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Tandem Aza[4 + 2]/Allylboration: A Novel Multicomponent Reaction for the Stereocontrolled Synthesis of α-Hydroxyalkyl Piperidine Derivatives†

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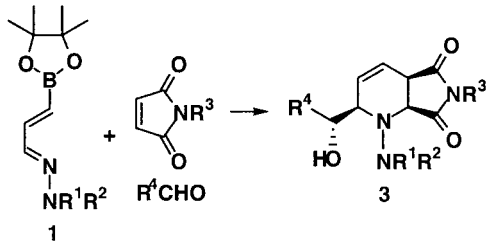
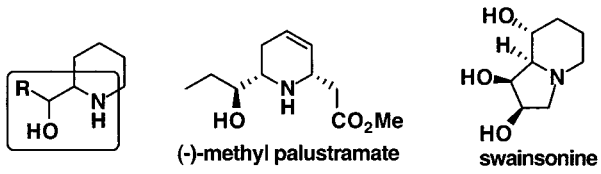
ABSTRACT



The α-hydroxyalkyl piperidine unit is common to several naturally occurring alkaloids and azasugar analogues. Polysubstituted piperidine derivatives of this kind (3), embodying four stereogenic centers, are formed in just a single operation from the highly stereocontrolled reaction of 4-borono-1-azadienes (1), maleimides, and aldehydes. This novel multicomponent reaction which affords as many as four elements of diversity should prove highly valuable in combinatorial chemistry and natural product synthesis.

Tandem processes and multicomponent reactions (MCR) that provide new products with optimal change in structure and functionality from simple substrates, in a single highly atom-economical operation, are particularly attractive both for natural product synthesis[1] and in the more recent context of combinatorial chemistry.[2] There are still very few versatile MCRs to this day. We are aware of only one MCR to construct piperidine derivatives[3] and apparently none to access cyclic β-amino alcohols.[4] Several biologically interesting alkaloids and azasugar analogues such as the polyhydroxylated indolizidine family, exemplified by swainsonine, contain a piperidine ring flanked with a stereodefined hydroxyalkyl group at the α-position.[5] The synthesis of such β-amino alcohol units presents a challenging problem of stereochemical control. Although many approaches were reported, most of them require several linear steps to establish the correct stereochemistry prior to or after a ring closure event.[6]



Herein, we present our preliminary investigations on a simple stereoconvergent MCR strategy shown in Scheme 1. We envisioned that a tandem reaction initiated by the hetero-[4 + 2] cycloaddition of 1-aza-4-borono-1,3-butadienes (**1**)

† In memory of Professor Raymond U. Lemieux of this department.

(1) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(2) For recent reviews on MCRs for combinatorial chemistry, see: (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (b) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329.

(3) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855−5858.

(4) For a MCR to access acyclic β-amino alcohols, see: Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798−11799.

(5) *Dictionary of Alkaloids*; Southon, I. W., Buckingham, J. Eds.; Chapman and Hall: London and New York, 1989.

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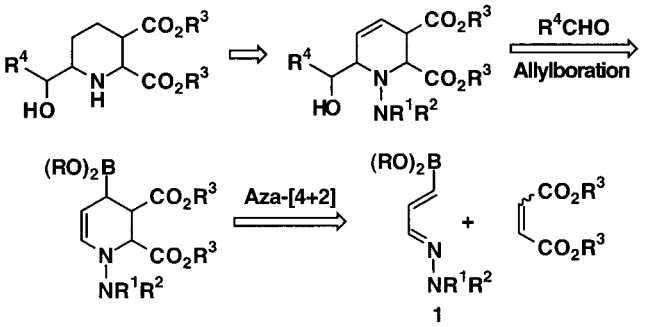
Scheme 1. Retrosynthetic Approach to Substituted Piperidine Derivatives Using a Tandem Aza[4 + 2]/Allylboration Reaction

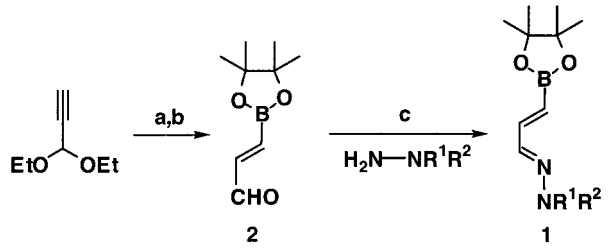


with appropriate dienophiles could be followed by reaction of the allylboronate intermediate with added aldehydes, thus providing α-hydroxyalkyl piperidine derivatives in one operation.

