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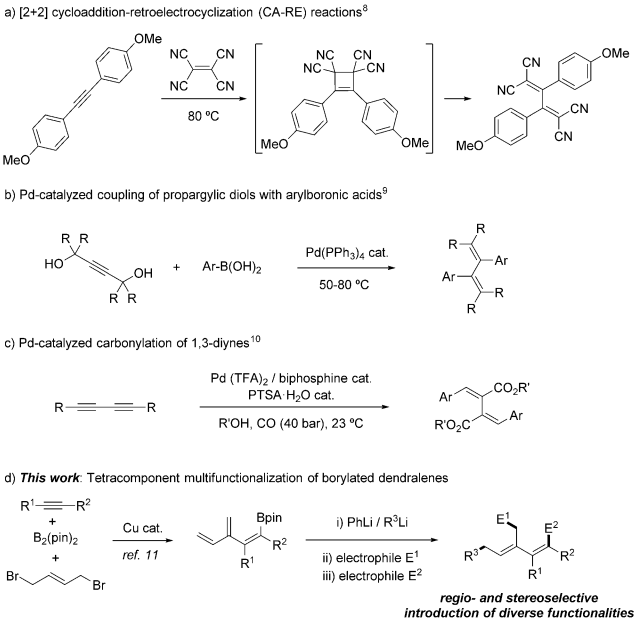
Stereoselective Synthesis

Stereoselective Synthesis of Highly Substituted 1,3-Dienes via "à la carte" Multifunctionalization of Borylated Dendralenes

*Eva Rivera-Chao and Martín Fañanás-Mastral**

Abstract: *Despite the high relevance of 1,3-dienes, stereoselective methods to access tetrasubstituted conjugated dienes are still scarce. We here report an efficient and modular approach that provides access to multifunctional tetrasubstituted 1,3-dienes with excellent levels of regio- and stereoselectivity. This methodology is based on a tetracomponent reaction between a borylated dendralene, an organolithium reagent and two different electrophiles. Mechanistic studies reveal that this transformation proceeds through a regio- and stereoselective carbolithiation/electrophilic trapping of an in situ formed dendralenic boron-ate complex, followed by a stereoretentive halodeborylation. The ease in which complex structural dienes can be accessed and their synthetic versatility highlight the importance and utility of this method.*

Owing to their versatile application in chemical synthesis[1] and their ubiquitous presence in a wide range of biologically active natural products,[2] and functional materials and devices,[3] 1,3-dienes represent an important class of compounds. Accordingly, a number of methods for the preparation of conjugated dienes have been developed.[4–7] Despite the effectiveness of these methods, the stereoselective construction of tetra- or more highly substituted 1,3-dienes is still scarce. Recent advances include [2+2] cycloaddition-retroelectrocyclization reactions between tetracyanoethylene and electron rich alkynes (Scheme 1 a),[8] Pd-catalyzed coupling of propargylic diols with arylboronic acids (Scheme 1 b)[9] or Pd-catalyzed carbonylation of 1,3-diynes (Scheme 1 c).[10] Although highly efficient, these methods somewhat lack the possibility to install structurally diverse substituents at the different positions of the diene core. Moreover, besides the challenge associated to the substitution pattern, the synthesis of 1,3-dienes bearing substituents at all four positions imposes another big selectivity issue since every double bond must be constructed stereoselectively while substituents being incorporated in a regioselective manner. Thus, the development of new methodologies, particularly those that allow stereoselective synthesis of highly substituted conjugated dienes with "à la carte" introduction of diverse substituents remains a challenge.



Scheme 1. State-of-the-art methods for the stereoselective synthesis of highly substituted 1,3-dienes.

