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To cite this version:

Benjamin François, Ludovic Eberlin, Fabienne Berrée, Andrew Whiting, Bertrand Carboni. Access to Fused Pyrroles from Cyclic 1,3-Dienyl Boronic Esters and Arylnitroso Compounds. Journal of Organic Chemistry, 2020, 85 (8), pp.5173-5182. 10.1021/acs.joc.9b03214. hal-02563405

HAL Id: hal-02563405
https://univ-rennes.hal.science/hal-02563405
Submitted on 14 May 2020

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Access to Fused Pyrroles from Cyclic 1,3-Dienyl Boronic Esters and Arylnitroso Compounds

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RECEIVED DATE (will be automatically inserted after manuscript is accepted).

ABSTRACT. Complimentary to classical hydroboration and boron-Wittig reactions, a new, efficient access to cyclic 1,3-dienyl boronic esters has been developed via diene or triene metathesis. Subsequently, fused pyrroles were synthesized with a broad substrate scope from the reaction of cyclic 1,3-dienyl boronic esters with aryl nitroso compounds using a one-pot hetero-Diels–Alder/ring contraction sequence.

INTRODUCTION

Nitrogenous heterocycles are one of the most commonly investigated and essential families of organic compounds, mainly due to their presence in many important molecules used in various fields ranging from life to materials sciences. Pyrroles and their derivatives in particular occupy a prominent place in this family, for example, as basic structural units in many natural products, such as the porphyrins of heme, the constituents of hemoglobins and oxygen-carrying myoglobins, and chlorophyll, a pigment porphyrins of heme, the constituents of hemoglobins and chlorophyll, a pigment essential to life. They are also found in vitamin B12 and in many alkaloids isolated from marine organisms such as lamellars or spiroglandin B. In addition to natural products, many pyrrole derivatives of synthetic origin have remarkable biological activities, including anticancer, anti-inflammatory, antibiotic, anti-HIV, anti-tuberculosis, antimalarial, fungicides, etc. Some of them are used for medicinal purposes, such as atorvastatin and tolmetin, or for plant treatments, such as chlorfenapyr.

Among all the molecules of interest having a pyrrole core, a number of them have also a cyclic structure juxtaposed with this moiety. While benzofused derivatives, as indoles, isoindoles and carbazoles, are the most prominent examples of this family, other compounds for which the adjacent ring is not aromatic also exhibit remarkable biological activities. This includes, in particular, 1 which acts as an inhibitor of the HSP90 protein for regulation of the dopaminergic pathway in Parkinson's disease, 2 which blocks CFTR protein for the treatment of severe diarrhea, 3 for the prevention of cellular replication of hepatitis C virus (HCV), 4 and, an inhibitor of histone deacetylases that play an important role in the regulation of gene expression. Also, ketorolac 5 is a nonsteroidal anti-inflammatory drug with analgesic activity 9 and molindone 6 (Moban) has been used in the United States as an antipsychotic for the treatment of schizophrenia.
RESULTS AND DISCUSSION

1,3-Dienyl boronic esters 7a-d were first prepared in 70-86% yields by hydroboration of the corresponding 1,3-enynes with pinacolborane in the presence of the Schwartz’ reagent (Scheme 2). In parallel, an (E)-stereoselective boron-Wittig reaction between bis[(pinacolato)boryl] methane and α,β-unsaturated aldehydes with lithium tetramethylpiperidide as base furnished 7e-g in good yields.

To increase the range of cyclic dienyl boronic esters, we then turned our attention to another approach, i.e. the ring closing enyne metathesis (RCEM), a powerful tool for the synthesis of 1,3-diene. Such a reaction could be followed by a cross-metathesis reaction (CM) that then allowed the post-functionalization of the initial dienyl structure. The reactants used in this second step were generally mono-substituted alkenes, whether activated or not. Although 2-

Hence, our investigations started with enyne 9h as a model substrate. Conducting the RCEM reaction in DCM at RT for 18h in the presence of the 1st-generation Grubbs catalyst afforded a mixture of dienes 10 and 7h (55/45 with no residual starting material) (Eq 1). In the absence of vinyl-Bpin, the ring closure was complete under the same experimental conditions (Eq 2). Conversely, a 15% conversion was observed with enyne 11 where the boronic ester function was already present on the alkene moiety (Eq 3). In parallel, cross metathesis of the isolated diene 10 with vinyl-Bpin was carried out, to deliver only moderate amounts of 7h (Eq 4). These results suggest that the cyclization step takes place first in the tandem RCEM/CM sequence. Finally, the best results were obtained by conducting this process at reflux in DCM with three equivalents of vinyl-Bpin over 4h to give boronate-substituted diene 7h in 48% isolated yield (Eq 5).

The scope of this approach was then evaluated under these optimized conditions with various other enynes.
(Scheme 4). As previously observed for 7h, besides variable amounts of pinBCH=CHBpin resulting from the self-coupling of pinacol vinylboronate, dienes 7h-7k were obtained as (E)-isomers (J_H,H = 18.2 to 18.5 Hz) in moderate isolated yields mainly due to the low stability of these compounds during the purification step, in particular in the case of the dihydrofuran derivative 7i.