Whereas [4 + 2] cycloadditions of 1-aza-1,3-butadienes[7] and 1,3-dienylboronates[8] are known, the hybrid heterodienes (e.g., **1**) combining both substitution patterns are unprecedented. The elegant work of Vaultier and others has demonstrated the great versatility of 1,3-dienylboronates in [4 + 2] cycloadditions.[8a] From the intermediate cycloadducts, oxidation of the boronate group affords secondary alcohols, whereas addition of aldehydes leads to homoallylic alcohols via a highly diastereoselective allylboration.

The hydrazonodienes **1** required in the current investigation were easily synthesized by the acid-catalyzed condensation of aldehyde **2** with the desired hydrazines (Scheme 2).[9]

Scheme 2. General Route for the Preparation of Azadienes **1**[a]

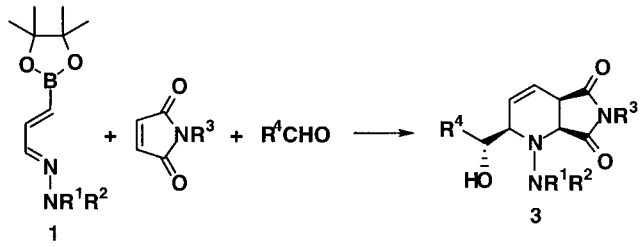


[a] (a) i. $(C_6H_{11})_2BH$ (1.0 equiv) in DME, 0 °C, 0.5 h; rt, 0.5 h; ii. $(CH_3)_3NO{\cdot}2H_2O$ (2.0 equiv), reflux; iii. pinacol, rt, 12 h; (b) cat. HCl/dioxane, anhydrous acetone; (c) $R^1R^2NNH_2$ (1.0 equiv), Na_2HPO_4 (1.0 equiv), water, 50 °C, 0.5 h.

Common precursor **2** was made from propionaldehyde diethyl acetal using a modified literature procedure.[10,11]

Maleimides were chosen as model electron-poor dienophiles since they are known to afford complete *endo*-selectivity in their [4 + 2] cycloadditions.[8a] Thus, reaction optimization was carried out with 1-(dimethylamino)-1-azadiene **1a**, *N*-phenylmaleimide, and benzaldehyde to give bicyclic product **3a** (Table 1). By carrying out the reaction

Table 1. Bicyclic Products **3** from Tandem Aza[4 + 2]/Allylboration[a]



entry	diene (R^1, R^2)	dienophile R^3	aldehyde R^4	product	yield (%)[b]
1	**1a** (Me, Me)	Ph	Ph	**3a**	47
2	**1a** (Me, Me)	Me	Ph	**3b**	50
3	**1a** (Me, Me)	Ph	4-$NO_2C_6H_4$	**3c**	48
4	**1a** (Me, Me)	Ph	4-$MeOC_6H_4$	**3d**	52
5	**1a** (Me, Me)	Ph	*i*-$PrCH_2$	**3e**	50
6	**1b** (H, Ph)	Ph	Ph	**3f**	46
7	**1c** (Me, Ph)	Ph	Ph	**3g**	46
8	**1d** (H, Ac)	Ph	Ph	**3h**	42

[a] All reactions were carried out by heating a 1:2:1 mixture of diene/dienophile/aldehyde in dry toluene [~0.2 M] at 80 °C for 72 h. [b] Unoptimized yields of products isolated after flash chromatography purification.

in two distinct operations, it was found that the [4 + 2] step proceeds rather slowly at room temperature and is thus better carried out at elevated temperatures. Given that the allylboration step also occurs above ambient temperature, we have opted for a one-pot procedure[8h] in which the three reagents are mixed and heated together in toluene at 80 °C. The use of a 1:2:1 diene/dienophile/aldehyde ratio and a reaction time of 72 h were the optimal conditions found to achieve full consumption of the diene. The bicyclic adducts **3** were obtained following a basic aqueous workup required to hydrolyze the resulting pinacol borate and flash chromatographic purification. Several combinations of substrates were explored to assess the generality of this process (Table 1). Unsurprisingly, the maleimide substituent (R^3) can be varied

(6) For recent reviews on the synthesis of piperidine-containing natural products, including indolizidines, see: (a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677−1716. (b) Michael, J. P. *Nat. Prod. Rep.* **1998**, 571−594. (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633−640. (d) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553−2581.

(7) For a review, see: Boger, D. L. Section 4.3.4.1 in Paquette, L. A. Ed.; *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M., Fleming, I., Series Eds.; Pergamon: Elmsford, NY, 1991; pp 451−512.

