A Dienyl Boronate-Aryl Nitroso Ene Reaction Entry to *C*-Pyrrolyl Nitrones and Subsequent Conversion to Isoxazolidines

Ludovic Eberlin,[a,b] Aurélie Macé,[a] Andrei S. Batsanov,[b] Bertrand Carboni*[a] and Andrew Whiting*[b]

Abstract: A new cascade reaction to access *C*-pyrrolyl nitrones en route to isoxazolidines is reported; a process that involves four successive steps, the first key step being an ene-reaction of a 3-methyl-1,3-dienylboronate ester with an aryl nitroso compounds to derive uncommon 1,3-dipoles which react with various alkenes to access isoxazolidines. The scope and mechanism of the cascade sequence is discussed.

Introduction

One-pot, multiple-step processesare increasingly important in organic chemistry, especially in order to access drug-like compounds.[1] The main advantages of such sequences include: atom economy; reduction of waste and need for chromatographic purification steps; and saving of time and effort. Boronic acids and their derivatives are increasingly and extensively used as building blocks in organic synthesis [2] and, as such, have proved to be particularly effective in multicomponent processes.[3] On the other hand, nitrones have been also recognized as valuable synthetic intermediates in organic and medicinal chemistry[4] and are generally prepared either by condensation of *N*-alkylhydroxylamines with carbonyl compounds, or oxidation of hydroxyl amines, secondary amines or imines or via other miscellaneous methods.[5] We report herein a novel route to *C*-pyrrolyl nitrones **3** from a boron-substituted diene and an arylnitroso compound, the scope and some mechanistic considerations of this cascade sequence and the behaviour of these 1,3-dipoles towards activated alkenes in order to access isoxazolidines (Scheme 1).[6]

[a] Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes) - UMR 6226, F-35000 Rennes, France.
E-mail: bertrand.carboni@univ-rennes1.fr
[b] Centre for Sustainable Chemical Processes, Department of Chemistry, Durham University, Science Laboratories, South Road, Durham DH1 3LE, U.K.
E-mail: andy.whiting@durham.ac.uk

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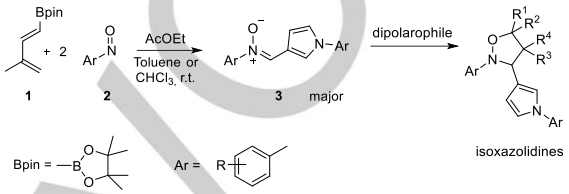
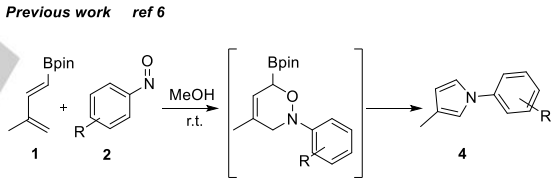


Scheme 1. Access to nitrones **3** from 1-boronated 1,3-dienes **1** and arylnitroso compounds **2**.

Results and Discussion

We previously reported that 1-boronated-1,3-dienes react with substituted nitrosobenzene in methanol to afford the resulting pyrroles **4** *via* a hetero-Diels-Alder, followed by ring contraction sequence (Scheme 2).[7]



Scheme 2. Synthesis of pyrroles **4** from 1-boronated 1,3-dienes and arylnitroso compounds.

We here describe that the course of these reactions are greatly impacted by solvent change, i.e. from methanol to ethyl acetate. Nitrones **3** then become the major product of a new and efficient cascade process, together with formation of the azoxy dimer. Nitroso compound **2b** (R = 4-CO_2Et) was first selected as a model compound. Addition to the diene **1** resulted in the spontaneous precipitation of nitrone **3b** from the reaction mixture (See Scheme 1) and, after addition of hexane, it was readily isolated in a 54% yield. The nitrone structure was established by spectroscopic methods (diagnostic ^{1}H NMR signals at δ 8.99 (t, 1H) for C<u>H</u>=N(Ar)O, 8.08 (d, 1H), 7.24 (dd, 1H) and 6.70 (dd, 1H) ppm for the pyrrole hydrogens). This structure of **3b** was also unambiguously confirmed by single crystal X-ray analysis (Figure 1)[8,9] showing an *E*-relationship between the large groups (aromatic ring and pyrrole substituent). The bond lengths, N_1-C_{12} = 1.301 Å and N_1-O_3 = 1.2991 Å, and the bond angle O_3-N_1-C_{12} = 121.8°, are in agreement with other related nitrones described in the literature.[10]