Scheme 4. Synthesis of cyclic dienyl boronic esters 7h-7k via a RCEM/CM sequence.

Having at our disposal the triene 12, we also envisaged whether this compound could constitute a valuable precursor of a different cyclic dienyl boronic ester 7l, provided that the metathesis reaction was regioselective. This was indeed found to be the case and, after heating in DCM for 24h at 45°C in the presence of the Grubbs 2nd generation catalyst, the expected boronate 7l was obtained in 70% yield, without any traces of the 7-membered ring (Scheme 5). Its structure was confirmed by single crystal X-ray diffraction analysis.

Scheme 5. Synthesis of diene 7l from 12 via a RCM reaction.

Having developed access to a series of different cyclic boryl dienes 7a-1, we then undertook to evaluate their reactivity in the presence of aryl nitroso compounds in order to obtain the corresponding fused pyrroles. Mechanistic aspects of this reaction have been already investigated and we rationalized the observed formation of pyrroles by a [4+2]-Diels–Alder cycloaddition, followed by a ring contraction of the resulting oxazine (Scheme 6).

Scheme 6. Proposed mechanism for the formation of pyrroles from the corresponding boronodienes and arylnitroso compounds.

To our knowledge, the only example of cyclic reactants described to date was reported by us, giving a low yield of pyrrole 8ba from 7b and nitrosobenzene 13a. Replacement of pinacol by diethanolamine (which causes quaternization of boron, making the diene more electron-rich, and thus increases the reactivity towards ArNO) had a beneficial effect as exemplified in Scheme 7.

Scheme 7. Synthesis of pyrrole 8ba from 7b or its diethanolamine derivative 7'b.

However, although tetracoordinated diethanolamine esters, such as 7'b, appear a priori to be more suitable in these cycloaddition reactions through higher reactivity towards nitroso species, their synthesis is sometimes challenging, often involving only modest yields due to the products not always being crystalline or readily isolated in a pure form. Pinacol boronate esters remain the most readily accessible, stable derivatives and are by far the most used in organic synthesis. Therefore, we decided to study the influence of an additional, external base/nucleophile, that could be added in situ to achieve quaternization of the boron atom as in the case of 7'b and, thus, significantly potentially increase the yield in the nitroso additions reactions. Indeed, this strategy was viable and improved reactivity was observed with different basic/nucleophilic additives compared to those involving the pinacol ester alone, as exemplified in Table 1.

Table 1. Optimization of the Diels-Alder cycloaddition/cycle contraction cascade for 7b and PhNO.

| entry | additive | equiv. | yield (%) |<ref>

| 1    | -        | -      | 21       |
| 2    | PPh3     | 1.0    | 20       |
| 3    | TMP      | 1.0    | 27       |
| 4    | DMAP     | 1.0    | 30       |
| 5    | Diethanolamine | 1.0 | 33       |
| 6    | BuNOH    | 1.0    | 36       |
| 7    | DBN      | 1.0    | 44       |
| 8    | DBU      | 1.0    | 49       |
| 9    | DBU      | 0.8    | 51 (41)<ref>  |
| 10   | DBU      | 0.5    | 26       |
| 11   | DBU      | 0.8    | 44       |
| 12   | DBU, mol. sieves | 0.8 | 49       |

<ref>Yield determined by <sup>1</sup>H NMR on the reaction crude with 1,3,5-trimethoxybenzene as internal standard. Yield in isolated product after purification.**


purification by silica gel chromatography. Dropwise addition of a diene solution to a mixture DBU and PhNO. Under argon with anhydrous DBU and molecular sieves previously activated under 1 mbar at 150 °C for 16 h.

Examining Table 1, it can be seen that the addition of triphenylphosphine was only poorly effective (20%, entry 2) compared with no additive (entry 1). However, the use of an amine, in general terms, enhanced product yields, perhaps surprisingly so considering that even the use of a highly hindered secondary amine, i.e. 2,2,6,6,6-tetramethylpiperidine (TMP, entry 3), increased the yield of pyrrole 8ba to 27%. The use of the more nucleophilic DMAP did not show any marked enhancement over the more hindered TMP (entry 4). Diethanolamine and tetra-n-butylammonium hydroxide both gave slightly better results (entries 5 and 6). However, it was the bicyclic and stronger amidine bases, DBN and DBU, that were the most efficient in assisting the conversion of diene 7b to the pyrrole 8ba (entries 7 and 8). Focussing more on the use of DBU, it was found that its amount could be advantageously reduced to 0.8 equivalents (see entry 9 and 10). Further optimization by slow addition of the diene to the nitrosobenzene/DBU mixture or the presence of molecular sieves gave no positive significant improvement (see entries 11-12). Hence, using the best conditions developed herein, the yields, although still moderate, were significantly improved up to 41% (entry 9), therefore providing a useful entry to the desired pyrrole systems considering that two successive reactions were involved in this process.

We then examined the wider application of this reaction to establish the scope of the Diels Alder cycloaddition/cycle contraction cascade to access fused pyrroles from a variety of cyclic dienes 7.

