless of the starting materials. Moreover, *N*-tosylhydrazone **1b** could be combined with methyl, primary and secondary alkylboronic acids, to give 2-alkyl-2-arylpyrrolidines (**3a**, **3ab**, **3ac**, **6ad**, **6af**) and with arylboronic acids to give 2,2-diarylpyrrolidines (**3ag**, **3ah, 3ai**). Thus, the same methodology can be applied to prepare 2,2-dialkyl, 2,2-diaryl, and 2-alkyl-2-arylpyrrolidines, revealing the high versatility of the domino reaction. Furthermore, the reaction could be applied for the direct synthesis of the bicyclic lactams **7** by employing boronic acids featuring an ester functionality. In these cases, the amino ester initially formed undergoes spontaneous lactamization under the reaction conditions. These transformations may represent a straightforward entry into novel pyrrolizidine and indolizidine structures, commonly present in many bioactive alkaloids.[22,23] Finally, as previously mentioned for **3a**, these

This article is protected by copyright. All rights reserved.

Accepted Manuscript

domino reactions are not totally limited to the employment of microwave heating, and proceed also under conventional heating at 120 ºC overnight. Comparable yields were obtained for 2,2-dialkylpyrrolidines and 2-alkyl-2-arylpyrrolidines (see the selected examples **3u**, **3ac** and **7b)**. However, in the case of the 2,2,-diarylpyrrolidine **3ah**, under conventional thermal conditions the cyclization product was obtained in a very poor 10 % yield, and the major product of the reaction was the azide **4** derived from the reductive alkylation.



Scheme 3.[a, b] Scope of the C-C/C-N domino cyclization with γ-azido-*N*-tosylhydrazones and boronic acids. [a] Reaction conditions as in Scheme 2, boronic acid **2** (2-3 equiv). [b] Isolated yields after acid-base extraction or column chromatography. [c] Yield of the reaction under conventional heating at 120 ºC overnight. [d] A 70 % isolated yield for the open chain azide **4** was obtained. [e] In situ acetylation was required to facilitate isolation

