A Three-Component Reaction for Diversity-Oriented Synthesis of Polysubstituted Piperidines: Solution and Solid-Phase Optimization of the First Tandem Aza[4+2]/Allylboration

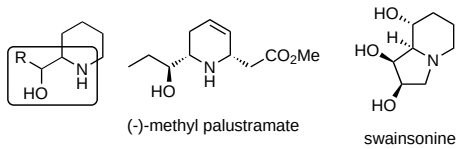
Barry B. Touré,[a] Hamid R. Hoveyda,[a, b] Jyoti Tailor,[a] Agnieszka Ulaczyk-Lesanko,[a] and Dennis G. Hall*[a]

Abstract: This article describes the design and optimization of a simple three-component aza[4+2]/allylboration reaction to access polysubstituted α-hydroxyalkyl piperidines in a highly diastereocontrolled fashion from maleimides, 4-boronohydrazonodienes, and aldehydes. The aldehyde component does not interfere with the first aza[4+2] step, and it was found that this tandem reaction provides better yields of piperidine products **5** when carried out in one-pot. The required 4-borono-hydrazonodienes **1** are synthesized efficiently from the condensation of 3-boronoacrolein pinacol ester (**4**) with hydrazines. Overall, the three-component process using N-substituted maleimides as dienophiles produces four stereogenic centers and is quite general. It tolerates the use of a wide variety of aldehydes and hydrazine precursors with different electronic and steric characteristics. By allowing such a wide substrate scope and up to four elements of diversity, this reaction process is particularly well adapted towards applications in diversity-oriented synthesis of polysubstituted piperidine derivatives. The suitability of the aza[4+2]/allylboration reaction for use in solid-phase chemistry was also demonstrated using a *N*-arylmaleidobenzoic acid functionalized resin. This novel multicomponent reaction thus offers a high level of stereocontrol and versatility in the preparation of densely functionalized nitrogen heterocycles.

Keywords: boron · diastereoselectivity · heterocycles · multicomponent reactions · solid-phase synthesis

Introduction

Multicomponent reactions (MCR) can be broadly defined, regardless of their mechanistic nature, as "one-pot" processes that combine three or more substrates simultaneously.[1] The most effective MCRs provide new products with optimal change in structure and functionality from simple substrates, and in a simple, highly atom-economical fashion. MCR processes are particularly attractive both towards natural product synthesis and in the more recent contexts of combinatorial chemistry and diversity-oriented synthesis (DOS).[2] Yet, to this day there are still only a few versatile MCRs displaying a wide substrate generality suitable towards applications in DOS. We were interested in the development of novel MCRs to access polysubstituted piperidine derivatives, and in particular, those possessing an α-hydroxyalkyl side chain. Several biologically interesting alkaloids and azasugar analogues contain a piperidine ring flanked with a stereodefined hydroxyalkyl group at the α-position (Figure 1).[3]



(-)-methyl palustramate swainsonine

Figure 1. Selected examples of natural products containing α-hydroxyalkyl piperidine units.

As judged by the popularity of synthetic polysubstituted derivatives in pharmaceutical drug development,[4] the piperidine subunit can be considered a privileged structure with respect to biological properties. To the best of our knowledge, there are very few MCRs for the construction of piperidine derivatives. These specific cases include the Grieco three-component reaction[5] and a limited number of Ugi-type condensations[6] [Eqs. (1) and (2) in Figure 2] which cannot, however, easily accommodate the formation of an α-hydroxy-

[a] Prof. D. G. Hall, B. B. Touré, Dr. H. R. Hoveyda, J. Tailor, Dr. A. Ulaczyk-Lesanko
Department of Chemistry, Gunning-Lemieux Chemistry Centre
University of Alberta, Edmonton, AB T6G 2G2 (Canada)
Fax: (+1) 780-492-8231
E-mail: dennis.hall@ualberta.ca

[b] Dr. H. R. Hoveyda
Current address: Néokimia Inc.
3001 12e Avenue Nord, Fleurimont, QC J1H 5N4 (Canada)

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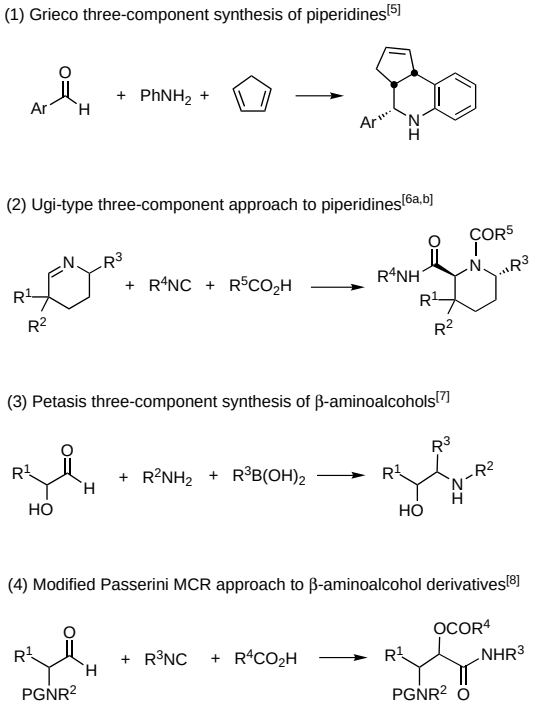


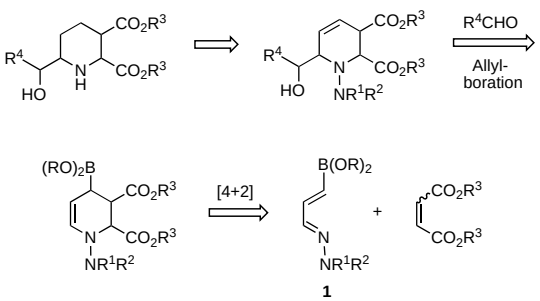
Figure 2. Examples of multicomponent reactions.