Scheme 8. Synthesis of fused pyrroles 8 from cyclic dienyl boronic esters 7.

As can be seen in Scheme 8, the borodiene additions proceeded in moderate to good yields using nitrosobenzene, i.e. yields varying from 41-89%. There does not appear to be any particular trend with respect to yields and ring size or electronics. Running the reactions of dienes 7b, 7c and 7g with nitrosobenzene and without the addition of DBU caused a considerable drop in the yields of cycloadduct in both cases, i.e. from 41% to 21% (for 7b), 66% to 31% (for 7c) and 66% to 42% (for 7g). This reinforces the positive role that DBU plays in this reaction, but it is not clear precisely what that is. In view of the production of azo and azo-oxide side products in competition with the main cycloaddition reaction, DBU may act to slow the disproportion reaction relative to the cycloaddition-rearrangement to the pyrrole, hence improving overall conversion. Nevertheless, Scheme 8 also shows that the DBU approach is not absolutely necessary if the diene is reactive enough. Hence, the reactions of substituted nitrosobenzenes to diene 7l successfully produced a range of 6,5-fused cycloadducts in 66-89% yields. The diene 7l seems to be the most reactive system examined in this reaction to date, whether reacting with either electron rich or electron deficient nitrosobenzenes (see adducts 8la-8lg, Scheme 8). All the NMR data were in agreement with the...
proposed structures and, in the case of **8ga**, it was confirmed by single crystal X-ray diffraction analysis.\(^{32}\)

The successful application of the aryl nitroso-cycloaddition to the cyclic boronate-substituted diene, rearrangement and pyrrole formation was also extended to outer-ring diene systems of type **15** (Scheme 9), thus giving access to 3,4-connected compounds **16**, another family of annulated pyrroles. To exemplify this type of approach, the precursors **15a** and **15b** were synthesized by a palladium-catalyzed cycloisomerization of the corresponding enynes **11** and **14** according our previously reported procedure.\(^{34}\) Due to a low stability observed during purification by chromatography on silica gel, these dienes were not isolated and we carried out the following step in the same pot without removing the palladium catalyst. Products **16a-b** were thus obtained in moderate yields, mainly due to a partial deboration of **15** during the cycloisomerisation process as previously observed for similar processes (Scheme 9).\(^{34}\)

**Scheme 9. Synthesis of fused pyrroles 16a-b from enynes 11 and 14.**

**CONCLUSION**

In summary, we have realized the synthesis of a series of fused pyrroles from the corresponding 1,3-dienyl boronate esters, which adds to the chemist’s armory of classical synthetic methods for accessing pyrrole-containing products and especially the more unusual fused bicyclic systems. For this particular application, a new route involving a ring closing enyne metathesis / cross-metathesis sequence was also developed to access novel boryl dienes that, subsequently, give access to a supplementary range of products with diversified structures.

**EXPERIMENTAL SECTION**

Solvents were freshly distilled from sodium/benzophenone (THF, toluene) or phosphorus pentoxide (DCM). Methanol and other commercially available chemicals were used without further purification. Column chromatography purifications were performed over silica gel (Merck Gelurin 60, 0.063–0.200 mm). Flash chromatography purifications were performed on a Grace Reveleris™ with Puriflash™ 15µm flash cartridges (Interchim). NMR spectra were recorded at 300 or 400 MHz for \(^1H\), 75 or 101 MHz for \(^13C\) and 96 or 128 MHz for \(^11B\). \(^1H\) and \(^13C\) NMR chemical shifts were referenced to Me$_4$Si as internal reference, and \(^11B\) NMR chemical shifts to external BF$_3$OEt$_2$. All \(^13C\) and \(^11B\) NMR were proton-decoupled. High-resolution mass spectra (HRMS) were obtained on a Q-TOF instrument and measured using either electrospray ionization (ESI) or atmospheric solids analysis probe (ASAP). X-ray crystallographic data were collected on an ApexII crystal diffractometer. Specific rotation (in deg cm$^2$ g$^{-1}$) was measured on a Perkin Elmer-341 polarimeter. Melting points were measured on a melting point apparatus. Stuart SMP10.

1-Ethynylcyclopent-1-ene,\(^{35}\) 1-ethynylcyclohex-1-ene,\(^ {36}\) 1-ethynylcyclohept-1-ene,\(^ {37}\) 1-ethynylcyclooct-1-ene,\(^ {35}\) 5,6-dihydro-2H-pyran-3-carbaldehyde,\(^ {38}\) 1-tosyl-1,2,3,6-tetrahydropyridine-4-carbaldehyde,\(^ {39}\) 9h,\(^ {40}\) 10,\(^ {41}\) 11,\(^ {34}\) 9f,\(^ {42}\) 9k were prepared as previously described. Perillaldehyde and 3-(allyl oxy)-1-propyne **9i** are commercially available.