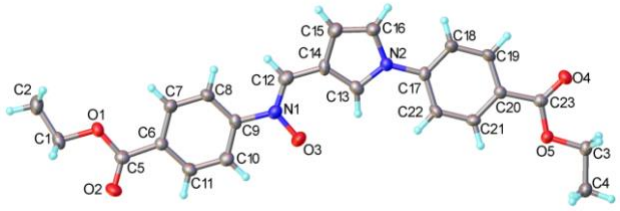
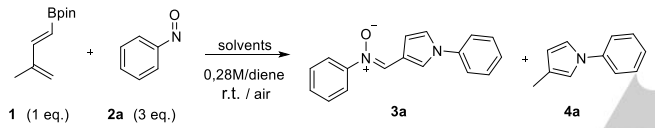


Figure 1. X-Ray crystallographic structure of nitrone **3b**.

The unambiguous identification of **3b** showed the efficiency of the cascade process involved in its formation, which requires two molecules of nitrosoarene, combining with one of diene, providing high conversion considering the number of new bonds being created and the competing pyrrole formation. To study this unexpected behaviour in more detail, the influence of different solvents upon this reaction with nitrosobenzene as model reactant was first examined (see Table 1).

Table 1. Influence of the solvent upon the formation of **3a** and **4a** from **1**.

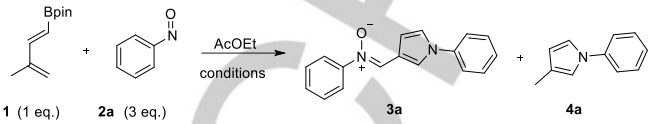


Entry	Solvent	Ratio **1**/ **3a** / **4a** [a]	Ratio nitrone /pyrrole [b]
1	$CDCl_3$	15/66/19	78/22
2	Toluene d_8	20/50/30	63/37
3	MeOD	0/20/80	20/80
4	THF d_8	22/62/16	79/21
5	Acetone d_6	27/49/24	67/33
6	CD_3CN	14/65/21	76/24
7	AcOEt	15/65/20	75/25
8	AcOEt [c]	32/51/17	75/25
9	AcOEt [d]	19/63/18	78/22

[a] Ratio measured by ^{1}H NMR analysis on the crude reaction mixture after 2 h with % (diene + nitrone + pyrrole) = 100. [b] Ratio measured by ^{1}H NMR analysis on the crude reaction mixture after 2 h with % (nitrone + pyrrole) = 100. [c] Concentration of diene: 0,14 M. [d] Concentration of diene: 1.1 M.

Running the reaction in MeOH substantially increased the relative efficiency of pyrrole compared to nitrone formation. No significant differences were found for the other solvents (entry 3 compared with entries 1-2 and 4-7) (Table 1) and there was little influence of concentration, as noted for reactions carried out in AcOEt, except the expected increase in conversion of the diene (Table 1, entries 7, 8 and 9). A further set of experiments were carried to improve the oxidation step, necessarily present in the cascade process (see the mechanistic hypothesis below) while keeping EtOAc as solvent (see Table 2).

Table 2. Influence of the reaction conditions upon the formation of **3a** and **4a** from **1**.