alkyl side chain. Similarly, although the Petasis borono-Mannich reaction[7] and modified Passerini condensations[8] are powerful MCRs to access acyclic β-aminoalcohol units [Eqs. (3) and (4)], these processes have not been applied to the construction of α-hydroxyalkyl piperidines.[9]

Herein, we present a detailed study on the design and optimization of a simple, stereoconvergent MCR strategy for the construction of polysubstituted α-hydroxyalkyl piperidines based on a tandem aza[4+2]/allylboration reaction.[10]

Results and Discussion

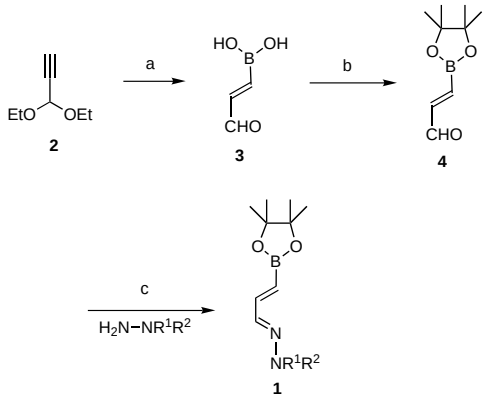
Design: To access α-hydroxyalkyl piperidine derivatives in one operation with a high degree of stereocontrol, we envisioned a tandem reaction initiated by the hetero[4+2] cycloaddition of 1-aza-4-borono-1,3-butadienes (**1**) with appropriate dienophiles that could be followed by reaction of the allylboronate intermediates with aldehydes (Scheme 1).



Scheme 1. Retrosynthetic approach to substituted piperidine derivatives using a tandem aza[4+2]/allylboration reaction.

Whereas [4+2] cycloadditions of 1-aza-1,3-butadienes[11] and 1,3-dienylboronates[12] 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.[12a] From the intermediate cycloadducts, oxidation of the boronic ester group affords secondary alcohols, whereas allylboration of aldehydes leads to homoallylic alcohols in a very high diastereoselectivity. In the case of 1-aza-4-borono-1,3-butadienes **1**, we anticipated that the tandem hetero[4+2]/allylboration reaction planned in Scheme 1 could be carried out as a "one-pot" three-component reaction.[13] This hypothesis was based on the premise that the aldehyde component would not interfere with the first stage of the tandem process, the hetero[4+2] cycloaddition, for example by acting as a heterodienophile vis-à-vis heterodienes **1**.

Solution-phase studies: The hydrazonodienes **1** required in the current investigation were easily synthesized by the condensation of aldehyde **4** with the desired hydrazines (Scheme 2).[14] As described in our first report,[10] the common



Scheme 2. General preparation of azadienes **1**. a) i) (*R*)-α-pinene (2 equiv) in THF, $BH_3 \cdot Me_2S$ (1 equiv), 0 °C, 15 min; then RT, 2 h; add **2** (1 equiv), 0 °C, 1 h; then RT, 1 h; add CH_3CHO (10–20 equiv), 0 °C; then reflux (45 °C), 12 h. ii) H_2O (75 equiv), 0 °C, 3 h (80%). b) Dry pinacol (1 equiv), THF (100%). c) Hydrazine (1 equiv) CH_2Cl_2, $MgSO_4$ (1.3 equiv), reflux, 2 h (90–95%).

precursor **4** can be made from propiolaldehyde diethyl acetal (**2**) using a literature procedure involving two consecutive distillations.[15, 16] The whole process proved rather cumbersome and low yielding. Since then we have improved the synthesis of **4** by developing a simple and practical procedure that avoids any distillation, and provides this key aldehyde **4** in high yield and purity. Hydroboration of **2** with diisopinocampheylborane, followed by acetaldehyde promoted oxidative dealkylation and hydrolysis afforded 3-boronoacrolein (**3**) directly. The latter, which precipitates as a white solid upon evaporation of the ethereal extraction layer, can be readily separated from the residual pinene by a simple filtration followed by washing with cold hexanes or dichloromethane. Formation of the corresponding ester **4** was easily carried out by reaction with an equimolar amount of pinacol. This key intermediate was isolated with ease in high yield, and

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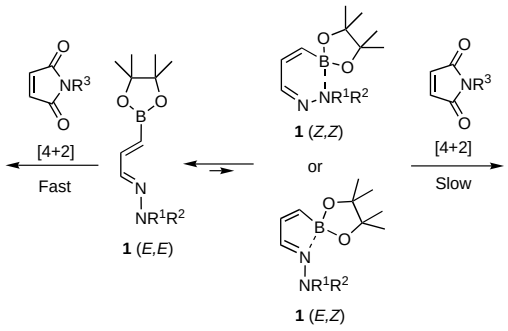
in essentially pure form, by evaporation of the THF solution. Both **3** and **4** can be stored for a few months at 0 °C and used when required towards the preparation of azadienes **1**. We initially reported the preparation of these hydrazonodienes **1** by acid catalyzed condensation of aldehyde **4** with the required hydrazines.[10] Since then, we have employed a simpler and more efficient procedure using anhydrous magnesium sulfate as dehydrating agent.