**General procedure for the synthesis of boronates 7a-7d by catalytic hydroboration.** To a mixture of 1-ethynylcycloalk-1-ene (1.86 mmol) and Schwartz catalyst (104 mg, 0.37 mmol) at 0 °C under argon atmosphere, was added dropwise H-Bpin (216 µL, 1.49 mmol). The reaction mixture was stirred at room temperature for 64 h, then diluted with EtO (10 mL). H$_2$O (5 mL) was cautiously added. The azeo was extracted with EtO (3×15 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous MgSO$_4$ and evaporated. The crude product was purified by filtration on silica gel pad, eluted with 95/5 pentane/EtO mixture or by distillation.

\[(E)-2-(2-(\text{Cyclopent-1-en-1-yl})\text{vinyl})-4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolane (7a)}\] 158 mg (72%). Colorless oil, bp = 70-80°C/0.1 mbar. \(^1H\) NMR (300 MHz, CDCl$_3$) δ 7.25 (d, \(J = 18.0\) Hz, 1H), 5.94-5.86 (m, 1H), 5.41 (d, \(J = 18.0\) Hz, 1H), 2.44 (t, \(J = 7.6\) Hz, 4H), 1.91 (quint, \(J = 7.6\) Hz, 2H), 1.28 (s, 12H). The spectroscopic data match with those reported in the literature.\(^{44}\)

\[(E)-2-(2-(\text{Cyclohex-1-en-1-yl})\text{vinyl})-4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolane (7b)}\] 197 mg (84%). Colorless oil, bp = 90-110°C/0.1 mbar. \(^1H\) NMR (400 MHz, CDCl$_3$) δ 7.02 (d, \(J = 18.2\) Hz, 1H), 6.01-5.92 (m, 1H), 5.42 (d, \(J = 18.2\) Hz, 1H), 2.19-2.10 (m, 4H), 1.70-1.54 (m, 4H), 1.27 (s, 12H). The spectroscopic data match with those reported in the literature.\(^{44}\)

\[(E)-2-(2-(\text{Cyclohept-1-en-1-yl})\text{vinyl})-4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolane (7c)}\] 325 mg (70%). Colorless oil. \(^1H\) NMR (300 MHz, CDCl$_3$) δ 6.99 (d, \(J = 18.2\) Hz, 1H), 6.09 (t, \(J = 6.8\) Hz, 1H), 5.45 (d, \(J = 18.2\) Hz, 1H), 2.37-2.29 (m, 2H), 2.29-2.19 (m, 2H), 1.80-1.70 (m, 2H), 1.54-1.42 (m, 4H), 1.26 (s, 12H). \(^{13C}\) \(^1H\) NMR (75 MHz, CDCl$_3$) δ 153.9, 144.4, 139.1, 133.2, 129.0, 26.7, 26.4, 26.2, 24.9. The carbon α to boron was not observed. \(^11B\) \(^1H\) NMR (96 MHz, CDCl$_3$) δ 29.8. HRMS (ESI+) (M+Na)$^+$ calculated for C$_{14}$H$_{28}$O$_2$Na: 271.1840, found 271.1843.

\[(E)-2-(2-(\text{Cyclooct-1-en-1-yl})\text{vinyl})-4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolane (7d)}\] 421 mg (86%). Colorless oil, bp = 100-120°C/0.1 mbar. \(^1H\) NMR (300 MHz, CDCl$_3$) δ 6.98 (d, \(J = 18.2\) Hz, 1H), 5.92 (t, \(J = 8.3\) Hz, 1H), 5.48 (d, \(J = 18.2\) Hz, 1H), 2.44-2.35 (m, 2H), 2.27-2.15 (m, 2H), 1.58-1.36 (m, 8H), 1.28 (s, 12H). \(^{13C}\) \(^1H\) NMR (75 MHz,
General procedure for the synthesis of boronates 7e-7g via a Boron-Wittig reaction. An oven-dried Schlenk flask charged with bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (429 mg, 1.6 mmol) and dry THF (2.1 mL) was sealed under argon with a septum cap. The reaction vial was cooled to 0°C, and a solution of LiTMP (235 mg, 1.6 mmol) in dry THF (1.6 mL) was added dropwise. The reaction was allowed to stir for 5 min. at 0°C and then cooled to -78°C. After addition of a solution of the aldehyde (1.3 mmol) in dry THF (2.8 mL), the reaction mixture was stirred at -78°C for additional 5 h. Upon completion, the solvent was removed under reduced pressure. The product was isolated by silica gel chromatography (cyclohexane/EtOAc: 100/0 to 90/10).

(E)-2-(2-(3,6-Dihydro-2H-pyranyl-4-yl)-1,3,2-dioxaborolane (7f). 174 mg (56%). Colorless oil, Rf 0.24 (Cyclohexane/EtOAc: 9/1). 1H NMR (400 MHz, CDCl3) δ 7.03 (d, J = 18.2 Hz, 1H), 6.00-5.92 (m, 1H), 5.42 (d, J = 18.2 Hz, 1H), 4.76-4.64 (m, 2H), 2.37-2.22 (m, 2H), 2.21-2.01 (m, 3H), 1.94-1.82 (m, 1H), 1.72 (d, J = 1.0 Hz, 3H), 1.55-1.38 (m, 1H), 1.26 (s, 12H). 13C{1H} NMR (75 MHz, CDCl3) δ 152.7, 149.5, 136.9, 133.5, 111.27 (br), 108.9, 83.1, 41.2, 31.7, 27.4, 24.9, 24.3, 20.9. 11B{1H} NMR (96 MHz, CDCl3) δ 31.0. HRMS (ESI+) (M+Na)+ calculated for C_{18}H_{24}O_{6}^{+}Na^{+} 297.1996, found 297.1996.