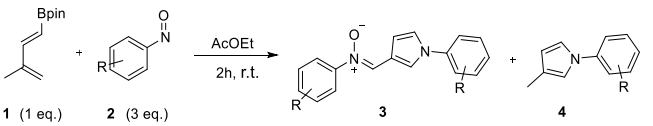
Entry	Experimental conditions [a]	Additive	Ratio **1** / **3a** / **4a** [b]	Ratio **3a** /**4a** [c]
1	rt / air	no	20/58/22	72/28
2	rt / O_2	no	21/57/22	72/28
3	rt / Ar	no	23/55/22	71/29
4	rt / air	TEMPO (0.1 eq.)	20/68/12	81/15
5	rt / air	TEMPO (0.5 eq.)	10/79/11	88/12
6	rt / air	TEMPO (1 eq.)	0/91/9	91/9

[a] Concentration of diene: 0.53 mol.L^{-1}. [b] Ratio measured by ^{1}H NMR analysis on the crude reaction mixture after 1.5 h with % (diene + nitrone + pyrrole) = 100. [c] Ratio measured by 1H NMR analysis on the crude reaction mixture after 1.5 h with % (nitrone + pyrrole) = 100.

Hence, no modification was observed, either when the reaction was carried out under either air, oxygen or argon (Entries 1-3, Table 2). The addition of 2,2,6,6-tetramethylpiperidineoxyl (TEMPO) caused the total consumption of **1a** and an increase in the final ratio of compounds **3a** to **4a** (Table 2, entries 4, 5, 6). However, there was only a moderate effect, more consistent with the suppression of any competing radical reactions, rather than having a direct impact upon the process itself.

Finally, the influence of the substituent on the aromatic ring of compounds **2** was examined with respect to the ratio of pyrrole to nitrone (see Table 3) while keeping EtOAc as solvent.

Table 3. Influence of the substituent on the aromatic ring upon the ratio **3 / 4**



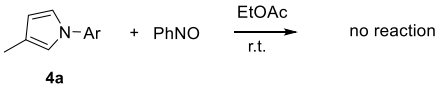
Entry	Starting nitroso compound	R	Ratio **3** /**4** [a]
1	**2a**	H	75/25
2	**2b**	4-CO_2Et	95/5
3	**2c**	4-Br	83/17

4	**2d**	4-Me	68/32
5	**2e**	2-Me	43/57
6	**2f**	4-OMe	57/43

[a] Ratio measured by ^{1}H NMR analysis on the crude reaction mixture after 2 h with % (nitrone + pyrrole) = 100.

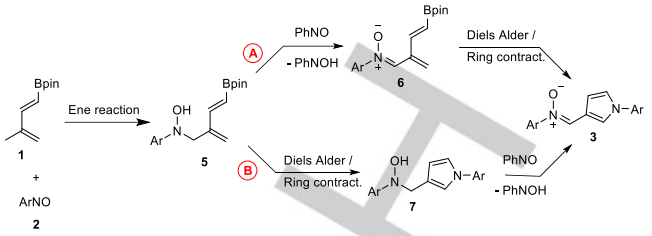
Table 3 shows that with an electron-withdrawing group (CO_2Et or Br), the ratio of nitrone to straight pyrrole formation was higher than with a simple phenyl group, and conversely, with an electron donating substituent, more pyrrole formation was observed; the lowest ratio being detected with an *ortho*-methyl substituent (see Entry 4).

Overall, these experimental results suggest the following mechanistic rationale, i.e. involving the formation of nitrones **3** from **1**. The first step of this process could be the formation of a pyrrole **4**, as previously reported followed by nitrone formation.[7] However, this hypothesis was readily excluded since pyrrole **4a** was recovered unchanged when it was brought into contact with excess of nitrosobenzene in EtOAc (see Scheme 3).



Scheme 3. Behaviour of pyrrole **4a** in the presence of nitrosobenzene.