Maleimides were chosen as model electron-poor dienophiles since they are known to afford complete *endo*-selectivity in their [4+2] cycloadditions.[12a] Thus, optimization of reaction conditions was carried out with 1-dimethylamino-4-borono-1-azabutadiene **1a**, *N*-phenylmaleimide, and benzaldehyde to give bicyclic product **5a** (Table 1). By carrying out the reaction in two distinct operations, our initial investigations indicated that the [4+2] step proceeds rather slowly at room temperature, and should thus be carried out at elevated temperatures. Given that the allylboration step also occurs above ambient temperature, we have opted for a simple one-pot procedure[12h] in where a solution of the three reagents is heated in toluene at 80 °C. It appears that the presence of the aldehyde component does not interfere with the first, aza[4+2] stage of the MCR. Indeed, this one-pot procedure provided better yields of **5a** as compared to other procedures involving the sequential addition of the dienophile followed by the aldehyde. At the outset, we 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. The use of a 1:2:1 diene/dienophile/aldehyde ratio and a reaction time of 72 hours were the optimal conditions found to achieve full consumption of the diene (entry 5, Table 1). Unfortunately, all our attempts to accelerate this tandem process at lower temperatures through the use of Lewis acids were in vain.

Interestingly, we have noticed that some of the 4-borono-hydrazonodienes **1** tend to undergo a thermal *trans-cis* isomerization around the C3–C4 bond (Scheme 3). This phenomena was particularly significant for dialkylhydrazonodiene **1a**, which was formed from aldehyde **4** in a mixture



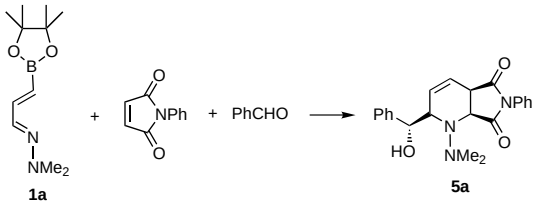
Scheme 3. Diene isomerization phenomena.

favoring the *E*,*E* isomer in a ratio varying between 2:1 to 5:1. The occurrence of the minor isomer may be explained by formation of a cyclic structure with favorable N-B coordination. At this time it is not yet possible to assess which particular isomer between the five-membered *Z*,*E* form or the six-membered *Z*,*Z* form is implicated. Nonetheless, the presence of a C3–C4 *Z* isomeric form of the hydrazonodienes was deduced from the coupling constants between all the olefinic hydrogens. The two isomers are not isolable by chromatography, thereby suggesting that isomerization may be a dynamic process even at room temperature. Indeed, recovered diene **1a** from incomplete [4+2]/allylboration reactions carried out at 80 °C typically consisted of about 5:1 mixture of 3*E* and 3*Z* isomers respectively. It appears that the *3Z* isomer was not consumed in the reactions as no cycloadducts with stereochemistry other than that expected from the predominant *E*,*E* heterodiene were ever observed. The lack of reactivity of the 3*Z* isomer could result from the considerable steric bulk of the pinacolate ester in the *endo* approach for that diene. Consequently, since the 3*Z* diene is thought to interconvert readily into the reactive 3*E* isomer at the reaction temperature, its presence would thus not affect the yield of final bicyclic products **5**.

Several combinations of substrates were explored in order to assess the generality of this tandem [4+2]/allylboration MCR process and its potential towards applications in diversity-oriented synthesis (Table 2).

The bicyclic adducts **5** were obtained following a basic aqueous work-up required to hydrolyze the resulting pinacol borate, and a flash-chromatographic purification. According to ^{1}H NMR analysis of crude reaction products, it appears that only one stereoisomer was observed in all cases. In general, the use of diene **1a** as a limiting reagent provided modest yields of product that were nonetheless comparable with those reported for the reactions of 1,3-dienylboronates.[12h] On the other hand, when excess diene **1a** was used (3:1:1 diene/dienophile/aldehyde) the yield of bicycle **5a** was raised significantly from 47 to 75% (entries 1–2, Table 2). We suspect that heterodienes made from non-aromatic hydrazines (for example, **1a**) are prone to thermal decomposition, thereby causing a reduction in the yield of desired product when they are used as limiting components. Unsurprisingly, the maleimide substituent (R^3) can be varied without affecting product yields significantly (i.e., **5a** vs **5b**, entries 1 and 3). It was found, however, that the N-aryl imide products tend to be

Table 1. Optimization of the tandem aza[4+2]/allylboration reaction.[a]



Entry	Reagent stoichiometry (equiv) Diene **1a**/*N*-Ph-maleimide/PhCHO	*t* [h]	Yield [%][b]
1	1:1:1	24	incompl.
2	1:2:1	24	incompl.
3	1:3:1	24	incompl.
4	1:3:1	72	78
5	1:2:1	72	80

[a] All reactions were carried out by heating a mixture of diene/dienophile/aldehyde in anhydrous toluene [~0.2 M] at 80 °C. [b] Crude yield of product.

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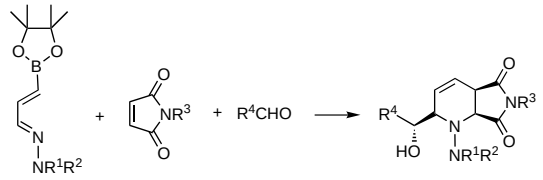
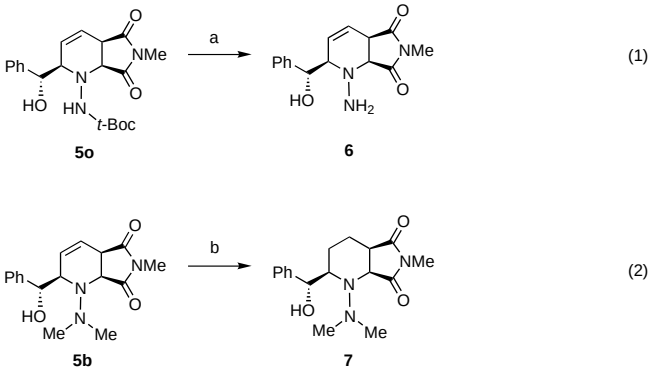
Table 2. Bicyclic products **5** from tandem aza[4+2]/allylboration reactions.[a]



