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Boronated Enynes as Versatile Sources of Stereodefined and Skeletally Diverse Molecules

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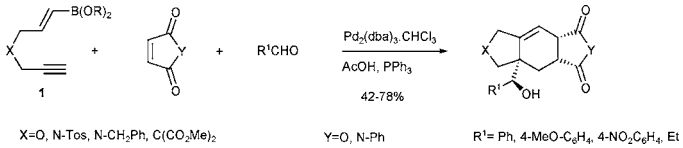
ABSTRACT



The application of a one-pot palladium-catalyzed cycloisomerization of enynes 1/Diels–Alder cycloaddition/allylboration sequence efficiently generates tricyclic structures with complete control of the four stereogenic centers. Ruthenium and platinum catalysts perform distinct transformations providing other isomeric boron-substituted cyclic compounds.

Diversity-oriented synthesis, which emerged from genomics and proteomics research, aims to synthesize series of small molecules with structural complexity and diversity for use in systematic explorations in biology.[1] Following the pioneering work of Schreiber et al., many developments have been recently reported in this field.[2] One possible strategy involves the conversion of a common substrate into a range of products having different structural cores.[3] Transition-metal-catalyzed cycloisomerizations of enynes and multicomponent processes both constitute very attractive and powerful tools to prepare a wide range of diversely substituted polycyclic compounds and are particularly well adapted to the demands of diversity-oriented synthesis. On the other hand, the reactivity and the functional group tolerance of boronic esters have led to an increasing use of these compounds in synthetic organic chemistry, for example, in tandem reactions involving dienyl- or diynylboronates.[4] As a part of our ongoing program related to new multicomponent processes involving boronic acids and their derivatives,[5] we reasoned that boronated enynes **1** could be used as versatile

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(1) Schreiber, S. L *Science* **2000**, *287*, 1964. For a discussion of the use of DOS to explore biology, see: Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51.

(2) Moulin, E.; Barluenga, S.; Totzke, F.; Winssinger, N. *Chem. Eur. J.* **2006**, *12*, 8819. Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R. C. *Eur. J. Org. Chem.* **2006**, 4998. Fitzmaurice, R. J.; Etheridge, Z. C.; Jumel, E.; Woolfson, D. N.; Caddick, S. *Chem. Commun.* **2006**, 4814. Kotha, S.; Mandal, K.; Tiwari, A.; Mobin, S. M. *Chem. Eur. J.* **2006**, *12*, 8024. Wyatt, E. E.; Fergus, S.; Galloway, W. R.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* **2006**, 3296. Freifeld, I.; Holtz, E.; Dahmann, G.; Langer, P. *Eur. J. Org. Chem.* **2006**, 3251. Oikawa, M.; Naito, S.; Sasaki, M. *Tetrahedron Lett.* **2006**, *47*, 4763. Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2006**, *8*, 1193.

(3) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. For a recent and elegant application of this strategy, see: Kumagai, N.; Muncipito, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635.

(4) (a) For a pioneering work, see: Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169. (b) For recent reviews, see: Hilt, G.; Bolze, P. *Synthesis* **2005**, 2091. Carboni, B.; Carreaux, F. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 343−376. (c) See also more recently: Kim, M.; Lee, D. *Org. Lett.* **2005**, *7*, 1865. De, S.; Welker, M. E. *Org. Lett.* **2005**, *7*, 2481. Yamamoto, Y.; Ishii, J.-I.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625. Yamamoto, Y.; Hattori, K.; Ishii, J.; Nishiyama, H. *Tetrahedron* **2006**, *62*, 4294. Hilt, G.; Hesse, W.; Harms, K. *Org. Lett.* **2006**, *8*, 3287.

(5) Gao, X.; Hall, D.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem. Eur. J.* **2006**, *12*, 3132. Berrée, F.; Debache, A.; Marsac, Y.; Collet, B.; Girard-Le Bleiz, P.; Carboni, B. *Tetrahedron* **2006**, *62*, 4027. Debache, A.; Boumoud, B.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2006**, *47*, 5697.