(8) (a) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169−4172. (b) Renard, P.-Y.; Lallemand, J.-Y. *Bull. Soc. Chim. Fr.* **1996**, *133*, 143. (c) Ohanessian, G.; Six, Y.; Lallemand, J.-Y. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1143−1148. (d) Garnier, L.; Plunian, B.; Mortier, J.; Vaultier, M. *Tetrahedron Lett.* **1996**, *37*, 6699. (e) Renard, P.-Y.; Lallemand, J.-Y. *Tetrahedron: Asymmetry* **1996**, *7*, 2523. (f) Renard, P.-Y.; Six, Y.; Lallemand, J.-Y. *Tetrahedron Lett.* **1997**, *38*, 6589. (g) Batey, R. A.; Thadani, A. N.; Lough, A. J. *Chem. Commun.* **1999**, 475−476. (h) Six, Y.; Lallemand, J. Y. *Tetrahedron Lett.* **1999**, *40*, 1295−1296.

(9) Tamura, Y.; Tsugoshi, T.; Nakajima, Y.; Kita, Y. *Synthesis* **1984**, 930−933.

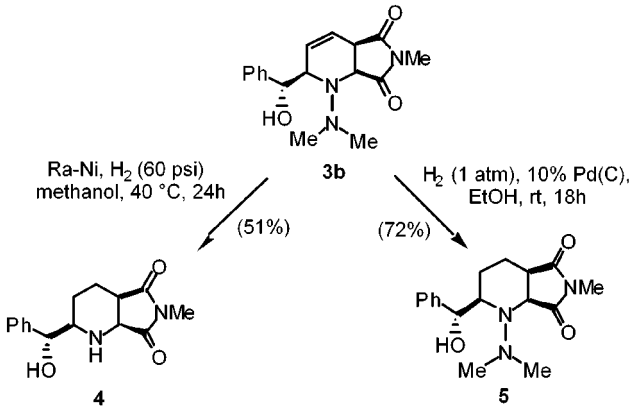
(10) Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A. *Synth. Comm.* **1993**, *23*, 2851−2859.

(11) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103−106.

(i.e., **3a** vs **3b**, entries 1 and 2). Most importantly, the isolation of compounds **3c**−**3e** (entries 3−5) shows that a wide range of aldehydes can be employed, including aliphatic and both electron-rich and electron-poor aromatic derivatives. As seen with the isolation of products **3f** and **3g** (entries 6 and 7), heterodienes made from both mono- and disubstituted phenylhydrazines are also valid substrates. In addition, the deactivated heterodiene **1d** made from acetylhydrazine reacted to provide product **3h** (entry 8). In all cases, a single or highly predominant stereoisomer is observed by ^{1}H NMR analysis of crude reaction products. We consider the moderate yields of purified compounds **3a**−**3h** quite acceptable considering the ready availability of starting materials and the simplicity of this MCR, as well as the high level of structural change and stereoselectivity afforded to the products. In fact, these yields are comparable with those reported for the reactions of 1,3-dienylboronates.[8h] In the present case, we have optimized the tandem reaction using a limiting amount of the diene in order to facilitate product purification and also because it is the most synthetically expensive component. When excess diene **1a** was used (3:1:1 diene/dienophile/aldehyde), the yield of bicycle **3a** was raised significantly to 75−80%.[12]

Although the prospect for using diverse hydrazone substituents is irrelevant to the synthesis of piperidine derivatives (they are accessible through reductive cleavage of the hydrazine), it is undoubtedly appealing toward combinatorial chemistry applications. Hydrazines and hydrazides are indeed present as pharmacophoric groups in several theraputic drugs. By including both hydrazone substituents in **1** (R^1, R^2), the three components in this multicomponent reaction deliver four elements of diversity into the compact bicyclic scaffold of products **3**. As shown with the formation of **4** from **3b** (Scheme 3), the corresponding piperidines can be obtained following Raney nickel catalyzed hydrogenolysis of the hydrazine moiety. On the other hand, the double bond in **3b** was selectively hydrogenated under palladium and charcoal to provide compound **5**. X-ray crystal structure determination[13] on the latter confirmed that the relative

Scheme 3. Hydrogenolysis Reactions of Bicycle **3b**



stereochemistry resulting from the tandem aza[4 + 2]/allylboration reaction of dienes **1**, as indicated in Table 1, mirrors that of the carbocyclic series.[8a]

Mechanistically, the [4 + 2] cycloaddition of heterodienes **1** with maleimides is expected to proceed with complete *endo*-selectivity to give the allylboronate intermediate shown in Figure 1. From the latter, the stereochemical outcome of

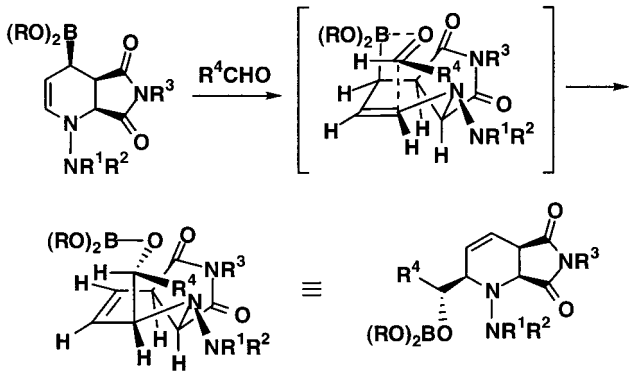


Figure 1. Proposed transition state to rationalize the stereochemistry resulting from the allylboration step.

the allylation step can be explained via a cyclic chairlike transition state involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the piperidine ring.