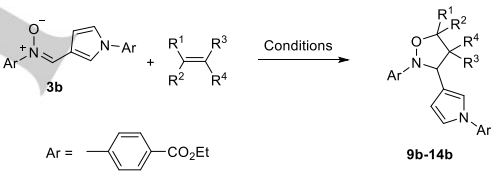
[4+2]-Hetero-Diels-Alder reactions of nitroso derivatives have been extensively studied over past decades,[11] and their use as enophiles for allylic nitrogen functionalisation has also been extensively reported.[12] In the case of aryl nitroso compounds and 1,3-dienes, the cycloaddition pathway nearly always prevails,[13] except in a few cases of metal-catalyzed amination reactions.[14] We therefore hypothesize that the first step of the formation of nitrones **3** was likely to involve a nitroso-ene reaction, to give the hydroxylamine **5** (Scheme 4); behaviour that is in agreement with the increase of enophilic reactivity observed for nitroso compounds possessing an electron-withdrawing group (see Table 3). However, it is not clear what role the solvent plays in this process, as mentioned above. After the ene reaction, the second step of the cascade process would then be the conversion of hydroxylaminodiene **5** to the corresponding nitrone **6** (path A). This oxidation step is likely caused by the nitrosoarene (present in excess), and indeed, such processes have been reported previously by Knight and Loadman for *N*-alkyl-*N*-arylhydroxylamines.[15] Also of note is the positive effect that TEMPO can have on the conversion of hydroxylamines to nitrones.[16] Finally, a hetero-Diels-Alder reaction with further nitroso species, followed by the already mentioned ring contraction-pyrrole formation reaction likely occurs to afford **3**. However, of course, the formation of the pyrrole ring could may precede the oxidation step of the hydroxylamine **5** (path B).

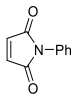
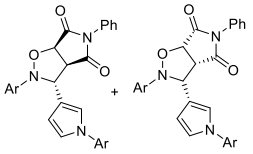
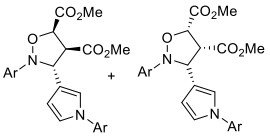
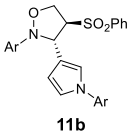
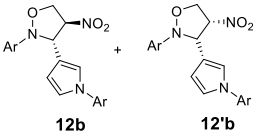


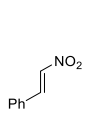
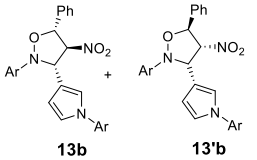
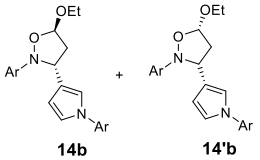
Scheme 4. Proposed mechanism for the formation of nitrones from the reaction of 1-boronated 1,3-dienes and nitrosoarenes.

To our knowledge, only three isolated examples of nitrones possessing a *C*-pyrrole substituent have been hitherto reported in the literature.[17] Due to the multiple synthetic applications of similar derivatives in organic synthesis,[5,18] we initiated a further study of their reactivity as 1,3-dipoles towards activated alkenes. Hence, starting with nitrone **3b** (obtained pure in good yield by precipitation from the reaction mixture, via the reaction shown in Scheme 1), cycloadditions were then carried out in toluene, except for ethyl vinyl ether which was used as reagent and solvent (see Table 4).

Table 4. [3+2] Cycloaddition of **3b** to activated alkenes



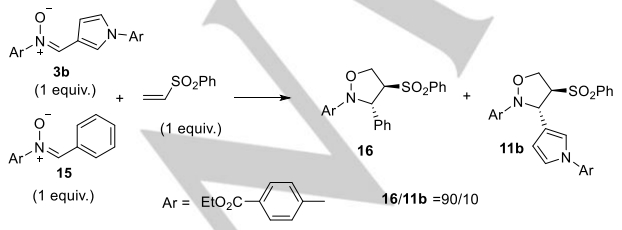
Entry	Alkene	Cycloadducts	Yield (d. r.) [a, b]
1		 **9b** **9'b**	76 [c] (**9b**/**9'b** = 75/25)
2		 **10b** **10'b**	50 [d,e] (**10b**/**10'b** = 50/50)
3		 **11b**	63 [d] (single isomer)
4		 **12b** **12'b**	67 [f] (**12b**/**12'b** = 33/67)