We recently reported a catalytic methodology that allows the synthesis of borylated dendralenes from readily available alkynes, 1,4-dibromo-2-butene and B_2pin_2.[11] As part of our studies on the functionalization of this new type of organoboronates,[11,12] we attempted to transform **1** into methyl-substituted dendralene **2** through a Zweifel coupling which would involve boronate complex formation, 1,2-metallate rearrangement and deiodoborylation.[13] Surprisingly, when **1** was sequentially treated with 1 equiv of MeLi and iodine, no tractable amount of Zweifel coupling product **2** was detected. By using 2 equiv of MeLi the reaction led to productive conversion although the only reaction product was the unexpected 1,2,3,4-tetrasubstituted *E*,*E*-diene **3** where three new C–C, C–H and C–I bonds were formed (Scheme 2).

Considering the high relevance of this type of structures and the scarcity of methods to access multisubtituted conjugated dienes, we decided to study this transformation and we now report a method that enables the stereoselective construction of multifunctional tetrasubstituted 1,3-dienes in

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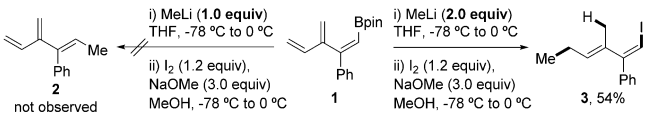


Scheme 2. Preliminary results.

a single one-pot operation that entails a tetra-component three bond-forming reaction (Scheme 1d).

In order to optimize and extend the scope of this reaction, we first decided to get insight on the mechanism of this new transformation. For this purpose, we analyzed the nature of the reaction intermediates by NMR spectroscopy (Figure 1 and Supporting Information). Upon addition of 1 equiv of MeLi to **1** we observed quantitative formation of boronate complex **4** (^{11}B NMR; 6.6 ppm) (Figure 1a). As expected from our preliminary result (Scheme 2), treatment of this intermediate with iodine did not afford the 1,2-metallate rearrangement[13] product **2** nor 1-iodo-1,3-diene **3**. Addition of 2 equiv of MeLi led to the formation of two different boronate complexes (6.6 and 4.8 ppm) along with a new boron species featuring a sharp singlet at −19.0 ppm which is consistent with a trimethyl boronate complex[14] (Figure 1b). Interestingly, addition of a solution of iodine in methanol to this mixture provided iododiene **3** in 40% yield. Two possible mechanistic scenarios for the C–C bond forming step were initially considered: an iodine-mediated intramolecular 1,6-migration of the Me group or an intermolecular regioselective carbolithiation. ^{1}H NMR analysis (see Supporting Information for details) of the mixture generated by addition of 2 equiv of MeLi revealed the presence of dienylboronate complex **5** as the major component, somewhat discarding a 1,6-metallate rearrangement pathway. Formation of **5** might arise from nucleophilic attack at the vinyl group of boronate complex **4** and subsequent stereoselective protonation of the resulting allylithium intermediate. Considering that the presence of multiple boron species was probably not the best situation to achieve an efficient transformation, we decided to use PhLi instead of MeLi. Addition of 1 equiv of PhLi to **1** quantitatively provided dendralenic boronate complex **7** (Figure 1c). Gratifyingly, addition of a second equivalent of PhLi followed by protonation cleanly generated a single boronate complex (**8**, 7.2 ppm), which afforded tetra-substituted diene **9** in 65% yield upon treatment with of a solution of iodine (1.2 equiv) in methanol (Figure 1d). To further prove a direct carbolithiation mechanism, boronate complex **7** was sequentially treated with 1 equiv of MeLi and iodine/methanol and the reaction exclusively afforded diene **3** in an improved 54% yield (vs. 40% yield with 2 equiv of MeLi). Similarly, addition of PhLi to boronate complex **4** followed by treatment with iodine and methanol led to the selective formation of diene **9** (Scheme 3).