Entry		Diene R^1	R^2	Dienophile R^3	Aldehyde R^4	Ratio	Product	Yield [%][b]
1	**1a**	Me	Me	Ph	Ph	1:2:1	**5a**	64
2	**1a**	Me	Me	Ph	Ph	3:1:1	**5a**	75
3	**1a**	Me	Me	Me	Ph	1:2:1	**5b**	50
4	**1a**	Me	Me	Ph	4-$NO_2C_6H_4$	1:2:1	**5c**	52
5	**1a**	Me	Me	Ph	4-$MeOC_6H_4$	1:2:1	**5d**	48
6	**1a**	Me	Me	Me	2-MeC_6H_4	2:1:1	**5e**	50
7	**1a**	Me	Me	Ph	*i*$PrCH_2$	1:2:1	**5f**	50
8	**1a**	Me	Me	Me	C_6H_{11}	2:1:1	**5g**	39
9	**1a**	Me	Me	Me	2,4,6-Me-C_6H_2	1:2:1	**5h**	–
10	**1b**	H	Ph	Ph	Ph	1:2:1	**5i**	76
11	**1c**	H	4-$CF_3C_6H_4$	Me	Ph	1:2:1	**5j**	77
12	**1d**	H	4-$MeOC_6H_4$	Me	Ph	1:2:1	**5k**	55
13	**1e**	Me	Ph	Ph	Ph	1:2:1	**5l**	65
14	**1e**	Me	Ph	Ph	2-$MeOC_6H_4$	2:1:1	**5m**	68
15	**1f**	H	Ac	Ph	Ph	1:2:1	**5n**	42
16	**1g**	H	Boc	Me	Ph	1:2:1	**5o**[c]	61

[a] All reactions were carried out by heating a mixture of diene/dienophile/aldehyde in anhydrous toluene [~0.2 M] at 80 °C for 72 h. [b] Unoptimized yields of products isolated after flash chromatography purification. [c] This compound was characterized as its deprotected primary hydrazine derivative **6** ($R^2 = H$) (see Scheme 4 and Experimental Section).

sensitive to hydrolysis, and must therefore be purified with more care for characterization purposes. The isolation of compounds **5c–g** (entries 4–8) shows that a wide range of aldehydes can be employed, including aliphatic ones, as well as both electron-rich and electron-poor benzaldehydes. Very hindered aldehydes such as *ortho*-disubstituted ones (for example, entry 9), however, failed to provide the desired products. Although the prospect for using diverse hydrazone substituents is irrelevant to the synthesis of free piperidines (they are accessible through reductive cleavage of the hydrazine), it is undoubtedly appealing towards combinatorial chemistry applications. Hydrazines and hydrazides are indeed present as pharmacophores in several pharmaceuticals.[17] 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 **5**. As shown with the isolation of products **5i–m** (entries 10–14), heterodienes **1b–e** made from both mono- and disubstituted arylhydrazines are also highly effective substrates. We observed that these heterodienes tend to show superior thermal stability as compared to **1a** and thus gave higher yields of products in the 65–75% range even when used as the limiting reagents. The deactivated heterodiene **1f** made from acetylhydrazine reacted to provide product **5n** although in a modest yield (entry 15). On the other hand, a similar diene (**1g**) featuring a carbamate-protected hydrazone afforded the corresponding cycloadduct **5o** in 61% yield (entry 16). The latter was treated with trifluoroacetic acid to provide the corresponding free primary hydrazine **6** after flash chromatography [Scheme 4, Eq. (1)] (see also footnote [c] in Table 2). Other dienophiles were tested (acrylates, maleic anhydride, dimethyl fumarate, *trans*-1,2-bis(phenylsulfonyl)-ethylene), but in all these cases the tandem reaction was either not proceeding, or gave products that apparently decomposed and/or gave unidentified side products at high temperatures. Nonetheless, by offering such a wide scope of substituents for the aldehyde and hydrazine components, this MCR offers significant potential towards diversity-oriented syntheses of polysubstituted piperidines derivatives. The double bond in **5b** could also be selectively hydrogenated under palladium on charcoal to provide compound **7** [Scheme 4, Eq. (2)]. X-ray crystal structure determination[18] on the latter confirmed that the relative stereochemistry resulting from the tandem aza[4+2]/allylboration reaction of dienes **1**, as indicated in Table 2, mirrors that of the carbocyclic series.[12a]



Scheme 4. Transformations of tandem aza[4+2]/allylboration products. a) CF_3CO_2H/H_2O 95:5, RT, 2 h (50%). b) H_2 (1 atm), 10% Pd(C), EtOH, RT, 18 h (72%).

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 3. From the latter, the stereochemical outcome of the

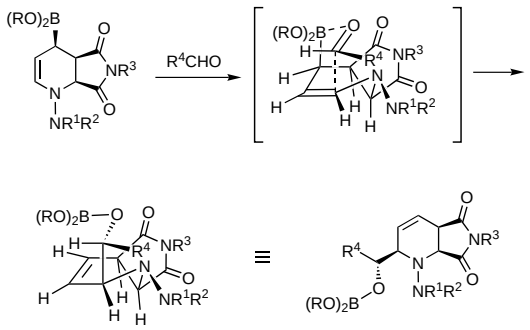
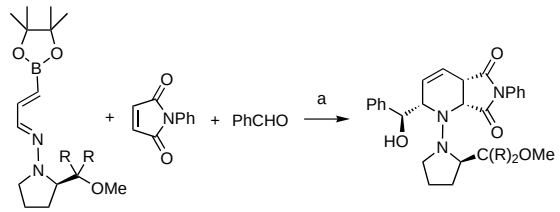


Figure 3. Proposed transition state to rationalize the stereochemistry resulting from the allylboration step.

allylation step can be explained via the usual cyclic chair-like allylboration transition state involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the piperidine ring. It is noteworthy that this system constitutes a rare example of allylboration reaction involving γ-amino-substituted allylboryl substrates.[19, 20] Moreover, the stereochemistry of the resulting 1,2-amino-alcohol unit is the same as that of several alkaloids including swainsonine and methyl palustramate (Figure 1), thus confirming the potential of this strategy in natural product synthesis.