(E)-2-(2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (7g). 318 mg (62%). White solid mp = 130-132 °C, Rf 0.18 (cyclohexane/EtOAc: 9/1). 1H NMR (300 MHz, CDCl3) δ 7.67 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 18.6 Hz, 1H), 5.97-5.92 (m, 1H), 5.36 (d, J = 18.6 Hz, 1H), 3.74-3.66 (m, 2H), 3.17 (t, J = 5.7 Hz, 2H), 2.42 (s, 3H), 2.38-2.29 (m, 2H), 1.26 (s, 12H). 13C{1H} NMR (75 MHz, CDCl3) δ 148.7, 143.7, 133.43, 133.41, 130.3, 129.8, 127.8, 83.5, 44.4, 42.7, 26.1, 24.9, 21.6. The carbon α to boron was not observed. 11B{1H} NMR (96 MHz, CDCl3) δ 30.1. HRMS (ESI+) (M+Na)+ calculated for C_{20}H_{22}N_{2}O_{2}^{+}Na^{+} 412.1724, found 412.1724.

General procedure for the synthesis of boronates 7h-7k via a RCECM sequence. In a dry 2-neck round-bottom flask, under an argon atmosphere, was dissolved enyne (1.0 mmol) in anhydrous DCM (35 mL). To this solution was added vinylboronic acid pinacol ester (509 μL, 3.0 mmol). The resulting mixture was degassed by slow bubbling of argon for 10 minutes before the introduction of Grubbs 1 catalyst (81 mg, 0.1 mmol). The reaction mixture was stirred at reflux for 4 hours. DCM was evaporated and the product was purified by flash chromatography (cyclohexane/EtOAc: 100/0 to 95/5). The reaction was also carried out on a 2.5 mmol scale for 7h.

Synthesis of benzyl (E)-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylvinyl)-3,6-dihydro-2H-1,2-oxazine-2-carboxylate (7k). In a flame dried Schlenk flask under an argon flow, boronated triene 12 (170 mg, 0.43 mmol) was dissolved in anhydrous degassed dry DCM (13 mL) and Grubbs catalyst 2nd generation (18 mg, 0.021 mmol) was...
added. The reaction mixture was stirred at 45 °C for 24 h. After evaporation of the solvent, the residue was purified by silica gel chromatography (cyclohexane/EtOAc: 100/0 to 80/20) to afford 71 as a white solid (98 mg, 70%). mp = 124–5 °C. Rf = 0.05 (cyclohexane/EtOAc: 8/1). 1H NMR (400 MHz, CDCl3) δ 7.74-7.29 (m, 5H), 6.97 (d, J = 18.5 Hz, 1H), 5.98 (brs, 1H), 5.48 (d, J = 18.5 Hz, 1H), 5.21 (s, 2H), 4.53 (d, J = 2.7 Hz, 2H), 4.31 (d, J = 2.1 Hz, 2H), 1.27 (s, 12H). 13C{1H} NMR (101 MHz, CDCl3) δ 155.5, 147.0, 136.0, 133.0, 128.7, 128.4, 128.3, 127.2, 115.8 (br), 83.6, 68.7, 67.9, 44.8, 24.9. 11B{1H} NMR (96 MHz, CDCl3) δ 30.0. HRMS (ESI+) (+M+H)+ calculated for C20H27NO3B371.1907, found 371.2015.

**General procedure for the synthesis of fused pyrroles 8aa to 8ba.** In a flame dried round-bottom flask under an argon atmosphere, was dissolved boronated diene 7 (0.30 mmol) in MeOH (0.3 mL) and DBU (38 mg, 37μL, 0.25 mmol). The resulting mixture was stirred at room temperature for 5 minutes and PhNO (64 mg, 0.60 mmol) was added. The reaction was stirred for 3.5 hours at room temperature. MeOH was evaporated and the residue was purified by silica gel chromatography (cyclohexane/EtOAc: 100:0 to 95:5).