To the best of our knowledge, the current examples are the first ones involving γ-amino-substituted allylboryl reagents.[14] Moreover, the stereochemistry of the resulting 1,2-amino alcohol unit is the same as that of several alkaloids, including swainsonine and methyl palustramate, thus confirming the potential of this strategy for natural product synthesis. In addition to the high level of diastereoselectivity observed in this tandem hetero[4 + 2]/allylboration process,

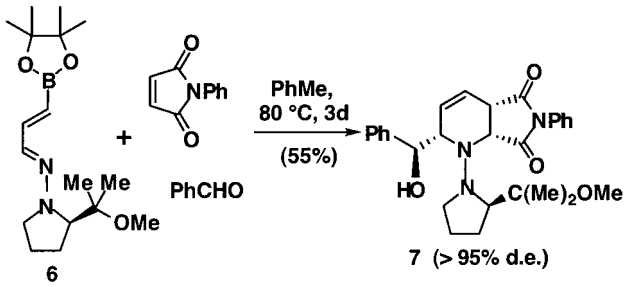
(12) We suspect that dienes **1** are prone to thermal decomposition, thereby causing a reduction in the yield of desired product when used as limiting component. In the preparation of **1**, minor amounts of the isomeric (*Z*)-vinylboronate was observed. Upon inspection of recovered material from incomplete aza[4 + 2]/allylboration reactions, this was shown not to affect the efficiency of the MCR, as no further isomerization of the diene was found.

(13) Crystal structure analysis for compound **5** (see ORTEP diagram in Supporting Information). Crystal dimensions (mm): 0.50 × 0.37 × 0.15; system: orthorhombic; space group: $Pna2_1$ (No. 33); unit cell parameters (obtained from least-squares refinement of 4472 centered reflections): *a* 8.3739(10), *b* 14.6832(18), *c* 13.4424(17) Å, *V* 1652.8(4) Å^3; *Z*: 4; ρ_{calcd} (g cm^{-3}): 1.275; μ (mm^{-1}): 0.089; 2ϑmax: 52.80°; radiation (λ [Å]): graphite-monochromated Mo Kα (0.71073); scan mode: ϕ rotations (0.3°)/ω scans (0.3°) (30 s exposures); temperature: −80 °C, no. of measured reflections: 7645; no. of independent reflections: 3385; no. of observed reflections ($F_0^2 \geq 2\sigma(F_0^2)$): 2364; absorption correction method: SADABS; range of transmission factors: 0.9803−0.3595, H atoms were generated in idealized sp^2 or sp^3 geometries based on the hybridization of their parent carbon or oxygen atoms; no. of parameters: 210, R_1 [$F_0^2 \geq 2\sigma(F_0^2)$]: 0.0474; wR_2 [$F_0^2 \geq -3\sigma(F_0^2)$]: 0.1188; largest difference peak and hole: 0.168 and −0.182 e Å^{-3}. Data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145481. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

(14) For a review on allylboration chemistry, see: Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; Chapter 7.

it is also possible to control the absolute stereochemistry of the bicyclic structure using a chiral auxiliary approach.[15] Remarkably, L-proline-derived diene **6** was reacted with *N*-phenylmaleimide and benzaldehyde to provide bicycle **7** in >95% de (Scheme 4).[16]

Scheme 4. Aza[4 + 2]/Allylboration of Chiral Diene **6**



Few multicomponent reactions offer such a high level of stereocontrol and versatility in the preparation of densely functionalized saturated heterocycles. Work toward extending the scope and applications of this tandem aza[4 + 2]/allylboration MCR is in progress.

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Supporting Information Available: Experimental details with characterization data for all final compounds. Copies of relevant proton and carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006626B

(15) Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* **1994**, *5*, 557−560.

(16) The absolute stereochemistry of **7** is assigned tentatively on the basis of ref 15. The de is estimated from the ^{1}H and ^{13}C NMR spectra by comparison with products from the cycloaddition of the non-methylated analogue of **6**, which provided a 80% de. No related NMR signals of the minor isomer from the latter could be found in the crude spectra of **7**.