In addition to the high level of diastereoselectivity observed in this tandem hetero[4+2]/allylboration process, it was also possible to control the absolute stereochemistry of the bicyclic structure using a chiral auxiliary approach. While L-proline derived diene **8** failed to give **9** in high *de*, the dimethyl analogue **10** was reacted with *N*-phenylmaleimide, and benzaldehyde to provide bicycle **11** in a remarkable $>95\%$ *de* (Scheme 5).[21, 22]

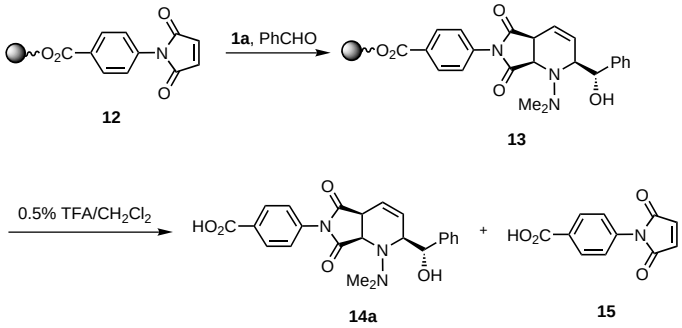


8: (R = H)
10: (R = Me)

9: (80% *de*)
11: (> 95% *de*)

Scheme 5. Tandem aza[4+2]/allylboration reaction of chiral dienes **8** and **10**. a) Conditions of Table 1; (55% for **11**).

Solid-phase studies: The possibility of carrying out this aza[4+2]/allylboration MCR on solid support could significantly simplify its application to the generation of parallel libraries of polysubstituted piperidine derivatives. In particular, the use of excess reagents, which can be easily eliminated through simple resin washes, could help drive forward the tandem process and shorten the long reaction times required for the solution phase reaction. From a design standpoint, one of the three components must be tethered to the solid support. The substrate to be conjugated to the support must be bifunctional, and since its immobilization usually impedes its use as a diversifiable element, it is most advantageous to avoid sacrificing those components that are the most easily accessible as cheap, commercial building blocks. Considering that there are far more commercial aldehyde and hydrazine building blocks as compared to N-substituted maleimides, we chose to tether the latter to the support. To this end, we made use of our recently published methodology for maleidobenzoic acid (MBA) resins.[23] Thus, optimization of the solid-supported aza[4+2]/allylboration MCR was carried out using SASRIN-*p*-MBA resin **12**, diene **1a**, and benzaldehyde (Scheme 6).



Scheme 6. Optimization of the solid-phase reaction.

Several experiments were performed whereby the relative stoichiometry of the three components, temperature, and time were varied with the goal of identifying the mildest, most economical reaction conditions that would provide full conversion of the resin bound maleimide (Table 3). Following the usual resin rinses, cleavage of supported material **13** to give **14a** was effected with 0.5% trifluoroacetic acid in dichloromethane followed by HPLC analysis (both UV and ES-MS). Inasmuch as absence of cleaved maleimide **15** from the crude product represents a complete reaction, these assays confirmed that the solid-phase tandem reaction was indeed faster than its solution-phase counterpart. This effect is likely due to the use of excess reagents and also to the use of a more electron-poor *N*-(*p*-carboxyphenyl)imide dienophile. While the conditions of entry 1 (72 hours at 80 °C) were a prerequisite to ensure reaction completion in the solution-phase variant, we were able to significantly reduce the reaction time to 14 h and

Table 3. Optimization of the tandem aza[4+2]/allylboration reaction on solid-phase.[a]

Entry	Reagent stoichiometry (equiv) MBA resin **12**/diene **1a**/PhCHO	*T* [°C]	*t* [h]	Outcome[b]
1	1:20:20	80	72	full conversion
2	1:20:20	80	24	full conversion
3	1:20:20	80	14	full conversion
4	1:20:20	40	14	incomplete
5	1:10:10	80	14	full conversion
6	1:5:10	80	14	full conversion

[a] All reactions were carried out by heating a mixture of SASRIN MBA resin **12**:diene **1a**:benzaldehyde in anhydrous toluene [$\sim$0.2M] at 80 °C. [b] The extent of conversion was determined by HPLC (UV and ES-MS).

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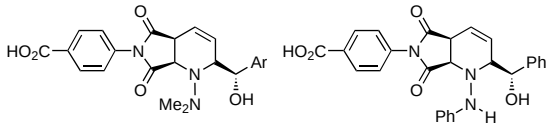
obtain cleaner product by using a 20-fold excess of reagents. Furthermore, as shown with entry 6 (Table 3), full conversion was maintained by using a smaller amount of the diene (5 equiv). In the end, the parameters of entry 6 were selected as the optimal reaction conditions for this solid-phase MCR process. In addition, we found much to our surprise that the basic treatment required to hydrolyze the final borate intermediate in solution phase was not necessary in the solid-phase variant. This could be explained by the use of excess methanol during the resin rinsing operations, which may cause transesterification of the borate ester.