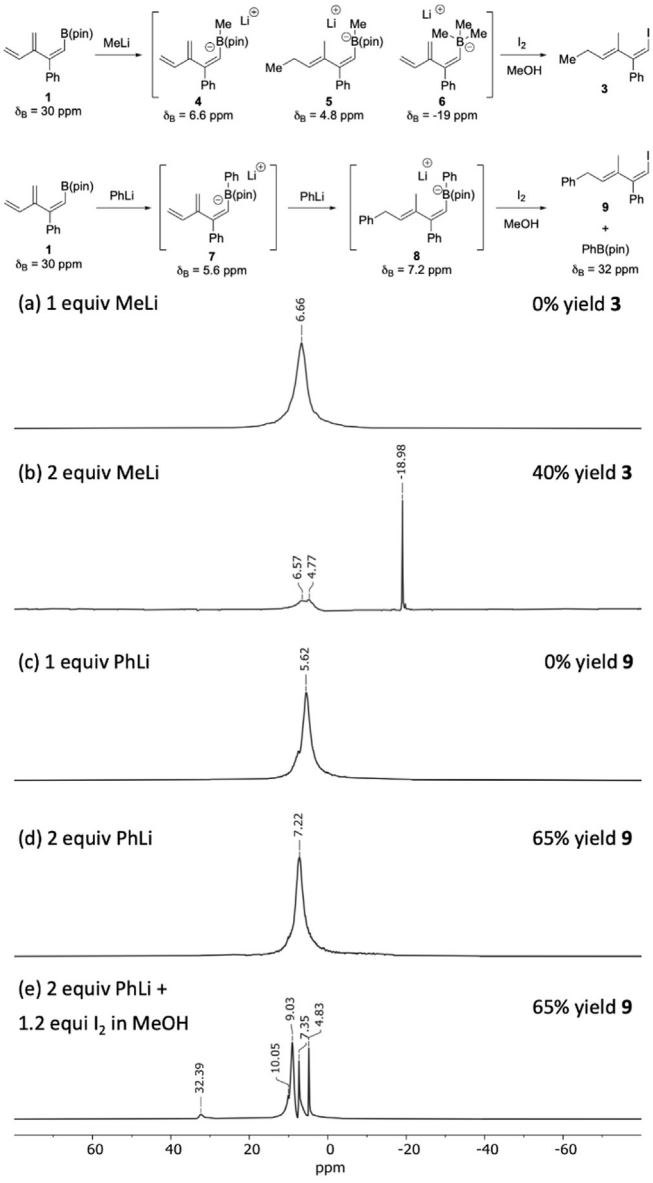
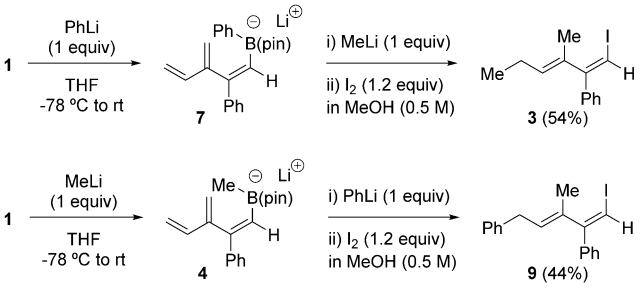


Figure 1. Mechanism investigation and reaction optimization via ^{11}B NMR analysis.

It is important to note that few examples of carbolithiation of dendralenes have been described. Besides anionic polymerization[15] and a carbolithiation/electrocyclization of cyclic [3]dendralenes,[16] only one example involving carbolithiation/electrophilic trapping of dendralenes has been reported to date.[17] Interestingly, in our system carbolithiation occurs via a regioselective addition of the organolithium reagent to the vinyl moiety of the borylated dendralene which generates an allyllithium intermediate. This is in sharp contrast with previous examples where dendralene carboli-

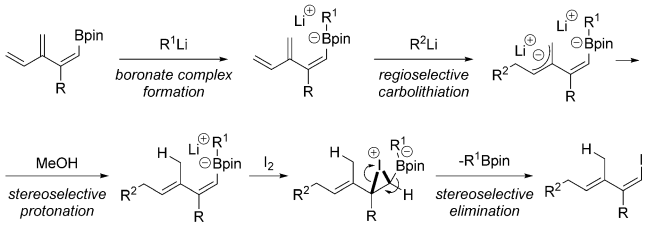


Scheme 3. Experiments supporting a carbolithiation pathway.