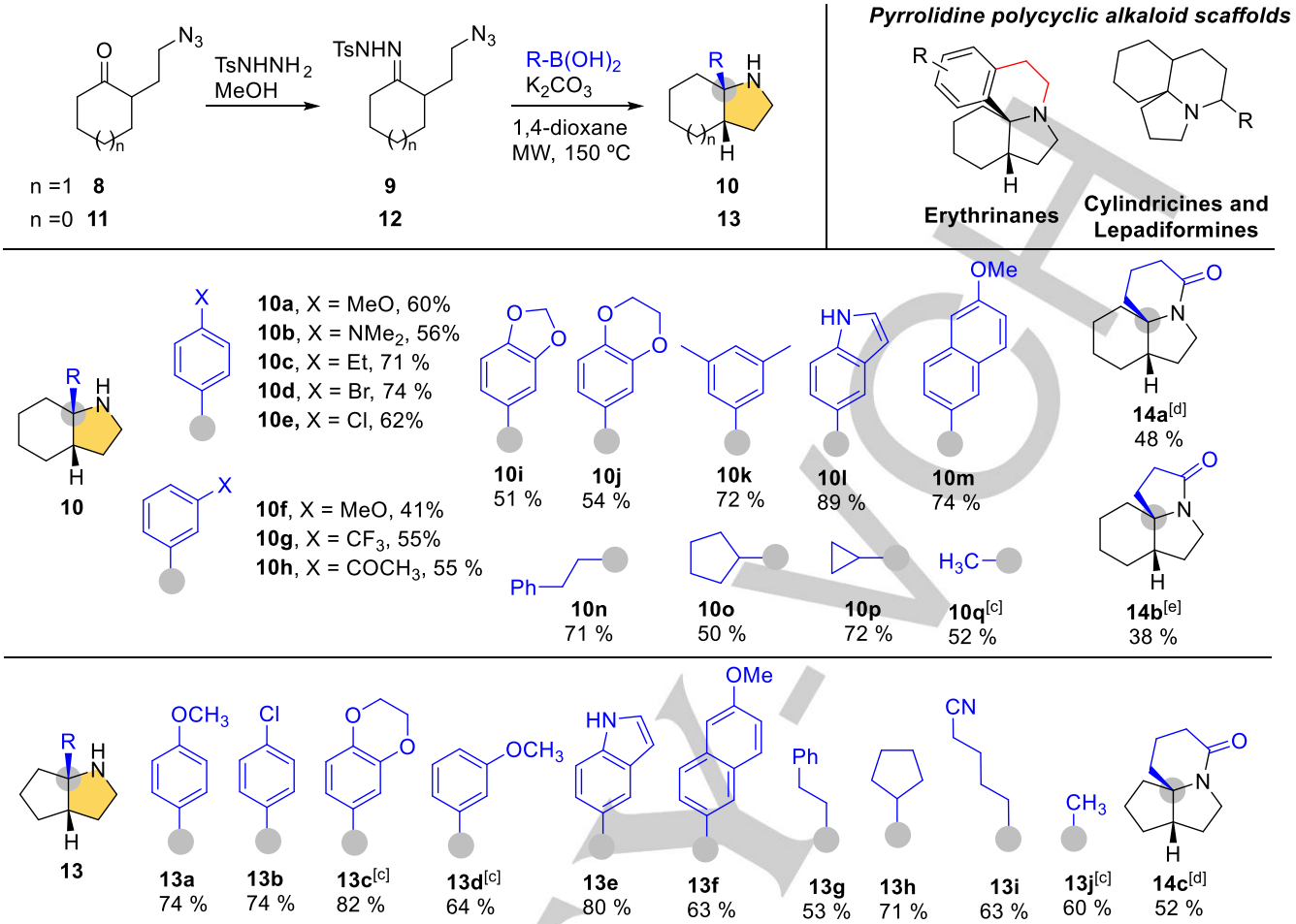
One challenge in the transition-metal-free reactions of boronic acids with diazoalkanes or *N*-tosylhydrazones is to control the stereochemistry of the processes. This issue still remains unsolved for most linear diazoalkanes. However, we have previously demonstrated that it is possible to conduct diastereoselective reactions when *N*-tosylhydrazones derived from substituted cyclic ketones are employed.[4b,7] Thus, the diastereoselectivity of the domino C-C/C-N cyclization process was examined on cyclic systems. We chose as our model the *N*-tosylhydrazone **9** derived from 2-(2-azidoethyl)cyclohexan-1-one **8**. To our delight, the domino processes took place efficiently to yield a single diasteroisomer of the octahydro-1*H*-indole derivatives **10** that corresponded to the *cis*-fused bicyclic system (scheme 4). Noteworthy, the stereochemistry observed is in agreement with our previous observations on the diastereoselective reactions of cyclic *N*-tosylhydrazones.[4b,7]

Similarly, the cascade cyclization was also examined with the analogous five-membered ring *N*-tosylhydrazone **12**. The reactions proceeded also with total diastereoselectivity to render the *cis*-fused substituted octahydrocyclopenta[*b*]pyrroles **13** as single diastereoisomers (scheme 4).

The scope of the reactions with the cyclic *N*-tosylhydrazones **9** and **12** is remarkable. The bicyclic amines **10** and **13** were obtained for the reactions with arylboronic acids (**10a-10m; 13a-13f**) with moderate to good yields, including the incorporation of a condensed aromatic system (**10m**, **13f**), and an unprotected N-H-indole (**10l**, **13e**). Importantly, these reactions are less sensitive to the electronic nature of the aryl boronic acid than the reactions with the linear hydrazone **1a**, and even boronic acids substituted with electronwithdrawing substituents led to the bicyclic products with high yields (**10d**, **10e, 10g**, **10h** and **13b**). In particular, the synthetically versatile chloro- and bromophenyl fragments could be introduced with high efficiency. Also, the process proceeded successfully in the presence of an unprotected carbonyl (**10h**). The different behavior of the cyclic systems when compared with the linear *N*-tosylhydrazone **1a** could be rationalized considering that the more hindered tertiary boronic acid generated upon carboborylation of the cyclic diazo compound is less prone to undergo protodeboronation than in the case of intermediate **A** (scheme 2, B), enabling the cyclization pathway. Moreover, the reaction allows also the introduction of aliphatic rests at the angular position through the employment of primary (**10n**, **13g**) and secondary alkylboronic acids (**10o**, **10p**, **13h**), as well as functionalized substituents such as the 5-cyanobutyl (**13i**). Finally, bicyclic systems featuring an angular methyl group, a motif present in many natural products, could be prepared employing methylboronic acid (**10q**, **13j**).