We have examined substrate generality in the solid-phase MCR, although in less detail since this issue was thoroughly studied in the solution phase. All three piperidine derivatives **14a–14c** were obtained in moderate crude yields following cleavage from the solid support (Figure 4). Furthermore, according to HPLC-MS analysis, the compounds were isolated with a reasonable level of purity (80–90%) typically suitable towards HTS of combinatorial libraries. In the design of such libraries, however, it may be advisable to consider the synthesis of more hydrolytically stable N-alkyl imide products (see above) from supported *N*-alkylmaleimide dienophiles.



14a: Ar = C_6H_5 (62%)
14b: Ar = 4-Br-C_6H_4 (54%)
14c (60%)

Figure 4. Polysubstituted piperidines synthesized on solid-support.

Conclusion

In summary, we have described the first three-component aza[4+2]/allylboration reaction to access polysubstituted α-hydroxyalkyl piperidines in a highly diastereocontrolled fashion from maleimides, 4-boronohydrazonodienes, and aldehydes. The required 4-borono-hydrazonodienes are synthesized efficiently from the condensation of 3-boronoacrolein pinacol ester (**4**) with hydrazines. Overall the tandem aza[4+2]/allylboration process is quite general. It tolerates the use of a wide variety of aldehydes and hydrazine precursors with different electronic and steric characteristics. By allowing a wide substrate scope and up to four elements of diversity, this MCR is particularly well adapted towards applications in diversity-oriented synthesis of polysubstituted piperidine derivatives. The suitability of this MCR for use in solid-phase chemistry was also demonstrated using an N-arylmaleidobenzoic acid functionalized resin. Few multicomponent reactions offer such a high level of stereocontrol and versatility in the preparation of densely functionalized nitrogen heterocycles.

Experimental Section

General: Unless otherwise noted, all operations were carried out in oven or flame-dried glassware under a dry, oxygen-free nitrogen atmosphere. Solid-phase reactions were carried out in silanized glass vessels or in small polypropylene (PP) filter vessels (Bio-Rad). In the latter case, agitation of the vessels was provided by an orbital shaker. The workups of solid-supported reactions were carried out by rinsing the resin several times with different solvents (usually toluene, methanol, and methylene chloride). Acetone, CH_2Cl_2, and toluene were freshly distilled from calcium hydride prior to use. Anhydrous THF was distilled from sodium/benzophenone in a recycling still. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Pinacol was recrystallized from dichloromethane and dried under vacuum. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure. Chromatography refers to flash chromatography on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed on 0.25 mm Merck precoated silica-coated plates (60F-254). Visualization was obtained by exposure to 5% phosphomolybdic acid in ethanol or aqueous $KMnO_4$ solution. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300, 400, or 500 MHz in $CDCl_3$ as solvent unless otherwise mentioned. Protons chemical shifts are expressed in parts per million (ppm) and recorded relative to tetramethylsilane as an internal standard. Coupling constants are expressed as J values in hertz units (Hz) and are accurate to $\pm 0.4–0.6$ Hz. The following abbreviation are used: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, m = multiplet and br = broad. For broad singlets and symmetrical multiplets, only the central shift value may be provided, while a shift range was provided for borader unsymmetrical signals. ^{13}C NMR spectra were recorded on a Bruker WH-300 (75 MHz) NMR spectrometer in $CDCl_3$ as solvent, and chemical shifts are expressed in ppm. Infrared spectra were obtained on a Nicolet Magna-IR 750. Frequencies are expressed in cm^{-1}. Melting points were determined in a capillary tube on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed by the microanalytical laboratory of our department. High resolution electrospray mass spectra (HRMS) were obtained on a Micromass ZabSpec oa TOF instrument. Significant protonated molecular ions $[M+H]^+$ as well as peaks corresponding to sodiated molecular ions $[M+Na]^+$ were present in most of the spectra because of trace amounts of sodium salts in the samples. X-ray analysis was performed on a Bruker SMART 1000/P4/RA diffractometer by Dr. R. MacDonald at the University of Alberta.

3-Borono-acrolein (3): A 100 mL round bottom flask equipped with a septum inlet was charged with borane/dimethylsulfide complex (10 M stock solution, 3.3 mL, 33 mmol) and tetrahydrofuran (THF) (10 mL) under nitrogen. (*R*)-(+)-α-pinene (91% *ee*) (10.8 mL, 66.7 mmol) was then added dropwise at 0 °C. The mixture was stirred for 10 min followed by 2 h at room temperature. The resulting white diisopinocampheylborane suspension was cooled to 0 °C and propiolaldehyde diethyl acetal (4.5 mL, 31 mmol) was added slowly. The resulting mixture was stirred at 0 °C for 1 h and further stirred at room temperature for an additional 1 h, and cooled back to 0 °C again prior to the quick addition of freshly distilled acetaldehyde (20 mL). The solution was stirred for 30 minutes, warmed up, then the flask was fitted with a condenser and heated to 45 °C overnight. The solution obtained was cooled to 0 °C, and water (12 mL) was added. After 3 h, the solution was transferred to a separatory funnel. The aqueous phase was extracted two times with Et_2O (50 mL) and ethyl acetate (50 mL). The combined organic layers were concentrated under reduced pressure. Under these conditions, the boronic acid precipitates as a white solid. It was then separated from pinene by addition of either cold hexane or cold dichloromethane and filtration (2.5 g, 76%).

Pinacol ester 4: The 3-boronoacrolein (**3**) (1.00 g, 10.0 mmol) was dissolved in THF (25 mL) at room temperature, and dry pinacol (recrystallized from dichloromethane) (1.12 g, 10.0 mmol) was added. The solution was stirred for 30 minutes then the solvent was evaporated under reduced pressure at 45 °C to afford a colourless oil in quantitative yield. Addition of THF followed by concentration may be necessary to complete the condensation by azeotropic removal of the water.

