

# A novel, efficient synthesis of *N*-aryl pyrroles via reaction of 1-boronodienes with arylnitroso compounds†

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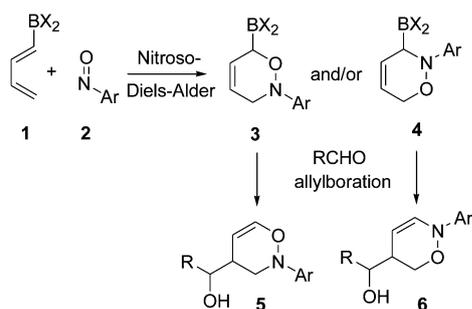
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**A one-pot hetero-Diels–Alder/ring contraction cascade is presented from the reaction of 1-boronodienes and arylnitroso derivatives to derive *N*-arylpyrroles in moderate to good yields (up to 82%).**

The biological activity associated with pyrroles and *N*-aryl pyrroles<sup>1</sup> makes them a target for the development of novel synthetic approaches.<sup>2</sup> This communication reports a new and unexpected *N*-aryl pyrrole synthesis resulting from the reaction of an arylnitroso compound with a 1-boronodiene.

The reaction of nitroso compounds with dienes is well known,<sup>3</sup> deriving 3,6-dihydro-1,2-oxazines, which can be used as bioactives and in synthetic applications.<sup>4</sup> As part of a programme to examine the potential of nitroso-dienophiles and 1-boronodienes<sup>5</sup> for the cascade reactions,<sup>6</sup> we examined the reaction of dienes **1** with arylnitroso compounds **2** with the expectation of obtaining the oxazines **3** and/or **4** from which cascade reactions could be carried out to access allylic alcohols **5** and/or **6** (Scheme 1).



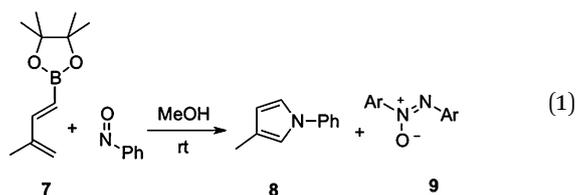
**Scheme 1** Proposed cascade process initiated by a boronodiene-nitroso-dienophile cycloaddition.

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However, instead of cycloadducts of type **3** and/or **4** being observed, the unexpected *N*-phenylpyrrole **8** was identified (eqn (1)) from the reaction of boronate ester **7** with nitrosobenzene. This prompted a more detailed investigation of this novel and intriguing process.

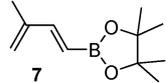
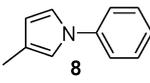
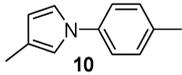
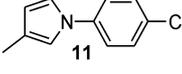
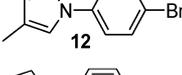
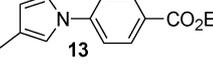
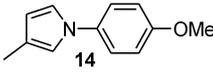
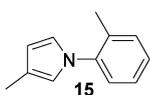
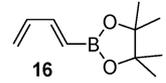
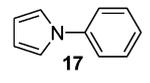
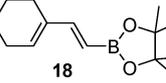
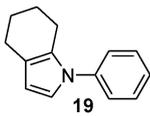
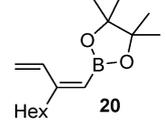
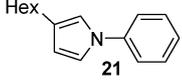
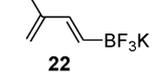


When this reaction (eqn (1)) was repeated and followed *in situ* by <sup>1</sup>H NMR, no cycloadduct (of either type **3** or **4**) could be observed; only **8** and **9** were identified, together with starting materials. After 5 h, the reaction was complete and the pyrrole **8** was isolated in up to 82% yield (entry 3, Table 1).

As shown in Table 1, different arylnitroso compounds undergo this conversion with boronated dienes to provide *N*-aryl pyrroles (Table 1). Yields were moderate to good and the reaction could be conducted in either methanol or DCM (see entries 1, 2, Table 1) without an obvious solvent effect. A slightly higher yield appears to result from an excess of the arylnitroso compound (compare entries 3 and 1, Table 1) and hence, 2.5 equivalents of arylnitroso compound was used for most reactions. Surprisingly, there was no influence of the nature of the aromatic ring substituent; major electronic effects were not apparent and yields for pyrroles **10–15** varied from 52 to 82% (entries 4–9, Table 1).