5			77 [d,g] (**13b/13'b** = 84/16)[h]
		13b **13'b**	
6			77 [i] (**14b/14b'** = 75/25)
		14b **14'b**	

[a] Isolated yields. [b] Diastereomeric ratio are determined on the ^{1}H NMR spectrum of the crude material. [c] Toluene, 90 °C, 15 h. [d] Toluene, 80 °C, 15 h. [e] 73% yield based on recovered starting material. [f] Toluene, r.t., 19 h. [g] 85% yield based on recovered starting material. [h] Another isomer **13"b** (inverse regioselectivity) was also identified (**13b**/**13'b**/**13"b**=73/15/12 in the crude product). [i] Ethylvinylether as solvent, 80 °C, 72 h.

As expected, this versatile pericyclic process tolerates a range of electron-poor and electron-rich dipolarophiles and cycloadducts **9b**-**14b** were obtained in moderate to good yields, usually after heating at 80-90°C, except for nitroethylene which reacted at room temperature. Their structures were determined by comparison with the literature [19] and by ^{1}H, ^{13}C and ^{1}H-^{1}H NOESY NMR experiments. In the case of unsymmetrical dipolarophiles, the [3+2] cycloaddition, controlled by the frontier molecular orbitals on the nitrone and the alkene,[20] is highly regioselective leading to the 4-substituted isoxazolidine(s) when the dipolarophile is electron poor (Entry 3-5, Table 4) and to the 5-substituted isomers in the case of an electron-donating group (Entry 6, Table 4). Concerning the stereoselectivity, *endo* cycloadducts (*trans* relationship when a single electron activating group is present) were predominantly obtained with *N*-phenylmaleimide, β-nitrostyrene and ethyl vinyl ether, a sole isomer being only observed with phenyl vinylsulfone. In agreement with the literature related to *C,N*-diaryl nitrones,[19c] this selectivity was reversed for nitroethylene.

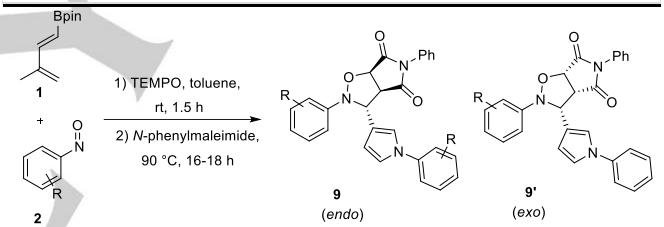
Compared to a *C*-phenyl substituent, the presence of the pyrrole moiety on the nitrone core leads to a decrease in reactivity towards electron poor partners. This was confirmed by carrying a competitive cycloaddition using equimolar amounts of **3b** and **15** [21] to phenyl vinyl sulfone, selected as a model dipolarophile. A 9/1 mixture of **16** and **11b** was obtained after 15 h in toluene at 80 °C (Scheme 5).



Scheme 5. Competitive [3+2] cycloaddition of **3b** and **15** to phenyl vinyl sulfone.

Due to difficulties encountered during the purification of compounds **3** by column chromatography, we chose to carry out the successive formation of the nitrone and the subsequent cycloaddition in a one-pot sequence. *N*-Phenylmaleimide was selected as model dipolarophile and the reactions were accomplished in the presence of TEMPO, *i.e.* under the best conditions for the formation of the nitrone intermediate (Table 3). In order to enlarge the range of the reaction temperature, AcOEt was replaced by toluene, without any notable affect on the overall yield. The crude reaction mixture was checked by ^{1}H NMR after 1.5 h to ensure full consumption of diene **1**. *N*-Phenyl maleimide was then added and the mixture and stirred at 90 °C for 16 h. Although yields were moderate, they were the result of four reaction steps, the best results being obtained when an electron-withdrawing group was present on the aromatic moiety. With a *para*-methoxy substituent, no cycloadduct was observed, although the formation of the nitrone was evidenced by ^{1} H NMR. Concerning the stereoselectivity, a mixture of *endo*- and *exo*-isomers, respectively **9** and **9'**, was always obtained. The stereochemistry of these isomers was established by ^{1}H, ^{13}C and ^{1}H-^{1}H NOESY NMR spectroscopy and confirmed by three X-ray structures of **9'a** (R = H), **9d** (2-Me) and **9f** (R = 4-Cl) (see supporting information).[9]