This article is protected by copyright. All rights reserved.

Accepted Manuscript



Scheme 4.[a, b] Diastereoselective C-C/C-N domino cyclization with γ-azido-*N*-tosylhydrazones **9** and **12** and boronic acids. Synthesis of *cis*-fused octahydro-1*H*-indoles **10** and octahydrocyclopenta[b]pyrroles **13** respectively. [a]] Reaction conditions as in Scheme 2, boronic acid **2** (2-3 equiv). [b] Isolated yields after acid-base extraction or column chromatography. [c] Obtained as the corresponding acetamides **10Ac** and **13Ac** upon in situ acetylation to facilitate isolation. [d] Prepared from EtO_2C-$(CH_2)_3$-$B(OH)_2$. [e] Prepared from MeO_2C-$(CH_2)_2$-$B(OH)_2$

The octahydro-1*H*-indole substructure of bicyclo **10** is present in natural alkaloids and biologically active molecules such as the erythrina alkaloids,[24] and in particular, aryl substituted octahydro-1*H*-indoles such as **10a** and **10h** have been employed in the synthesis of erythrinanes and homoerythrinanes.[25] Additionally, when the reactions were conducted with the alkoxycarbonyl containing boronic acids, the corresponding tricyclic lactams **14** were obtained as unique stereoisomers. It is noteworthy that these relative complex tricyclic scaffolds, which resemble the basic structure of several natural alkaloids such as lepadiformines and cylindricines,[26] are assembled in one single step from readily available materials. Therefore, this methodology might be adapted into convergent approaches to novel alkaloid-like interesting polycyclic moieties.