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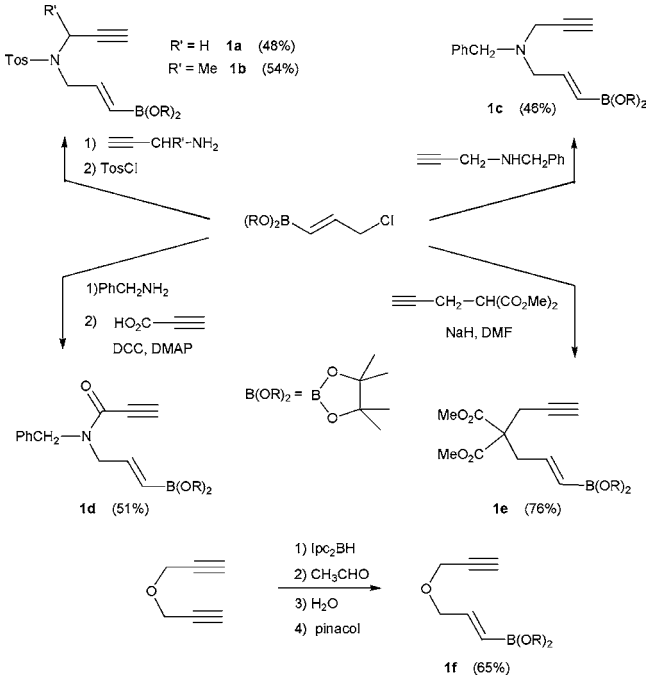
sources of stereodefined and skeletally diverse small molecules.[6] We first started with the palladium-catalyzed synthesis of 1,3-dienes, pioneered by Trost et al.[7] and report herein our preliminary results concerning a one-pot sequential three-component cycloisomerization/Diels−Alder/allylboration sequence. As an extension of this study, we also present two examples of ruthenium and platinum cycloisomerization reactions, which give access to other isomeric cyclic boronic esters.

The enynes **1a,b** were first synthesized from (*E*)-3-chloro-1-propenylboronic ester[8] by addition of an excess of the corresponding primary amines, followed by tosylation. Similarly, *N*-propargylbenzylamine and propargyl malonate directly afforded, respectively, **1c** and **1e** in 46% and 76% yield. For **1d**, the *N*-benzyl derivative was acylated with 2-propynoic acid in the presence of DCC and DMAP. The oxygenated enyne **1f** was best prepared in 65% yield by monohydroboration of dipropargylether with diisopinocampheylborane, followed by dealkylation with an excess of acetaldehyde and transesterification with pinacol (Scheme 1). All of these enynes have controlled *E* double bond

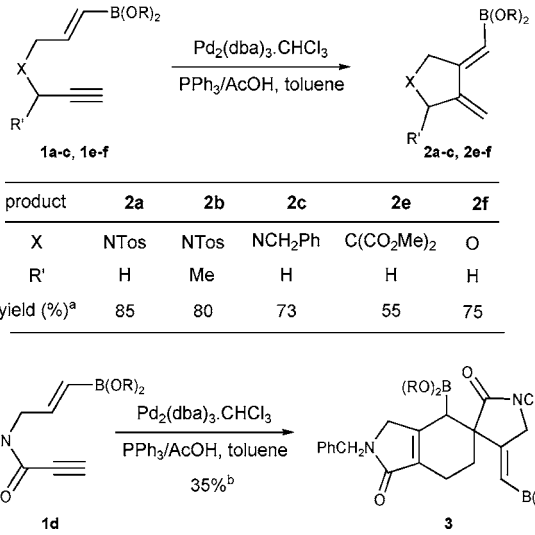
Scheme 1. Preparation of Boronated Enynes **1**



stereochemistry due to the hydroboration step used for the introduction of the boronate group.

Enyne **1a** was first selected as test substrate for the cycloisomerization reaction. Among several palladium sources, $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3/AcOH$ gave best results, whereas yields and purities were lower with $Pd(OAc)_2/PPh_3$ or $Pd(OAc)_2$/([bis(benzylidene)ethylenediamine]. The conversion of **1a** to the 1,3-diene **2a** was complete after 2 h at room temperature (85% yield, measured by ^1H NMR spectroscopy of the crude reaction mixture in the presence of an internal standard). The *Z* geometry of **2a** was determined to be by NOE experiments. For other enynes, **1e,f**, full conversions were readily achieved under the same experimental conditions, whereas 18 h at room temperature and 2 h at 50 °C were necessary for **1c** and **1b**, respectively. It should be noted that significant amounts of non-boronated diene (≈30%) were produced in the case of the malonate derivative **1e**.[9] For **1d**, the only product observed in the crude reaction product was the dimer **3**, even if the cycloisomerization was carried out in the presence of *N*-phenylmaleimide to trap the expected diene (Scheme 2).[10]

Scheme 2. Palladium-Catalyzed Cycloisomerization of Enynes **1**



product	2a	2b	2c	2e	2f
X	NTos	NTos	NCH_2Ph	$C(CO_2Me)_2$	O
R'	H	Me	H	H	H
yield (%)[a]	85	80	73	55	75

[a] Yield estimated by ^1H NMR spectroscopy of the crude reaction mixture with 4-nitroanisole as an internal standard. [b]After purification by chromatography on silica gel.