Table 5. One pot nitrone formation/[3+2]-cycloaddition sequence



Entry	R	Cycloadducts	Yield (%)[a]	Diastereomeric ratio *endo/exo* [b]
1	H	**9a** + **9'a**	40	67/37
2	4-CO_2Et	**9b** + **9'b**	40	51/49
3	4-Br	**9c** + **9'c**	45	58/42
4	2-Me	**9d** + **9'd**	25	67/33
5	4-OMe	**9e** + **9'e**	-	-
6	4-Cl	**9f** + **9'f**	51]	55/45

[a] Isolated yields. [b] Determined on the ^{1}H NMR spectrum of the crude material.

Conclusions

In summary, the synthesis of *C*-pyrrolyl nitrones from a dienyl boronic ester and nitroso arenes was investigated. A presumed mechanism for this new cascade process involves an ene reaction as key first step, favoured by the presence of an sp_3 boron substituent. *In situ* oxidation and Diels-Alder / ring

contraction sequence (in this or the reverse order**)** occurred in a second phase of the reaction. The regio- and stereo-chemical course of cycloadditions to activated alkenes was similar to those observed for the analogous *C*-phenyl nitrones, a small decrease of reactivity being observed.

Supporting Information Summary

Experimental details, compound data, and copies of NMR spectra of new compounds.

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Keywords: cascade • boronic esters • 1,3-diene • arylnitroso • nitrone

[1] For some reviews, see : a) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866-880. b) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442-524. c) D. B. Ramachary, S. Jain, *Org. Biomol. Chem.* **2011**, *9*, 1277-1300. d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134-7186. e) L. F. Tietze, *Chem. Rev*. **1996**, *96*, 115-136. f) Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions;* Wiley-VCH: Weinheim, Germany, 2005.

[2] a) *Boronic acids: Preparation, Applications in Organic Synthesis and Medicine,* 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, **2011**. b) *Boron reagents in synthesis;* Coca, A. Eds, ACS Symposium Series 1236; American Chemical Society: Washington, DC, **2016**.

[3] For recent selected examples, see: a) B. François, L. Szczubelek, F. Berrée, T. Roisnel, B. Carboni *Adv. Synth. Cat.* **2018**, *360*, 235-241. b) M. Gao, M. C. Willis, *Org. Lett.* **2017**, *19*, 2734-2737. c) A. Mace, S. Touchet, P. Andres, F. Cossio, V. Dorcet, F. Carreaux, Carboni, B. *Angew. Chem., Int. Ed.* **2016,** *55*, 1025-1029. d) C. A. Guerrera, T. R. Ryder, *ACS Symposium Series* **2016**, *1236*, 275-311. e) D. G. Hall, T. Rybak, T. Verdelet, *Acc. Chem. Res*. **2016**, *49*, 2489-2500. f) Y. Yu, K. J. Shin, J. H. Seo, *J. Org. Chem.* **2017**, *82*, 1864-1871. g) K. S. Barbato, Y. Luan, D. Ramella, J. S. Panek, S. E. Schaus, *Org. Lett.* **2015**, *17*, 5812-5815. h) T. Beisel, G. Manolikakes, *Org. Lett.* **2015**, *17*, 3162-3165.