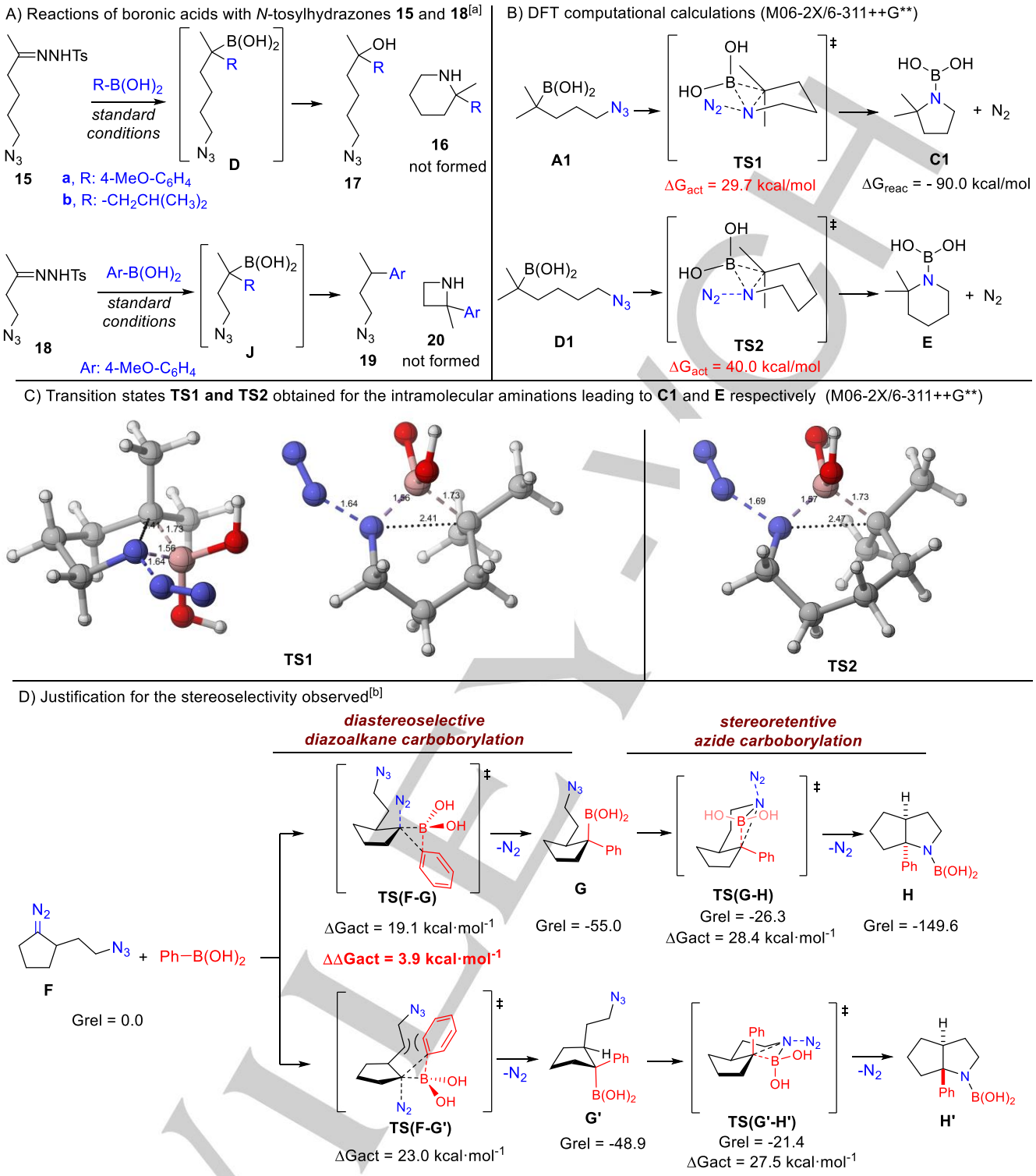
The cascade process seems to be limited to the construction of pyrrolidines. When the same reaction was conducted with the δ-azido-*N*-tosylhydrazone **15** the analogous piperidines **16** were not obtained. The reactions with both an electron-rich arylboronic acid and an alkylboronic acid led to the tertiary alcohols **17** (scheme 5, A). In these reactions the protodeboronation of the tertiary boronic acids **D** is very slow, but the cyclization seems to be also disfavoured. Therefore, after the carboborylation to give the intermediate boronic acid **D**, autooxidation of the boronic acid occurs to give the observed alcohols **17**. A justification of the different behavior of *N*-tosylhydrazones **1** and **15** based on DFT computations is provided below. Also, the reaction of *N*-tosylhydrazone **18** with *p*-MeO-Ph-$B(OH)_2$ gave the reductive alkylation azide **19** instead of azetidine **20**. Thus, the protodeboronation of intermediate **J** is favoured towards the formation of the highly strained four-membered ring (Scheme 5, A).

Mechanistic considerations

The formation of the pyrrolidines by reaction γ-azido-*N*-tosylhydrazones and boronic acids can be explained by the domino process proposed in scheme 2, B. To provide additional support to this proposal, the intramolecular amination of the boronic acid was studied through DFT calculations starting from the model system **A1** (scheme 5, B) (see SI for further details). According to the calculations, the conversion of **A1** into **C1** takes place in one single concerted step, where the boronate species is indeed a saddle point (**TS1**) and not an intermediate in the potential energy surface. **TS1** features a six-centers chair-like arrangement (scheme 5, C), and reveals that the process is indeed highly asynchronous, since in **TS1** the new N-B bond is highly developed ($d_{B\text{-}N}$ = 1.56 Å) but the C-N distance of the new

This article is protected by copyright. All rights reserved.

Accepted Manuscript



Scheme 5. A) Reactions of boronic acids with δ-azido-*N*-tosylhydrazone **7**. B**)** DFT computational calculations for the intramolecular amination of a boronic acid with an azide for the construction of pyrrolidines and piperidines at the M06-2X/6-311++G** level**.** C) 3D representations of the transition states for the intramolecular carboborylation of the azides **A1** and **D1**. D) DFT-based modelling of the diastereoselective carboborylation / stereoretentive carboborylation at the M06-2X/6-311++G** (PCM) level. [a] Reaction conditions as in scheme 5. [b] Gibbs free energies in kcal·mol^{-1}.

bond is still very long ($d_{C\text{-}N}$ = 2.41 Å). A Gibbs free energy of activation of 29.7 kcal/mol was obtained for the transformation, an accessible energy barrier for reactions take place at high temperature. As previously discussed, the formation of piperidines from δ-azido-*N*-tosylhydrazone **15** does not take place under the same conditions (scheme 5, A). Starting from model system **D1**, a similar transition state **TS2** was found for the conversion of **D1** into **E**. However, a much higher energy barrier of 40 kcal/mol was obtained [ΔG_{act}(**D1→E**) − ΔG_{act}(**A1→C1**) = 10.3 kcal·mol^{-1}], which justifies clearly why in

This article is protected by copyright. All rights reserved.