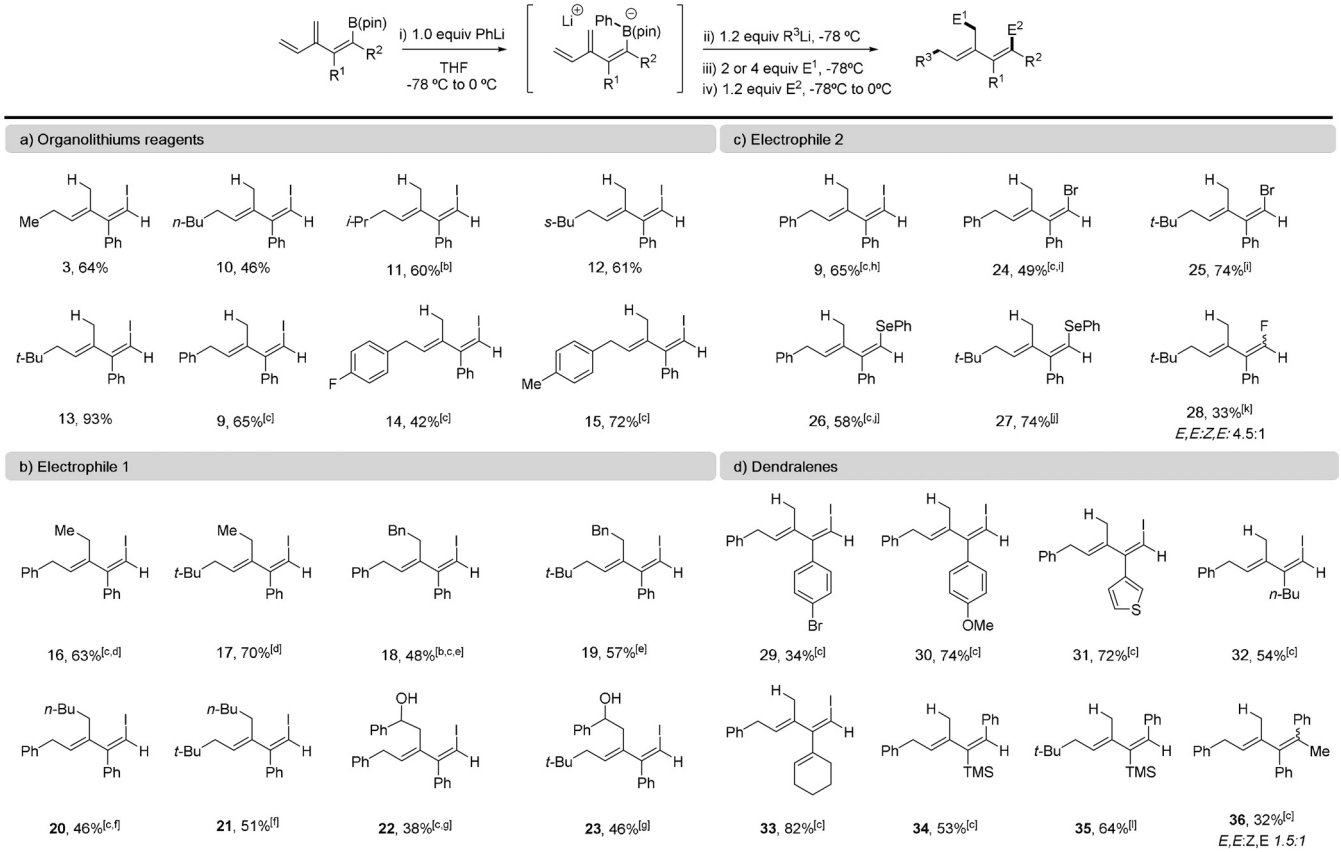
thiation generates a stabilized pentadienyllithium intermediate.[15–17] We hypothesized that the presence of the polarized C–B bond in our system might hamper both the formation of the pentadienyllithium intermediate and the carbolithiation at the alkenyl boronate moiety, thus providing a favored scenario for nucleophilic addition at the vinylic terminus. Another important feature of the carbolithiation step is the high level of regio- and stereoselectivity achieved after the electrophilic trapping. Given that allyllitium species tend to rapidly equilibrate,[18] this high selectivity might likely arise from the formation of the thermodynamically most stable *E*-isomer after electrophilic attack at the less hindered allylic terminus.