Although stable in solution, partial decomposition of dienes **2** was observed throughout purification by chromatography on silica gel, which led us to carry out the following step in the same pot without removing the palladium catalyst. Compound **2a** readily underwent Diels−Alder reaction with *N*-phenylmaleimide and maleic anhydride to yield the

(6) For some reviews on cycloisomerization of enynes, see: Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. Trost, B. M.; Toste, D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.

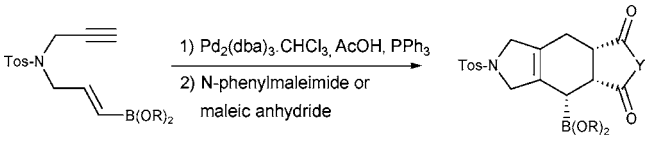
(7) Trost, B. M.; Dong, L.; Schroeder, G. M. J. *J. Am. Chem. Soc.* **2005**, *127*, 10259 and references therein.

(8) Lombardo, M.; Morganti, S.; Tozzi, M.; Trombini, C. *Eur. J. Org. Chem.* **2002**, 2823.

(9) We have no explanation for this different behaviour, compared with other enynes. Such a protodeboronation is often associated with metal-catalyzed reactions of boronic acids. Only the boronated allylboronate **4** can react with the aldehyde, and the final product was easily separated from the non-boronated Diels−Alder cycloadduct.

(10) This behaviour could be attributed to the presence of an electron-withdrawing group in position 2 of **2d** that favors the dimerization process. See, for example: McIntosh, J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, *43*, 4431.

Scheme 3. Diels−Alder Cycloaddition of Diene **2a**



1a

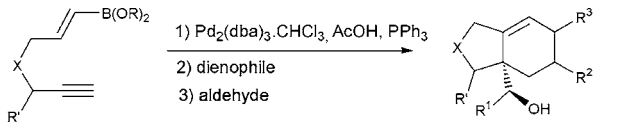
Y= N-Ph **4a** (77%)
Y= O **4b** (83%)

corresponding cycloadducts **4a** and **4b** in 77% and 83% yield as single diastereoisomers. The relative configurations of the three stereogenic centers were attributed on the basis of NOESY experiments and are in agreement with an endo approach as expected[4a] (Scheme 3). The use of a boronic ester derived from (+)-pinanediol did not lead to significant asymmetric induction.

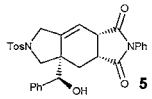
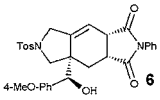
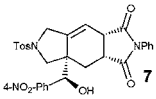
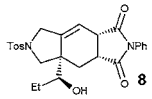
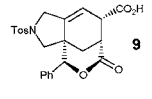
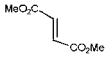
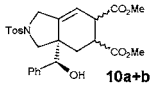
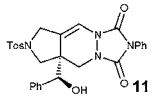
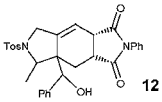
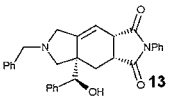
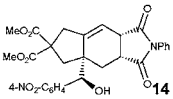
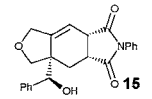
Having in hand an efficient access to new tricyclic allylboronates, we then focused our attention to their addition to aldehydes and, in order to prevent tedious intermediate purification, decided to carry out the palladium-catalyzed cycloisomerization/Diels−Alder cycloaddition/allylboration sequence in the same pot (Table 1). When *N*-phenylmaleimide and maleic anhydride were employed, a successful three-component process occurred in high yields, with complete control of stereochemistry. An X-ray crystal structure determination of **5** confirmed the assignments previously proposed for the allylboronate **4a** and established the relative configuration of the R[1]*C*H(OH) created in the last step, in agreement with a chairlike six-membered transition state.[11] For **9**, a spontaneous intramolecular cyclization was observed, as previously reported,[4a] whereas 4-phenyl triazolidinedione produced a mixture of products, partially as a result of the competitive addition of the starting azo compound to the intermediate Diels−Alder cycloadduct, instead of the expected addition to benzaldehyde.[12] The presence of a methyl group in an α-position to the triple bond of the starting enyne **1b** caused an important decrease in the reactivity of the corresponding cyclic allylboronate, probably due to steric hindrance. Only minor amounts of expected allylic alcohol **12** were obtained, even after heating in toluene at reflux overnight, although the Diels−Alder cycloadduct has been quite quantitatively produced after 50 °C for 5 h.