Accepted Manuscript

this case the cyclization reaction does not occur, and instead the intermediate boronic acid evolves through an alternative reaction pathway. The remarkable difference in the activation Gibbs free energies of both processes could be understood considering that the transition state **TS1** features a nearly perfect six-membered ring chair-like arrangement (scheme 5, C), while **TS2** consists on a less favoured seven-membered ring.[27]

The diastereoselectivity observed in the synthesis of octahydroindoles **10** and octahydrocyclopenta[*b*]pyrroles **13** can be also rationalized in agreement with the mechanistic proposal, and considering 1) a diastereoselective carboborylation of the diazo compound,[28,29] 2) a stereoretentive carboborylation of the azide. Retention of configuration on the latter step is expected considering that 1,2-migrations of boronate complexes are stereospecific and proceed with retention of configuration on the migrating group.[17a,20,30] Therefore we propose that the stereochemistry must be defined in the first step. DFT-based computations were carried out on these stereoselective reactions to support this proposal (see SI for a complete discussion). We assumed the decomposition of the *N*-tosylhydrazone to give the diazoalkane **F** as a preliminary step, and studied the model reaction between **F** and phenylboronic acid (scheme 5, D). The modeling studies indicate that formation of the tertiary boronic acid **G** through the transition state **TS(F-G)** is favoured by 3.9 kcal·mol^{-1} towards the formation of the diastereomer **G'** through the analogous **TS(F-G')**. Both transition states show a similar structure that corresponds to an asynchronous concerted process where the boron atom approaches the carbon of the diazoalkane through an equatorial trajectory, and the aryl group occupies a pseudoaxial disposition, nearly antiperiplanar with the leaving N_2 molecule. However, this structure is much less favoured in **TS(G'-H')** due to the destabilizing interaction between the aryl group and the azidoethyl substituent that are in a *syn* arrangement. Then, the intramolecular stereoretentive amination of the boronic acid **G**, through the cyclic transition state **TS(G-H)** (ΔG_{act} = 28.4 kcal·mol^{-1}), gives the *cis*-fused bicyclic systems **H** observed. According to the computations, if the diastereomeric boronic acid **G'** were formed, it should also undergo the cyclization through the same type of concerted 1,2-alkyl migration through **TS(G'-H')** (ΔG_{act} = 27.5 kcal·mol^{-1}) to give **H'**, because the energy barriers for both pathways are of the same magnitude. However, the *trans*-fused diastereoisomers **H'** have not been observed experimentally. Therefore, the combination of experimental and computational evidences rule out the possibility of the formation of **G'**, and support that the diastereoselectivity of the reactions is determined in the carboborylation of the cyclic diazo compound.

Conclusion

We have presented herein a novel synthesis of 2,2-disubstituted pyrrolidines that takes place through a transition-metal free domino cyclization. The mechanism involves the carboborylation of a *N*-tosylhydrazone with a boronic acid followed by the intramolecular capture of the transient boronic acid by an azide through a second carboborylation event. Synthetically, the reaction features wide scope, as both aryl and alkylboronic acids are competent substrates in the transformation, allowing for the preparation of diversely substituted pyrrolidines. Moreover, the reactions with cyclopentanone and cyclohexanone derived γ-azido-*N*-tosylhydrazones are highly diastereoselective providing the bicyclic amines as single diastereoisomers. The mechanism proposed is supported by DFT computations and comprises two consecutive concerted carboborylation processes – a diastereoseletive carboborylation of the diazoalkane generated from the *N*-tosylhydrazone, and the intramolecular carboborylation of the azide. This last step takes place through a chair-like transition state. Considering the wide availability of boronic acids, the simple synthesis of the precursor γ-azidoketones, and the wide scope already shown of the reaction, we consider that this novel transformation will be very useful for the synthesis of pyrrolidine-containing structures and to introduce the interesting pyrrolidine moiety into different natural and unnatural structures.