NMR and GC-MS analysis after iodine addition revealed the formation of PhBpin together with phenyl boronate complexes which might originate from reaction between in situ generated LiOMe and the phenyl boronic ester (Figure 1e). This suggests that C–B to C–I transformation would occur through a two-step iodonium formation/elimination sequence (see below for further details). Overall, on the basis of these experiments, a mechanism involving 1) dendralenic boronate complex formation, 2) regio- and stereoselective carbolithiation/electrophilic trapping and 3) stereoretentive iododeborylation[19] of the resulting dienyl boronate complex, can be proposed for this novel transformation (Scheme 4).

Having disclosed the mechanistic intricacies of this tetracomponent reaction, we set out to explore the scope of this transformation (Scheme 5). We first investigated the behavior of different organolithium compounds (Scheme 5a). Primary, secondary, and tertiary alkyllithium reagents all proved to be efficient for this transformation. With those nucleophiles, carbolithiation took place at −78 °C and subsequent quench-



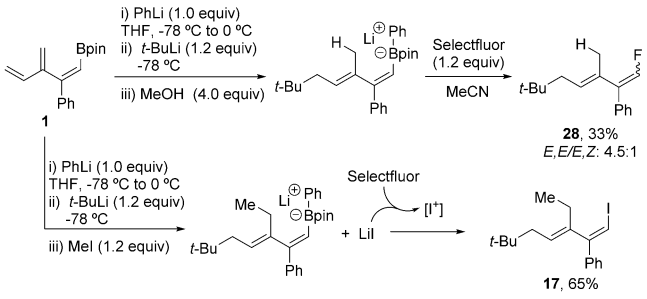
Scheme 4. Proposed mechanism for the formation of tetra-substituted 1-iodo-1,3-dienes.



Scheme 5. Scope of the reaction. [a] Reaction conditions: dendralene (1.0 equiv, 0.2 mmol) in 1.0 mL of dry THF, PhLi (1.0 equiv), −78 °C to 0 °C and stirred for 5 min; then, R^3Li (1.2 equiv), −78 °C, then, I_2 (1.2 equiv, E^2) 0.5 M in MeOH (E^1), −78 °C to 0 °C and stirred for 30 min. [b] Obtained as a mixture of regioisomers (see SI for details); [c] PhLi (or ArLi, 2.2 equiv), −78 °C to 0 °C, then E^1 and E^2; [d] MeI (E^1, 2 equiv), −78 °C to 0 °C; then, I_2 (1.2 equiv); [e] BnBr (E^1, 2 equiv), 0 °C; then, I_2 (1.2 equiv); [f] *n*-BuBr (E^1, 2 equiv), −78 °C to 0 °C; then, I_2 (1.2 equiv); [g] PhCHO (E^1, 2 equiv), −78 °C to 0 °C; then, I_2 (1.2 equiv) 0.5 M in MeOH; [h] MeOH (E^1, 4 equiv), then NIS (E^2, 1.2 equiv) instead of I_2/MeOH; [i] MeOH (E^1, 4 equiv), then NBS (E^2, 1.2 equiv) instead of I_2/MeOH; [j] MeOH (E^1, 4 equiv), then PhSeCl (E^2, 1.2 equiv, 0.5 M in THF) instead of I_2/MeOH; [k] MeOH (4 equiv, E^1), −78 °C to rt; solvent evaporation, then, MeCN (1.0 mL), Selectfluor® (E^2, 1.5 equiv), rt; [l] Warmed to 0 °C after addition of *t*-BuLi, then I_2/MeOH at 0 °C.