[4] For recent reviews, see: a) M. Rosselin, B. Poeggeler, G. Durand, *Curr. Top. Med. Chem.* **2017**, *17*, 2006-2022. b) P. Merino, T. Tejero, I. Delso, R. Matute, *Org. Biomol. Chem* **2017**, *15*, 3364-3375. c) A. I. Padwa, S. Bur, *Chem. Heterocycl. Compd*. **2016**, *52*, 616-626. d) M. Berthet, T. Cheviet, G. Dujardin, I. Parrot, J. Martinez, *Chem. Rev.* **2016**, *116*, 15235-15283. e) L. L. Anderson, *Asian J. Org. Chem.* **2016**, *5*, 9-30. f) D. B. Huple, S. Ghorpade, R.-S. Liu, *Adv. Synt. Cat* **2016**, *358*, 1348-1367. g) W.-M. Shi, X.-P. Ma, G.-F. Su, D.-L. Mo, *Org. Chem. Front*. **2016**, *3*, 116-130.

[5] P. Merino in *Science of Synthesis (Houben-Weyl: Methods of. Molecular Transformations)*, Padwa, A. Ed., Thieme, Stuttgart, **2004**, pp. 511-580. I. A. Grigor'ev in *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons: Hoboken, **2008**; pp 129-434.

[6] For a pertinent review on cascade (domino) reactions, see: *Domino Reactions: Concepts for Efficient Organic Synthesis*, L. F. Tietze Ed., Wiley-VCH, Weinheim, 2014.

[7] L. Eberlin, B. Carboni, A. Whiting, *J. Org. Chem.* **2015**, 80, 6574-6583.

[8] To our knowledge, there is only one example of nitrone of this type: A. Treibs, G. Fritz, *Justus Liebigs Ann. Chem.* **1958**, 611, 162-193.

[9] CCDC 1587197, 1587198, 1587199 and 1587200 contain the supplementary crystallographic data for **3b**, **9'a**, **9d** and **9f**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] a) R. Herrera, A. Nagarajan, M. A. Morales, F. Mendez, H. A. Jimenez-Vazquez, L. G. Zepeda, J. Tamariz. *J. Org. Chem.*, **2001**, *66*, 1252-1263. b) W. Kliegel, J. Metge, S. J. Rettig, J. Trotter, *Can. J. Chem.*, **1998**, *76*, 389-399.

[11] For some reviews, see: a) B. Maji, H. Yamamoto, *J. Am. Chem. Soc.* **2015,** *137*, 15957-15963. b) S. Carosso, M. J. Miller, *Org. Biomol. Chem.* **2014**, *12*, 7445-7468. c) B. S. Bodnar, M. J. Miller, *Angew. Chem., Int. Ed.* **2011**, *50*, 5630-5647. d) Y. Yamamoto, H. Yamamoto, *Eur J Org Chem.* **2006**, 2031-2043.

[12] For some reviews, see: a) J. Ouyang, X. Mi, Y. Wang, R. Hong, *Synlett* **2017**, *28*, 762-772. b) L. I. Palmer, C. P. Frazier, J. Read de Alaniz, *Synthesis* **2014**, *46*, 269-280. c) M. Baidya, H. Yamamoto, *Synthesis* **2013**, *45*, 1931. d) W. Adam, O. Krebs, *Chem. Rev.* **2003**, *103*, 4131-4146.

[13] For isoprene: a) L. Brulíková, A. Harrison, M. J. Miller, J. Hlaváč, *Beilstein J. Org. Chem.* **2016,** *12,* 1949-1980. b) T. Sasaki, S. Eguchi, T. Ishii, H. Yamada, *J. Org. Chem.* **1970**, *56,* 4273-4275. c) G. Kresze, O. Korpiun, *Tetrahedron* **1966**, *22.* 2493-2504. For 2,3-dimethyl-1,3-butadiene: a) N. Jana, F. Zhou, T.G. Driver, *J. Am. Chem. Soc.* **2015**, *137*, 6738-6741. b) A. V. Velikorodov, N. G. Urlyapova, A. D. Daudova, *Pharm. Chem. J.* **2006**, 32-34. c) H. Labaziewicz, K. R. Lindfors, *Heterocycles* **1989,** *29*, 929-938; d) J. Hamer, R. E. Bernard, *J. Org. Chem.* **1963**, *28*, 1405-1406. For 1-phenyl 3- methyl butadiene: J.-M. Chen, C.-J. Chang, Y.-J. Ke, R.-S. Liu, *J. Org. Chem.* **2014**, *79*, 4306-4311.