In addition to these palladium-catalyzed cycloisomerizations, many other skeletal reorganizations are also commonly associated with enynes. To illustrate the potential of enynes **1** in such reactions, we selected ruthenium and platinum catalysts to perform distinct transformations providing other isomeric boron-substituted cyclic compounds (Scheme 4).[13] In the presence of Grubbs II catalyst, **1a** was readily converted to the corresponding cyclic diene **16**, which gave the

Table 1. Cycloisomerization /Diels−Alder Cycloaddition/ Allylboration Sequence



1 **5-15**

entry	enyne	diene	aldehyde	product	yield[a] (%)
1	1a		PhCHO	 **5**	71
2	1a		4-MeO-C_6H_4-CHO	 **6**	74
3	1a		4-NO_2-C_6H_4-CHO	 **7**	78
4	1a		EtCHO	 **8**	69
5	1a		PhCHO	 **9**	71[b]
6	1a		PhCHO	 **10a+b**	47[c]
7	1a		PhCHO	 **11**	23[d]
8	1b		PhCHO	 **12**	-[e]
9	1c		PhCHO	 **13**	52
10	1e		4-NO_2-C_6H_4-CHO	 **14**	42[f]
11	1f		PhCHO	 **15**	52

[a] Isolated yields. [b] Isolated as its methyl ester. [c] Mixture of two diastereoisomers (60/40). [d] Isolated with the addition product to 4-phenyl triazolidinedione and another unidentified byproduct. [e] The Diels−Alder cycloadduct, as a single diastereoisomer, was recovered unchanged. [f] Low yield due to partial deborylation in the cycloisomerisation step.

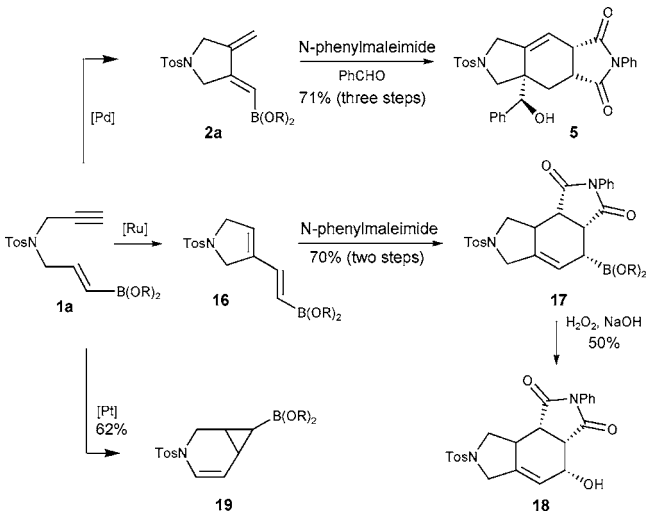
Diels−Alder cycloadduct **17** with *N*-phenylmaleimide in good yield. Unfortunately, the allylboration with benzaldehyde failed even refluxing in toluene. However, oxidation was efficiently carried out and afforded the alcohol **18** that

(11) See Supporting Information for X-ray cristallographic analysis of **5**.

(12) Zhang, A.; Kan, Y.; Jiang, B. *Tetrahedron* **2001**, *57*, 2305.

(13) For other reports dealing with metal-catalyzed synthesis of dienylboronic esters, see: ref 4c and Renaud, J.; Graf, C. D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101. Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272.

Scheme 4. Skeletal Reorganizations of Enyne **1a** with Further Functional Transformations



could be a useful partner in allylic substitution reactions. Platinium-catalyzed cycloisomerization of **1a** provided the expected bicyclo[4.1.0]heptene derivative **19**, with a minor amount (5−10%) of product originating from the metathesis pathway.[14] The presence of a boron-substituted cyclopropane makes it possible to envisage the further creation of new carbon−carbon bonds by Suzuki−Miyaura cross-coupling reaction.

In summary, three-component reactions of boronated enynes, activated alkenes, and aldehydes were found to afford stereodefined tricyclic compounds. The association of the enyne moiety, which can be engaged in various metal-catalyzed cycloisomerization reactions, with the boronate group, for further post-functionalization, should allow the construction of a range of stereodefined and skeletally diverse molecules from common organoboron precursors.

Supporting Information Available: Experimental procedures and spectroscopic data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070400S

(14) Fürstner, A.; Stelzer, F.; Szillat, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 11863.