Acknowledgements

Financial support of this work by Ministerio de Economía y Competitividad (MINECO) of Spain: Grants CTQ2016-76794-P (AEI/FEDER, UE) and PID2019-107580GB-I00 and Consejería de Empleo, Industria y Turismo del Principado de Asturias (Spain): (grant IDI/2018/000231). A Clarín postdoctoral fellowship (Principado de Asturias, Spain) to L. F. is gratefully acknowledged.

Keywords: Pyrrolidine • Azide • Boronic acid • *N*-tosylhydrazone • Metal-free

[1] a) H. Li, Y. Zhang, J. Wang, *Synthesis* **2013**, *45*, 3090–3098. b) M. Paraja, M. Plaza, C. Valdés, *Synlett* **2017**, *28*, 2373–2389.

[2] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat. Chem.* **2009**, *1*, 494–499.

[3] C. Peng, W. Zhang, G. Yan, J. Wang, *Org. Lett.* **2009**, *11*, 1667–1670.

[4] a) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem. Int. Ed.* **2012**, *51*, 5953–5957; *Angew. Chem.* **2012**, 124, 6055-6059. b) M. Plaza, M. C. Pérez-Aguilar, C. Valdés, *Chem. Eur. J.* **2016**, *22*, 6253–6257.

[5] a) L. Kupracz, A. Kirschning, *J. Flow Chem.* **2013**, *3*, 11–16. b) G. Wu, Y. Deng, C. Wu, X. Wang, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, *2014*, 4477–4481. c) D. Wang, M. J. M. De Wit, K. J. Szabó, *J. Org. Chem.* **2018**, *83*, 8786–8792. d) Y. Yang, Z. Liu, A. Porta, G. Zanoni, X. Bi, *Chem. Eur. J.* **2017**, *23*, 9009–9013. e) S. Nakagawa, K. A. Bainbridge, K. Butcher, D. Ellis, W. Klute, T. Ryckmans, *ChemMedChem* **2012**, *7*, 233–236. f) D. M. Allwood, D. C. Blakemore, A. D. Brown, S. V Ley, **2014**, *79*, 328-338. g) G. Wu, Y. Deng, H. Luo, J. Zhou, T. Li, Y. Zhang, J. Wang, *Chem. Commun.* **2016**, *52*, 5266–5268. h) A. Wegener, K. A. Miller, *J. Org. Chem.* **2017**, *82*, 11655–11658. i) X. Shen, N. Gu, P. Liu, X. Ma, J. Xie, Y. Liu, B. Dai, *Chinese J. Chem.* **2016**, *34*, 1033–1038. j) Y. Ma, B. R. P. Reddy, X. Bi, *Org. Lett.* **2019**, *21*, 9860–9863. k) R. R. Merchant, J. A. Lopez, **2020**, *22*, 2271-2275.

[6] 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*, 360–367. b) J. S. Poh, S. H. Lau, I. G. Dykes, D. N. Tran, C. Battilocchio, S. V. Ley, *Chem. Sci.* **2016**, *7*, 6803–6807. c) Y. Chen, D. C. Blakemore, P. Pasau, S. V. Ley, *Org. Lett.* **2018**, *20*, 6569–6572. d) A. Greb, J. S. Poh, S. Greed, C. Battilocchio, P. Pasau, D. C. Blakemore, S. V. Ley, *Angew. Chem. Int. Ed.* **2017**, *56*, 16602–16605; *Angew. Chem.* **2017**, *129*, 16829–16832. e) O. A. Argintaru, D. Ryu, I. Aron, G. A. Molander, *Angew. Chem. Int. Ed.* **2013**, *52*, 13656–13660; *Angew. Chem.* **2013**, *125*, 13901–13905. f) Y. Chen, D. C. Blakemore, P. Pasau, S. V. Ley, *Org. Lett.* **2018**, *20*, 6569–6572.

[7] a) M. Plaza, C. Valdés, *J. Am. Chem. Soc.* **2016**, *138*, 12061–12064. b) M. Plaza, S. Parisotto, C. Valdés, *Chem. Eur. J.* **2018**, *24*, 14836–14843. c) M. Plaza, M. Paraja, L. Florentino, C. Valdés, *Org. Lett.* **2019**, *21*, 632–635.