**1-Phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (8aa).** 25 mg (46%). Yellow oil, Rf = 0.68 (pentane/EtO: 94/6). 1H NMR (300 MHz, CDCl3) δ 7.45-7.34 (m, 4H), 7.25-7.18 (m, 1H), 6.94 (d, J = 2.8 Hz, 1H), 6.13 (d, J = 2.9 Hz, 1H), 2.89 (t, J = 7.0 Hz, 2H), 2.70 (t, J = 7.0 Hz, 2H), 2.47 (p, J = 7.1 Hz, 2H). 13C{1H} NMR (75 MHz, CDCl3) δ 140.9, 137.2, 129.5, 129.1, 129.2, 122.4, 120.1, 105.4, 29.4, 26.9, 25.5. 1H NMR (4,6,7-tetrahydro-1H-indole (8ba)). 24 mg (41%). Colorless oil, Rf = 0.43 (cyclohexane/EtOAc: 95:5). 1H NMR (300 MHz, CDCl3) δ 7.45-7.38 (m, 2H), 7.33-7.27 (m, 3H), 6.77 (d, J = 2.6 Hz, 1H), 6.10 (d, J = 2.6 Hz, 1H), 2.60 (m, 4H), 1.85-1.73 (m, 4H). 13C{1H} NMR (75 MHz, CDCl3) δ ppm 140.4, 129.2, 128.2, 126.2, 126.0, 119.1, 108.2, 23.8, 23.6, 23.5, 23.3. The spectroscopic data matched with those reported in the literature.

**1-Phenyl-1,4,5,6,7,8-hexahydrocyclohepta[b]pyrrole (8ca).** 41 mg (66%). Yellow oil, Rf = 0.59 (cyclohexane/EtOAc: 95:5). 1H NMR (300 MHz, CDCl3) δ 7.47-7.39 (m, 2H), 7.36-7.30 (m, 1H), 7.29-7.23 (m, 2H), 6.60 (d, J = 2.7 Hz, 1H), 6.06 (d, J = 2.7 Hz, 1H), 2.71-2.59 (m, 4H), 1.89-1.79 (m, 2H), 1.79-1.69 (m, 2H), 1.68-1.58 (m, 2H). 13C{1H} NMR (75 MHz, CDCl3) δ 140.7, 131.9, 129.0, 126.7, 126.3, 123.9, 119.0, 109.7, 32.4, 29.0, 28.7, 27.9, 27.1.

**1-Phenyl-4,5,6,7,8,9-hexahydro-1H-cycloocta[b]pyrrole (8da).** 31 mg (46%). Yellow oil, Rf = 0.63 (cyclohexane/EtOAc: 95:5). 1H NMR (300 MHz, CDCl3) δ 7.47-7.39 (m, 2H), 7.37-7.27 (m, 3H), 6.68 (d, J = 2.8 Hz, 1H), 6.06 (d, J = 2.8 Hz, 1H), 2.70-2.58 (m, 4H). 13C{1H} NMR (75 MHz, CDCl3) δ 140.9, 130.1, 129.1, 126.9, 126.4, 127.1, 120.1, 108.8, 31.3, 30.2, 26.1, 26.0, 25.8, 23.3. HRMS (ESI+) (+M+H)+ calculated for C37H32N2O3 596.2326, found 596.2320.

**1-Phenyl-5-tosyl-1,4,5,6-tetrahydropyrrolo[3,4-b]pyrrole (8ca).** 53 mg (52%). 270 mg (47%) on a 1 mmol scale. Yellow oil, Rf = 0.20 (cyclohexane/EtOAc: 9:1). 1H NMR (300 MHz, CDCl3) δ 7.77 (d, J = 8.3 Hz, 2H), 7.46-7.38 (m, 3H), 7.34-7.19 (m, 5H), 6.93 (d, J = 2.9 Hz, 1H), 6.07 (d, J = 2.9 Hz, 1H), 4.67-4.59 (m, 2H), 4.51-4.44 (m, 2H), 2.40 (s, 3H). 13C{1H} NMR (75 MHz, CDCl3) δ 143.6, 139.6, 134.8, 130.0, 130.0, 129.1, 127.6, 126.2, 123.5, 122.7, 104.1, 49.6, 49.0, 21.6. HRMS (ESI+) (+M+Na)+ calculated for C37H32N2O3Na 598.2343, found 598.2345.

**1-Phenyl-4,5,6-dihydro-1H-furo[3,4-b]pyrrole (8da).** 32 mg (58%). Colorless oil, Rf = 0.75 (cyclohexane/EtOAc: 8:2). 1H NMR (300 MHz, CDCl3) δ 7.46-7.37 (m, 2H), 7.26-7.18 (m, 3H), 7.05 (d, J = 2.8 Hz, 1H), 6.15 (d, J = 2.8 Hz, 1H), 5.10-5.03 (m, 2H), 5.00-4.93 (m, 2H). 13C{1H} NMR (101 MHz, CDCl3) δ 139.8, 133.5, 129.8, 126.6, 125.3, 123.2, 119.7.
103.2, 69.4, 67.6. HRMS (ASAP+) (M+H)+ calculated for C13H22NO 186.0919, found 186.0912.

**Ethyl 5-((benzoxycarbonylamino)-1-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-3-carboxylate (8Ja)**. 51 mg (42%). Yellow oil, Rf = 0.19 (cyclohexane/EtOAc: 9:1). 1H NMR (300 MHz, CDCl3) δ 7.44-7.28 (m, 9H), 7.23 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 2.9 Hz, 1H), 6.08 (d, J = 2.9 Hz, 1H), 5.56 (brs, 1H), 5.15-5.01 (m, 2H), 4.29-4.11 (m, 2H), 3.82 (q, J = 15.7 Hz, 1H), 3.33-3.36 (m, 2H), 2.88 (d, J = 15.3 Hz, 1H), 1.23 (t, J = 6.8 Hz, 3H). 13C{1H} NMR (75 MHz, CDCl3) δ 173.2, 155.5, 140.3, 136.4, 133.3, 129.6, 128.6, 128.3, 128.2, 125.6, 123.7, 123.2, 121.0, 105.2, 70.6, 67.0, 61.9, 39.4, 38.7, 14.2. HRMS (ESI+) (M+Na)+ calculated for C24H23NO6Na 427.1628, found 427.1634.