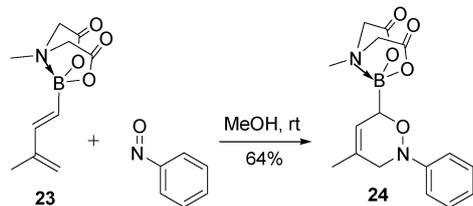
Diene **16** reacted with nitrosobenzene to give the corresponding pyrrole **17** in 78% yield. However, with a more sterically hindered diene **18**, there was a significant decrease of yield (16% for the pyrrole **19**) even after an extended reaction time (entry 11, Table 1). Changing the dienylboronate geometry to (*Z*) as in compound **20** also had a detrimental effect, with adduct **21** only being isolated in 34% yield, after 16 h (entry 12, Table 1). Interestingly, this reaction can be also carried out using a trifluoroborylated diene **22**, deriving the pyrroles **10**, **14** and **15** with slightly improved yields (entries 13–15, Table 1) compared to the pinacol esters. We then examined similar reactions using both *t*-butylnitroso and acylnitroso<sup>7</sup> with diene **7**, yet neither gave nitroso-Diels–Alder adducts.

**Table 1** Arylnitroso to *N*-aryl pyrrole conversions by reaction with diene boronates

Entry	Diene <sup>a</sup>	Nitroso	Product	Conditions	Yield <sup>b</sup> (%)
1		Ph-NO		ArNO 1.5 equiv., MeOH, RT, 5 h	67
2	7	Ph-NO	8	ArNO 1.5 equiv., CH <sub>2</sub> Cl <sub>2</sub> , RT, 48 h	61
3	7	Ph-NO	8	ArNO 2.5 equiv., MeOH, RT, 5 h	82
4	7	4-Me-C <sub>6</sub> H <sub>4</sub> -NO		ArNO 2.5 equiv., MeOH, RT, 5 h	60
5	7	4-Cl-C <sub>6</sub> H <sub>4</sub> -NO		ArNO 2.5 equiv., MeOH, RT, 5 h	68
6	7	4-Br-C <sub>6</sub> H <sub>4</sub> -NO		ArNO 2.5 equiv., MeOH, RT, 5 h	65
7	7	4-EtO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub> -NO		ArNO 2.5 equiv., MeOH, RT, 5 h	57
8	7	4-MeO-C <sub>6</sub> H <sub>4</sub> -NO		ArNO 2.5 equiv., MeOH, RT, 5 h	71
9	7	2-Me-C <sub>6</sub> H <sub>4</sub> -NO		ArNO 2.5 equiv., MeOH, RT, 5 h	52
10		Ph-NO		ArNO 2.5 equiv., MeOH, RT, 5 h	78
11		Ph-NO		ArNO 2.5 equiv., MeOH, RT, 16 h	16
12		Ph-NO		ArNO 2.5 equiv., MeOH, RT, 16 h	34
13		4-Me-C <sub>6</sub> H <sub>4</sub> -NO	10	ArNO 2.5 equiv., MeOH, RT, 5 h	66
14	22	4-MeO-C <sub>6</sub> H <sub>4</sub> -NO	14	ArNO 2.5 equiv., MeOH, RT, 5 h	77
15	22	2-Me-C <sub>6</sub> H <sub>4</sub> -NO	15	ArNO 2.5 equiv., MeOH, RT, 5 h	69

<sup>a</sup> For diene synthesis, see ref. 8. <sup>b</sup> Yields are isolated yields after silica gel chromatography. Lower yields tend to reflect the difficulty of separating azo and azo-oxide by-products from the pyrroles; all conversions were high (with the exception entry 11, which is a slow and less efficient reaction).