[8] a) T. K. Hyster, K. E. Ruhl, T. Rovis, **2013**, *135*, 5364-5367. b) A. J. Boddy, D. P. Affron, C. J. Cordier, E. L. Rivers, A. C. Spivey, J. A. Bull, *Angew. Chemie Int. Ed.* **2019**, *58*, 1458–1462; *Angew. Chem.* **2019**, *131*, 1472–1476. c) N. J. Flodén, A. Trowbridge, D. Willcox, S. M. Walton, Y. Kim, M. J. Gaunt, *J. Am. Chem. Soc.* **2019**, *141*,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

8426–8430.

[9] P. Starkov, T. F. Jamison, I. Marek, *Chem. Eur. J.* **2015**, *21*, 5278–5300.

[10] a) A. R. Reddy, C. Y. Zhou, Z. Guo, J. Wei, C. M. Che, *Angew. Chem. Int. Ed.* **2014**, *53*, 14175–14180; *Angew. Chem.* **2014**, *126*, 14399-14404. b) V. N. G. Lindsay, H. M. F. Viart, R. Sarpong, *J. Am. Chem. Soc.* **2015**, *137*, 8368–8371. c) Y. Wang, X. Wen, X. Cui, X. P. Zhang, *J. Am. Chem. Soc* **2018**, *140*, 10. d) L. W. Souza, R. A. Squitieri, C. A. Dimirjian, B. M. Hodur, L. A. Nickerson, C. N. Penrod, J. Cordova, J. C. Fettinger, J. T. Shaw, *Angew. Chem. Int. Ed.* **2018**, *57*, 15213–15216; *Angew. Chem.* **2018**, *130*, 15433–15436. e) X. Wen, Y. Wang, X. P. Zhang, *Chem. Sci.* **2018**, *9*, 5082–5086. f) M. Lankelma, A. M. Olivares, B. de Bruin, *Chem. Eur. J.* **2019**, *25*, 5658–5663.

[11] a) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301. b) Y. Liu, T. You, T. T. Wang, C. M. Che, *Tetrahedron* **2019**, *75*, 130607.

[12] a) E. T. Hennessy, T. A. Betley, *Science*, **2013**, *340*, 591–596. b) B. Bagh, D. L. J. Broere, V. Sinha, P. F. Kuijpers, N. P. Van Leest, B. De Bruin, S. Demeshko, M. A. Siegler, J. I. Van Der Vlugt, *J. Am. Chem. Soc.* **2017**, *139*, 5117–5124. c) K. P. Shing, Y. Liu, B. Cao, X. Y. Chang, T. You, C. M. Che, *Angew. Chemie - Int. Ed.* **2018**, *57*, 11947–11951; *Angew. Chem.* **2018**, *130*, 12123–12127. d) Y. Dong, R. M. Clarke, G. J. Porter, T. A. Betley, *J. Am. Chem. Soc.* **2020**, *142*, 10996–11005.

[13] a) S. Huh, S. Y. Hong, S. Chang, *Org. Lett.* **2019**, *21*, 2808–2812. b) M. Espinosa, H. Noda, M. Shibasaki, *Org. Lett.* **2019**, *21*, 9296–9299. c) S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M. H. Baik, S. Chang, *Science,* **2018**, *359*, 1016–1021.

[14] M. J. West, J. W. B. Fyfe, J. C. Vantourout, A. J. B. Watson, *Chem. Rev.* **2019**,119, 12491-12523.

[15] S. Roscales, A. G. Csáky, *Chem. Soc. Rev.* **2020**, DOI 10.1039/C9CS00735K.

[16] a) Q. Xiao, L. Tian, R. Tan, Y. Xia, D. Qiu, Y. Zhang, J. Wang, *Org. Lett.* **2012**, *14*, 4230–4233. b) S. Voth, J. W. Hollett, J. A. McCubbin, *J. Org. Chem.* **2015**, *80*, 2545–2553. c) C. Zhu, G. Li, D. H. Ess, J. R. Falck, L. Kürti, *J. Am. Chem. Soc.* **2012**, *134*, 18253–18256.