**Diethyl 1-phenyl-4,6-dihydrocyclopenta[b]pyrrole-5,5(1H)-dicarboxylate (8Ka)**. 37 mg (38%). Colorless oil, Rf = 0.61 (cyclohexane/EtOAc: 8:2). 1H NMR (400 MHz, CDCl3) δ 7.48-7.38 (m, 2H), 7.40-7.33 (m, 2H), 7.27-7.22 (m, 1H), 6.94 (d, J = 2.9 Hz, 1H), 6.08 (d, J = 2.9 Hz, 1H), 4.24 (qd, J = 7.1, 1.3 Hz, 4H), 3.59 (s, 2H), 3.39 (s, 2H, 1.29 (t, J = 7.2 Hz, 6H). 13C{1H} NMR (75 MHz, CDCl3) δ 171.8, 140.4, 132.5, 129.6, 125.5, 125.4, 123.4, 121.1, 105.2, 65.2, 61.9, 35.1, 34.3, 14.2. HRMS (ESI+) (M+Na)+ calculated for C24H22NO4Na 350.1368, found 350.1360.

**General procedure for the synthesis of fused pyrroles 8Ja to 8Lg**. In a flame dried round-bottom flask under an argon atmosphere, was dissolved boronated diene 7I (0.20 mmol) and ArNO (0.40 mmol) in DCM/MeOH (6/1) (2 mL). The resulting mixture was stirred at room temperature for 24h. The solvent was evaporated and the residue was purified by silica gel chromatography (cyclohexane/EtOAc: 100:0 to 95:5).

**Benzyl 1-phenyl-4,7-dihydroxyprolyl[3,2-d][1,2]oxazine-5(1H)-carboxylate (8Ja)**. 59 mg (89%). Orange oil, Rf = 0.30 (cyclohexane/EtOAc: 6/1). 1H NMR (400 MHz, CDCl3) δ 7.47-7.29 (m, 8H), 7.22-7.17 (m, 2H), 6.87 (d, J = 2.9 Hz, 1H), 6.19 (d, J = 2.9 Hz, 1H), 5.26 (s, 2H), 5.00 (s, 2H, 4.76 (s, 2H). 13C{1H} NMR (101 MHz, CDCl3) δ 155.6, 139.1, 136.1, 129.8, 128.7, 128.4, 128.3, 126.9, 123.3, 123.1, 121.0, 114.7, 106.3, 68.0, 67.9, 45.1. HRMS (ESI+) (M+H)+ calculated for C16H13NO3 335.1396, found 335.1391.

**Benzyl 1-(4-chlorophenyl)-4,7-dihydroxyprolyl[3,2-d][1,2]oxazine-5(1H)-carboxylate (8Ib)**. 57 mg (77%). Yellow oil, Rf = 0.35 (cyclohexane/EtOAc: 6/1). 1H NMR (400 MHz, CDCl3) δ 7.47-7.29 (m, 8H), 7.22-7.17 (m, 2H), 6.87 (d, J = 2.9 Hz, 1H), 6.19 (d, J = 2.9 Hz, 1H), 5.26 (s, 2H), 5.00 (s, 2H, 4.76 (s, 2H). 13C{1H} NMR (101 MHz, CDCl3) δ 155.6, 137.7, 136.1, 132.6, 130.0, 128.7, 128.4, 128.3, 124.3, 123.4, 121.0, 115.1, 106.7, 68.0, 67.9, 45.1. HRMS (ESI+) (M+H)+ calculated for C28H21Cl2NO3 413.0501, found 413.0507.

**Benzyl 1-(4-methylphenyl)-4,7-dihydroxyprolyl[3,2-d][1,2]oxazine-5(1H)-carboxylate (8Lb)**. 56 mg (75%). Yellow solid, mp = 143-144 °C, Rf = 0.30 (cyclohexane/EtOAc: 6/1). 1H NMR (400 MHz, CDCl3) δ 8.35 (d, J = 9.0 Hz, 2H), 7.46-7.28 (m, 7H), 6.97 (d, J = 3.0 Hz, 1H), 6.29 (d, J = 3.0 Hz, 1H), 5.29 (s, 2H), 5.06 (s, 2H, 4.76 (s, 2H). 13C{1H} NMR (101 MHz, CDCl3) δ 155.5, 145.5, 144.1, 135.8, 128.6, 128.4, 128.3, 125.6, 123.5, 122.2, 120.8, 116.9, 108.3, 68.0, 67.7, 45.0. HRMS (ESI+) (M+H)+ calculated for C28H21NO3 380.1246, found 380.1261.