ing with MeOH and iodine provided the corresponding tetrasubstituted dienes **3**, **10**–**13** in good yield with complete levels of regio- and stereoselectivity in nearly all cases. Interestingly, aryllitihium reagents which failed to provide carbometallation with other dendralenes,[16] worked well in this transformation albeit warming to 0 °C was necessary to achieve full carbolithiation. Under these conditions, dienes **9**, **14** and **15** were obtained in good yield and with excellent selectivity.[20] The nucleophilicity of the allyllithium intermediate also enabled efficient trapping of different carbon electrophiles thus providing a handle for the elongation of the 3-substituent of the dienic core through a second C–C bond formation. Use of iodomethane, benzyl bromide, 1-bromobutane or benzaldehyde, instead of MeOH, resulted in efficient two C–C, one C–I forming processes (Scheme 5b, **16**–**23**). The intermediate dienyl boronate complex generated after the carbolithiation/electrophilic trapping step could also be exploited in other electrophilic couplings to incorporate different functionalization on the diene structure. For this purpose, a series of electrophiles rather than iodine were investigated in reactions involving carbolithiation with PhLi or *t*-BuLi (Scheme 5c). We found that the use of NIS is equally effective than iodine to afford iododiene **9**. With NBS and PhSeCl the reactions also proceeded with total regio- and stereoselectivity, producing 1-bromo-1,3-dienes **24**–**25** and 1,3- dienyl selenides **26**–**27**, respectively, as single *E*,*E* isomers in very good yields. Interestingly, in sharp contrast with the conjunctive functionalization of β,β-disubstituted vinyl boronate complexes with PhSeCl reported by Aggarwal,[21] no formation of 1,2-migration products was observed in these cases.

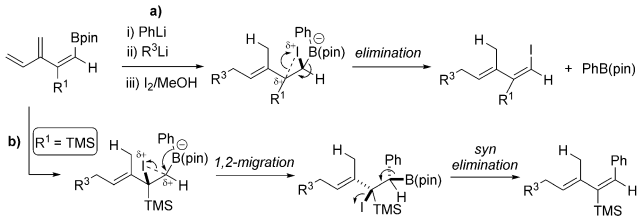
We next investigated a transformation involving a carbolithiation/protonation/fluorination process. Subsequent treatment of borylated dendralene **1** with PhLi, *t*-BuLi, MeOH and Selectfluor®, afforded 1-fluoro-1,3-diene **28** in moderate yield with excellent regioselectivity although with slightly diminished stereoselectivity (*E*,*E*:*E*,*Z* = 4.5:1).[22] These results suggest that the formation of a closed three-membered intermediate prior to the elimination step is important to achieve stereochemical retention. Interestingly, when a carbolithiation/alkylation/fluorination process was attempted by using MeI instead of MeOH, 1-iodo-1,3-diene **17** was exclusively obtained (Scheme 6). In this case, formation of **17** may be explained by the presence of LiI which is generated in the first electrophilic trapping and may be oxidized by



Scheme 6. Effect of first electrophile in the cascade reaction with Selectfluor®.

Selectfluor® to the iodine cation,[23] which might promote the electrophilic iodination of the dienylboronate intermediate.