[17] a) S. N. Mlynarski, A. S. Karns, J. P. Morken, *J. Am. Chem. Soc.* **2012**, *134*, 16449–16451. b) E. Edelstein, A. Grote, M. Palkowitz, J. Morken, *Synlett* **2018**, *29*, 1749–1752. c) N. Chatterjee, A. Goswami, *Org. Biomol. Chem.* **2015**, *13*, 7940–7945. d) H.-B. Sun, L. Gong, Y.-B. Tian, J.-G. Wu, X. Zhang, J. Liu, Z. Fu, D. Niu, *Angew. Chem. Int. Ed.* **2018**, *57*, 9456–9460; *Angew. Chem.* **2018**, *130*, 9600–9604.

[18] L. Ou, J. Shao, G. Zhang, Y. Yu, *Tetrahedron Lett.* **2011**, *52*, 1430–1431.

[19] D. S. Matteson, G. Y. Kim, *Org. Lett.* **2002**, *4*, 2153–2155.

[20] V. Bagutski, T. G. Elford, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2011**, *50*, 1080–1083; *Angew. Chem.* **2011**, *123*, 1112–1115.

[21] S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098.

[22] J. P. Michael, *Alkaloids Chem. Biol.* **2016**, *75*, 1–498.

[23] N. K. Ratmanova, I. A. Andreev, A. V. Leontiev, D. Momotova, A. M. Novoselov, O. A. Ivanova, I. V. Trushkov, *Tetrahedron* **2020**, *76*, 131031.

[24] a) F. Crestey, A. A. Jensen, M. Borch, J. T. Andreasen, J. Andersen, T. Balle, J. L. Kristensen, *J. Med. Chem.* **2013**, *56*, 9673–9682. B) R. Q. Xu, Q. Gu, W. T. Wu, Z. A. Zhao, S. L. You, *J. Am. Chem. Soc.* **2014**, *136*, 15469–15472.

[25] a) E. Reimann, C. Ettmayr, *Monatsh. Chem.* **2004**, *135*, 959–972. b) E. Reimann, C. Ettmayr, K. Polborn, *Monatsh. Chem.* **2004**, *135*, 557–579.

[26] a) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752–772. b) S. M. Weinreb, *Chem. Rev.* **2006**, *106*, 2531–2549. c) K. Srinivas, N. Singh, D. Das, D. Koley, *Org. Lett.* **2017**, *19*, 38. d) A. Kaga, S. Chiba, *Synthesis* **2018**, *50*, 685–699.

[27] An activation energy of 34 kcal·mol^{-1} was obtained for the cyclization of boronic acid **J** (R = Me) to form azetidine **20**.

[28] Although the diastereoselectivity on the carboborylation of substituted cyclic *N*-tosylhydrazones with aryl and alkylboronic acids is unknown, similar diastereoselectivity has been observed in the reactions with alkenylboronic acids (ref 4b).

[29] A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó, E. Fernández, *Org. Biomol. Chem.* **2015**, *13*, 9659–9664.

[30] For a recent review see H. Wang, C. Jing, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, 10.1002/anie.202008096.

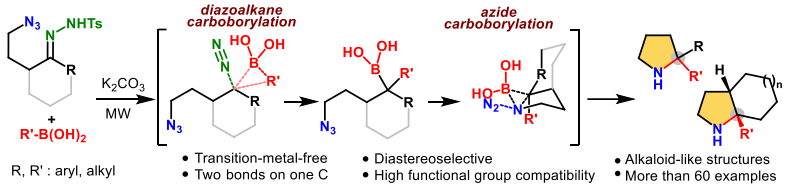
Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.202010528

WILEY-VCH

Entry for the Table of Contents



Playing together: Sequential geminal carboborylations of *N*-tosylhydrazones and azides, carbene and nitrene precursors respectively, have allowed for the development of a very general synthesis of 2,2-disubstituted pyrrolidines via a novel transition metal-free domino cyclization with concomitant incorporation of a side chain. With cyclic *N*-tosylhydrazones alkaloid-like *cis*-fused bicyclic and tricyclic structures are obtained with total diastereoselectivity.

Institute and/or researcher Twitter usernames: @iuqoem; @cvaldesuniovi

WILEY-VCH
Accepted Manuscript

This article is protected by copyright. All rights reserved.