Typical procedure for the preparation of 4-borono heterodienes 1a–e: Preparation of *N,N*-dimethylhydrazonodiene 1a: *N,N*-dimethylhydrazine (0.42 mL, 5.5 mmol) and magnesium sulfate (0.86 g, 7.2 mmol) were added to a solution of aldehyde **4** (1.0 g, 5.5 mmol) in freshly distilled dichloromethane. The resulting mixture was then heated under reflux for 2 h. Magnesium sulfate was removed by filtration through a predried fritted

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funnel. Solvent was evaporated under reduced pressure to afford a yellowish oil as the product (1.2 g, 90%).

All dienes **1a–e** were isolated as a mixture of two inseparable 3*E* and 3*Z* isomers (see text). NMR assignments are provided only for the major (*E*,*E*) isomers. These dienes were generally employed immediately in the tandem reactions.

Spectroscopic data for 1a (90% yield): IR ($CHCl_3$ cast): $\tilde{\nu}$ = 2977, 2931, 2865, 1548, 1412, 1213, 998, 882, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (dd, J = 8.9, 17.9 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 5.53 (d, J = 17.9 Hz, 1H), 2.95 (s, 6H), 1.22 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 148.2 (CH), 135.6 (CH), 134.5 (CH), 83.0 (C), 42.4, 24.9; MS (ES): *m*/*z*: 225 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{11}H_{22}BN_2O_2$: 225.1774; found: 225.1778 $[M+H]^+$.

Spectroscopic data for 1b (86% yield): IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3285, 2977, 2924, 1560, 1446, 1286, 1214, 1070, 899, 648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5H), 6.99 (d, J = 9.0 Hz, 1H), 6.87 (dd, J = 9.0, 18.0 Hz, 1H), 5.68 (d, J = 18.0 Hz, 1H), 1.25 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 146.4 (CH), 143.9 (C), 139.9 (CH), 129.2 (CH), 120.6 (CH), 120.4 (CH), 112.1 (CH), 82.7 (C), 24.7; MS (ES): *m*/*z*: 305 $[M+Na]^+$, 273 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{15}H_{22}BN_2O_2$: 273.1774; found: 273.1769 $[M+H]^+$.

Spectroscopic data for 1c (83% yield): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.48 (d, J = 6.8 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.20 (dd, J = 7.2, 14.6 Hz, 1H), 7.04 (d, J = 6.8, 1H), 5.75 (d, J = 14.5 Hz, 1H), 1.23 (s, 12H); ^{13}C (75 MHz, $CDCl_3$): δ = 147.0, 146.6, 141.7, 126.5, 122.7 (q), 112.6, 111.2, 83.6, 25.1; HRMS (EI): *m*/*z*: calcd for $C_{16}H_{20}BF_3N_2O_2$: 340.1570; found: 340.1572 $[M]^+$.

Spectroscopic data for 1d (88% yield): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.46 (br s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.19 (dd, J = 9.2, 18.3 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 5.63 (d, J = 17.7 Hz, 1H), 3.68 (s, 3H), 1.25 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 154.2 (C), 146.5 (CH), 139.3 (CH), 138.0 (C), 114.8 (CH), 114.6 (CH), 114.1 (CH), 83.4 (C), 55.6 (CH_3), 24.7 (CH_3); HRMS (ES): *m*/*z*: calcd for $C_{16}H_{23}BN_2O_3$: 302.1800; found: 302.1799 $[M]^+$.

Spectroscopic data for 1e (81% yield): IR ($CHCl_3$ cast): $\tilde{\nu}$ = 2977, 2926, 1651, 1611, 1552, 1457, 1215, 1030, 897, 668, 648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 5H), 6.98–6.89 (m, 2H), 5.70 (d, J = 15.3 Hz, 1H), 3.34 (s, 3H), 1.26 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 152.6 (C), 148.4 (CH), 135.7 (CH), 128.8 (CH), 118.4 (CH), 115.6 (CH), 114.8 (CH), 83.1 (C), 44.3, 24.7; MS (ES): *m*/*z*: 287 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{16}H_{24}BN_2O_2$: 287.1931; found: 287.1938 $[M+H]^+$.

Spectroscopic data for 1g (93% yield): IR (CH_2Cl_2 cast): $\tilde{\nu}$ = 3231, 2933, 1619, 1480, 1457, 1215, 1048, 1020, 900, 866, 764, 588, 457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.87 (s, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.08 (dd, J = 9.5, 17.9 Hz, 1H), 5.76 (d, J = 18.0 Hz, 1H), 1.44 (s, 9H), 1.20 (s, 12H); ^{13}C (125 MHz, $CDCl_3$, APT): δ = 154.2 (C), 146.1 (CH), 145.5 (CH), 145.4 (CH), 83.7 (C), 81.7 (C), 28.3 (CH_3), 24.8 (CH_3); HRMS (ES): *m*/*z*: calcd for $C_{14}H_{25}BN_2O_4Na$: 319.1799; found: 319.1802 $[M+Na]^+$; elemental analysis calcd (%) for $C_{14}H_{25}BN_2O_4$ (296.17): C 56.72, H 8.51, N 9.49; found: C 56.06, H 8.51, N 9.28.

Procedure for the preparation of diene 1f: Acetic hydrazide (0.41 g, 5.55 mmol) was added to a solution of aldehyde **4** (1.01 g, 5.55 mmol) in anhydrous EtOH (20 mL). The mixture was stirred vigorously for 1 h under refluxing conditions (85 °C), after which time it was allowed to cool down to RT. The solution was then evaporated and dried over vacuum to give crude product **1f** as a pale yellow solid. The crude product was subjected to flash chromatography on silica gel, eluting with 10% MeOH in dichloromethane, giving pure heterodiene **1f** in 62% yield. IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3205, 2978, 1958, 1618, 1560, 1270, 1214, 898, 667, 649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 9.1 Hz, 1H), 7.06 (dd, J = 8.8, 18.0 Hz, 1H), 5.92 (d, J = 18.0 Hz, 1H), 3.47 (s, 3H), 1.23 (s, 12H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 174.3 (CO), 146.5 (CH), 146.2 (CH), 145.0 (CH), 83.7 (C), 24.8, 20.2; MS (ES): *m*/*z*: 261 $[M+Na]^+$, 239 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{11}H_{20}BN_2O_3$: 239.1567; found: 239.1564 $[M+H]^+$.