**Synthesis of (E)-N-(But-3-yn-1-yl)-4-methyl-N-(4-(3,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allylbenzenesulfonamide 14**. To a Schlenk flame dried under an argon atmosphere were sequentially added N-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (214 mg, 0.96 mmol), (E)-2-(3-chloroprop-1-en-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (289 mg, 1.43 mmol), potassium carbonate (264 mg, 1.91 mmol), Bu4NI (177 mg, 0.48 mmol) and anhydrous DMF (8 mL). The Schlenk was closed with a...
glass stopper and the reaction mixture was heated to 50°C in an oil bath for 65 hours. After cooling to room temperature, water (30 mL) and EtOAc (35 mL) were added. Layers were separated and the organic phase was washed with water (2×30 mL), dried over anhydrous MgSO₄ and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc: 100/0 to 80/20) to afford 14 as a colorless oil (228 mg, 61%). Rf = 0.30 (cyclohexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 6.39 (dt, J = 18.0, 5.7 Hz, 1H), 5.53 (dt, J = 18.0, 1.6 Hz, 1H), 3.91 (dd, J = 5.7, 1.6 Hz, 2H), 3.31-3.27 (m, 2H), 2.46-2.39 (m, 5H), 1.95 (t, J = 2.7 Hz, 1H), 1.24 (s, 12H). ¹³C (¹H) NMR (101 MHz, CDCl₃) δ 147.0, 143.5, 137.0, 129.8, 127.3, 122.6, 83.5, 81.1, 70.3, 52.5, 46.6, 24.9, 21.6, 19.3. ¹¹B (¹H) NMR (128 MHz, CDCl₃) δ 29.4. HRMS (ESI+) (M+H)¹ calculated for C₂₀H₂⁹N₂O₈SNa 375.1143, found 375.1141.

General procedure for the palladium-catalyzed isomerisation/ring contraction sequence of boronated enynes 11 and 14.

A flame dried Schlenk was charged with Pd₃dba₂, CHCl₃ (5.2 mg, 0.05 mmol), tri-ο-tolyolphosphate (3.0 mg, 0.01 mmol), acetic acid (0.6 μL, 0.001 mmol) and toluene (1 mL). After stirring 15 min at room temperature, enyne 14 (0.2 mmol) was added and the mixture was kept 2 hours at room temperature under an argon atmosphere. To this crude mixture was then added PhNO (64 mg, 0.6 mmol). After stirring for 4 h at room temperature, the volatiles were removed and the residue was purified by silica gel chromatography (cyclohexane/EtOAc: 100/0 to 85/15).

5-Phenyl-2-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-c]pyrrole (16a). 32 mg (48%). Colorless oil. Rf = 0.44 (cyclohexane/EtOAc: 8/2). ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 8.2 Hz, 2H), 7.43-7.35 (m, 2H), 7.33-7.26 (m, 5H), 6.74 (s, 2H), 4.47 (s, 4H), 2.41 (s, 3H). ¹³C (¹H) NMR (101 MHz, CDCl₃) δ 143.5, 140.85, 134.45, 129.9, 129.8, 127.7, 126.1, 124.9, 120.8, 110.7, 48.2, 21.7. HRMS (ESI+) [(M+Na)⁺] calculated for C₁₄H₁₃N₂O₈SNa 361.0987, found 361.0981.

2-Phenyl-5-tosyl-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine (16b). 24 mg (35%). Colorless oil. Rf = 0.14 (cyclohexane/EtOAc: 9/1). ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.68 (m, 2H), 7.42-7.37 (m, 2H), 7.34-7.28 (m, 4H), 7.24 (tt, J = 7.1, 1.2 Hz, 1H), 6.78 (s, 2H), 4.25 (s, 2H), 3.39 (t, J = 5.9 Hz, 2H), 2.82 (t, J = 5.9 Hz, 2H), 2.44 (s, 3H). ¹³C (¹H) NMR (101 MHz, CDCl₃) δ 143.5, 140.7, 134.2, 129.7, 129.7, 127.8, 125.7, 120.3, 118.3, 117.3, 115.1, 113.6, 44.8, 43.7, 22.5, 21.7. HRMS (ESI+) [(M+Na)⁺] calculated for C₂₀H₂⁹N₂O₈SNa 375.1143, found 375.1141.

ASSOCIATED CONTENT

Supporting Information

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H, ¹³C and ¹¹B spectra of compounds 7, 8, 14 and 16a-b; X-ray diffraction data of 7l. This material is available free of charge on the ACS Publications website at DOI:

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge the Ministère de l’Éducation Nationale, de la Recherche et de la Technologie, the Centre National de la Recherche Scientifique (CNRS) and the Région Bretagne for financial supports. We also thank Andrei S. Batsanov (Chemistry Department, Durham University) and Marie Cordier (Centre de Diffractionométrie X, ISCR, Rennes) for X-ray crystallographic structure determinations.

REFERENCES


(32) For the X-ray structure of 7l and 8ga, see supporting information. CCDC 1950726 and 1983371 respectively contain the supplementary crystallographic data. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