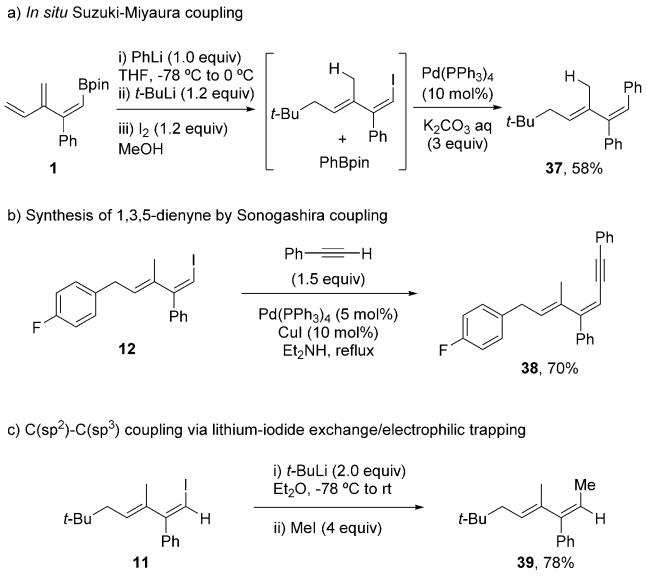
Finally, we explored the outcome of different borylated dendralenes in the carbolithiation/protonation/iodination reaction (Scheme 5d). Both electron withdrawing (**29**) and electron donating groups (**30**) were tolerated at the aromatic substituent in the 2 position, although reaction turned out to be more efficient with the latter. Gratifyingly, substrates bearing heteroaromatic and aliphatic substituents also worked well and afforded the corresponding tetrasubstituted dienes **31** and **32** in good yield with excellent regio- and stereoselectivity. Noteworthy, reaction with a borylated [4]dendralane, which adds an extra point of regioselectivity in the carbolithiation step, afforded iododendralene **33** as a single product in 82 % yield. Surprisingly, when a borylated dendralene bearing a TMS group in the 2 position was used in combination with PhLi and *t*-BuLi, products **34** and **35** arising from a Zweifel-type 1,2-metallate rearrangement-elimination sequence were obtained instead of the expected 1-iodo-1,3-dienes. A similar behavior was observed for a borylated dendralene bearing substituents both at 1 and 2 positions (formation of **36**).[24] A plausible mechanistic rationale accounting for this divergency is outlined in Scheme 7. After the carbolithiation/protonation step, treatment of the



Scheme 7. Mechanistic rationale for the divergent elimination pathways.

resulting diene boronate complex with iodine would form a zwitterionic iodonium intermediate. This species can either eliminate to afford the iododiene along with PhBpin or undergo a 1,2-rearrangement of the phenyl group. The commonly observed elimination may arise from a partial positive charge stabilization at the β carbon, likely due to the β,β-disubstitution,[21] which would allow lengthening of the C(β)–I bond thus favoring this pathway (Scheme 7a). However, the presence of a TMS group in the β position may rather stabilize positive charge at the α carbon,[25] facilitating the 1,2-migration of the phenyl group (Scheme 7b). Similarly, the presence of an extra substituent at the α position would also provide a good scenario to build up partial positive charge at that carbon.

An attractive feature of this new tetra-component reaction is the functional group diversity that can be installed in the diene core which allows to access more complex dienic structures (Scheme 8). Formation of PhBpin as side product could be exploited to perform an in situ Suzuki–Miyaura coupling with the 1-iodo-1,3-diene product just by adding a Pd catalyst and aq. K_2CO_3 to the reaction mixture. The synthesis of diene **37** showcases a route to incorporate the aryl group



Scheme 8. Synthetic transformations of products.

from the organolithium used to generate the initial dendralenic boronate complex into the final product. The obtained 1-iodo-1,3-dienes also served as good precursors to prepare stereodefined polyconjugated systems as illustrated with the synthesis of dienyne **38** by Sonogashira coupling. Moreover, the versatile reactivity of the C–I bond can also be used to perform lithium/halogen exchange to generate a dienyllithium reagent which can react with a carbon electrophile (e.g. MeI) to establish a new $C(sp^2)$–$C(sp^3)$ bond as shown for the synthesis of **39**.

In summary, we have developed an efficient tetracomponent reaction that entails the in situ formation of a dendralenic boronate complex, its regioselective carbolithiation and two subsequent stereoselective electrophilic trappings. This transformation allows a wide range of synthetically versatile 1,2,3,4-tetrasubstituted conjugated dienes to be synthesized in high yields and selectivity. A key feature of this method is the versatile introduction of diverse functionalities on different positions of the dienic core which provides a useful tool to prepare attractive building-blocks for organic synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 1,3-dienes · boron · carbolithiation · dendralenes · multicomponent reactions

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