[14] a) S. Murru, R. S. Srivastava, *Eur. J. Org. Chem.* **2014,** 2174-2181. b) S. Murru, B. McGough, R. S. Srivastava, *Org. Biomol. Chem.* **2014**, 12, 9133-9138.

[15] G. T. Knight, M. J. R. Loadman, *J. Chem. Soc. B,* **1971**, 2107-2112.

[16] P. Merino, I. Delso, T. Tejero, F. Cardona, A. Goti, *Synlett* **2007**, 2651-2654.

[17] a) T. Yoneyama, K. Teshima, F. Jinno, T. Kondo, S. Asahi, *J. Chromatogr. B* **2016,** *1015-1016*, 42-49. b) A. Treibs, G. Fritz, *Justus Liebigs Ann. Chem.* **1958,** *611*, 162-193.

[18] For reactions other than dipolar cycloadditions, see: a) J. Yang, *Synlett* **2012**, 23, 2293-2297. b) B. Hu, Z. Wang, N. Ai, J. Zheng, X.-H. Liu, S. Shan, Z. Wang, *Org. Lett.* **2011**, *13*, 6362-6365. c) S. Yang, D. Liao, X. Tian, X. Lei, *Org. Lett.* **2016,** *18*, 376-379.

[19] Cycloadducts of *C,N*-diaryl nitrones with the corresponding dipolarophiles were used for comparison. a) *N*-Phenyl maleimide: T. Hisano, K. Harano, T. Matsuoka, S. Watanabe, T. Matsuzaki, *Chem. Pharm. Bull.*, **1989**, *37*, 907-911. b) Phenyl vinyl sulfone: V. Ramamoorthy, A. Ramasubbu, S. Muthusubramanian, S. Sivasubramanian, *Synth. Commun.* **1999**, *29*, *21-26*. c) Nitroethylene: R. Jasiński, *Collect. Czech. Chem. Commun.* **2009,** *74***,** 1341-1349. d) Ethyl vinyl ether: U. Chiacchio, A. Liguori, G. Romeo, G. Sindona, N. Uccella, *Tetrahedron* **2009**, *48*, 9473-9482. e) β-Nitrostyrene: A. Banerji, P. K. Biswas, D. Bandyopadhyay, M. Gupta, T. Prangé, A. Neuman, *J. Het. Chem.* **2007**, *44*, 1045-1049.

[20] P. N. Confalone, E. M. Huie, *Org. React.* **1988**, *36,* 1-173.

[21] M. M.-C. Lo, G. C. Fu, *J. Am. Chem.* **2002**, *124*, 4572-4573.

[22] S. Pereira, M. Srebnik, *Organometallics* **1995**, *14*, 3127-3128.

[23] B. Priewisch, K. Rûck-Braun, *J. Org. Chem*. **2005**, *70,* 2350-2352.

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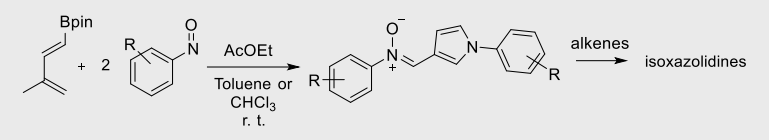

A new cascade reaction to access *C*-pyrrolyl nitrones is reported. This process involves four successive steps; the first key step being an ene-reaction of a 3-methyl-1,3-dienyl boronic ester with an aryl nitroso compound. The mechanism of the cascade sequence is discussed and the reactivity of these uncommon 1,3-dipoles towards various alkenes examined to access isoxazolidines.

Key Topic :Cascade reaction

Ludovic Eberlin, Aurélie Macé, Andrei S. Batsanov, Bertrand Carboni and Andrew Whiting**

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A Dienyl Boronate-Aryl Nitroso Ene Reaction Entry to *C*-Pyrrolyl Nitrones and Subsequent Conversion to Isoxazolidines