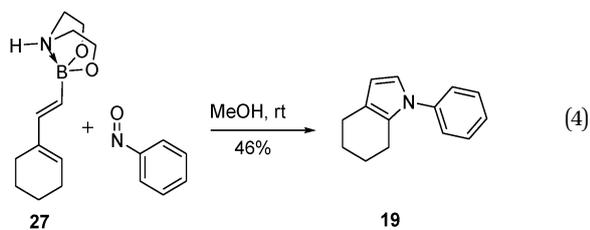
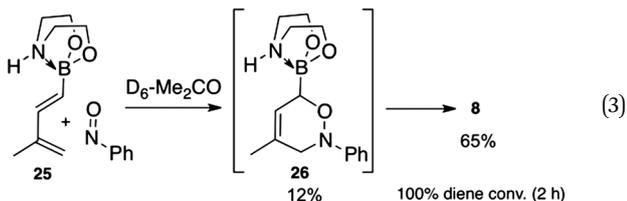
Interesting results were obtained when MIDA and diethanolamine dieneboronates were examined with nitroso benzene (eqn (2)–(4)). Using MIDA boronate **23** modifies the reactivity of the adjacent unsaturated moiety,<sup>9</sup> hence providing the stable



[4+2] cycloadduct **24** in 64% yield; the regiochemistry being assigned by NOESY NMR (see ESI†).

Using the diethanolamine ester **25** (eqn (3)) and following the reaction *in situ* by <sup>1</sup>H NMR, the cycloadduct **26** was identified by comparison of its <sup>1</sup>H NMR with those of **24**. After 2 h, all diene was consumed, the boronated 1,2-oxazine had disappeared and pyrrole **8** (with small amounts of azoxybenzene **9** and 12% cycloadduct **26**) were detected, which shows that the reaction is faster with a diethanolamine ester (50% conversion after 5 min at rt vs. 5 h for total conversion of the pinacol ester, Table 1, entry 2). This observation is reinforced by the reaction of the diethanolamine ester analogue of **18**, **27**<sup>10</sup> which in 2 h provided a 48% yield of pyrrole **19** (*cf.* 16% in 16 h, entry 11, Table 1).

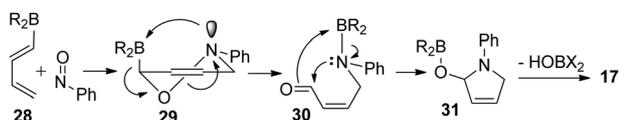
The observation of the boronated 1,2-oxazine **26** shows that in this case, pyrrole formation is preceded by a regioselective nitroso-Diels-Alder reaction. It is noteworthy that no pyrrole formation was observed if the cycloadduct is stable towards hydrolysis, as it is the case for the MIDA derivatives (see eqn (2)). Hence, tricoordinated  $sp^2$  boron species are required for ring contraction from the oxazine to the pyrrole to take place. Finally, it appears that the aryl nitroso is not required as an oxidant to effect pyrrole formation, hence a nitroso-based oxidation of the B-C bond of the oxazine might be ruled out as being involved in the ring contraction-pyrrole formation.



These results raise interesting mechanistic questions. Although it is known that 3,6-dihydro-1,2-oxazines can be converted to pyrroles, the conditions employed here (spontaneous ring contraction) are clearly different requiring several steps,<sup>11</sup> specific substituents,<sup>12</sup> photolysis,<sup>13</sup> high temperature,<sup>14</sup> samarium diiodide,<sup>15</sup> oxidants,<sup>16</sup> basic or acid reagents.<sup>17</sup> In this case, we propose that pyrrole formation proceeds (Scheme 2) through Diels-Alder reaction of boronodiene **28** to give **29**, followed by boryl rearrangement (to give **30**), intramolecular aza-boryl to aldehyde addition (to give **31**) and borate elimination (to give **17**). This is supported by intrinsic reaction coordinate pathways of model geometries related to compounds shown in Scheme 2 computed at B3LYP/6-31G\* (see ESI†). All steps were computed to be exothermic thus supporting the proposed cascade process. In the initial Diels-Alder reaction where four different pathways were determined, the lowest transition state (TS) barrier was found to be only 8.8 kcal mol<sup>-1</sup>.

In conclusion, we report a novel approach to *N*-aryl pyrroles which may proceed through a [4+2]-cycloaddition/ring contraction cascade process from aryl nitroso compounds and 1-boronodiene. This reaction reveals interesting mechanistic features that are in agreement with similar behaviour previously observed with related five-membered ring heterocycles.<sup>18</sup> Further investigations to confirm the proposed rearrangement mechanism, its generality and the influence of the boron substituents are underway.

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**Scheme 2** Proposed mechanism for the reaction of boronodienes aryl nitroso compounds to give pyrroles.

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