General solution-phase procedure for the preparation of bicyclic piperidine products 5a–o, 9, 11: The aldehyde (1 equiv) was added under a nitrogen atmosphere at room temperature to a solution of diene **1** (1 or 2 equiv) in toluene (5 mL). The dienophile (1 or 2 equiv) was added to the above mixture which was then heated at 80 °C for 3 d, then allowed to cool down to RT diluted with EtOAc, and stirred for 30 min with a saturated solution of sodium hydrogen carbonate. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **5** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane (or EtOAc/hexanes system) led to the isolation of the pure product **5** as pale yellow solid in 42–77% yield (see Table 2).

Spectroscopic data for 5a: m.p. 80–82 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3475, 2944, 1783, 1597, 1454, 1199, 1059, 864, 667, 646, 621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.55 (m, 10H), 6.01 (ddd, J = 1.5, 3.7, 10.5 Hz, 1H), 5.75 (ddd, J = 1.5, 4.3, 10.6 Hz, 1H), 4.62 (d, J = 8.4 Hz, 1H), 4.24 (br s, 1H, OH), 3.89 (d, J = 9.5 Hz, 1H), 3.62–3.58 (m, 1H), 3.54–3.48 (m, 1H), 2.50 (s, 6H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 176.1, 174.0(CO), 140.1, 131.6 (C), 130.6, 129.2, 128.7, 128.5, 128.2, 127.2, 126.3, 121.1, 76.6, 61.4, 57.2, 43.7 (N-CH_3), 38.9 (CH); MS (ES): *m*/*z*: 400 $[M+Na]^+$, 378 $[M+H]^+$, 360$[M-H_2O]^+$; HRMS (ES): *m*/*z*: calcd for $C_{22}H_{23}N_3O_3Na$: 400.1637; found: 400.1639 $[M+Na]^+$.

Spectroscopic data for 5b: m.p. 110–112 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3463, 2945, 1779, 1704, 1454, 1434, 1279, 1199, 1124, 990, 809, 775, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5H), 5.91 (dd, J = 2.2, 10.4 Hz, 1H), 5.63 (ddd, J = 2.2, 4.5, 11.6 Hz, 1H), 4.42 (d, J = 9.1 Hz, 1H), 4.26 (br s, 1H, OH), 3.73 (d, J = 9.6 Hz, 1H), 3.46–3.40 (m, 2H), 3.05 (s, 3H) 2.46 (s, 6H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 177.0, 175.1 (CO), 140.2 (C), 130.2, 128.4, 128.1, 127.1, 121.2, 75.6, 61.2, 57.3, 38.7 (CH), 43.7 [N-$N(CH_3)_2$], 25.3 (N-CH_3); MS (ES): *m*/*z*: 338 $[M+Na]^+$, 316 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{17}H_{21}N_3O_3Na$: 338.1481; found: 338.1481 $[M+Na]^+$; elemental analysis calcd (%) for $C_{17}H_{21}N_3O_3$ (315.16): C 64.8, H 6.7, N, 13.3; found: C 64.1, H 6.6, N 12.6.

Spectroscopic data for 5c: m.p. 90–92 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3439, 2922, 2852, 1778, 1597, 1499, 1376, 1197, 1108, 1072, 752, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.40 (d, J = 7.2 Hz, 2H), 7.55–7.38 (m, 5H), 7.29 (d, J = 6.8 Hz, 2H), 6.08 (dd, J = 3.7, 10.6 Hz, 1H), 5.75 (ddd, J = 1.5, 3.9, 9.8 Hz, 1H), 4.60 (d, J = 8.4 Hz, 1H), 4.14–4.04 (m, 1H), 4.02 (d, J = 9.3 Hz, 1H), 3.66–3.56 (m, 1H), 3.52–3.43 (m, 1H), 2.47 (s, 6H); ^{13}C (75 MHz, $CDCl_3$): δ = 176.1, 173.6, 155.8, 147.8, 131.5 (2), 130.5, 129.7, 129.3, 129.1, 127.8, 126.5, 126.1, 123.7, 75.5, 60.4, 56.3, 43.6 [N-$N(CH_3)_2$], 39.1; MS (ES): *m*/*z*: 445 $[M+Na]^+$, 423 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{22}H_{22}N_4O_5Na$: 445.1488; found: 445.1482 $[M+Na]^+$.

Spectroscopic data for 5d: m.p. 107–110 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3476, 2919, 2850, 1651, 1597, 1513, 1302, 1137, 832, 806, 692, 405 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.35 (m, 5H), 7.30–7.20 (m, 4H), 6.75 (d, J = 6.0 Hz, 2H), 5.98 (ddd, J = 1.1, 3.6, 10.6 Hz, 1H), 5.71 (ddd, J = 2.3, 4.6, 10.5 Hz, 1H), 4.60 (d, J = 8.5 Hz, 1H), 3.88 (s, 1H), 3.82 (d, J = 9.1 Hz, 1H), 3.77 (s, 3H), 3.53–3.51 (m, 1H), 3.51–3.44 (m, 1H), 2.50 (s, 6H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 176.0, 174.0 (CO), 159.6, 132.1, 131.6 (C), 130.7, 129.3, 128.9, 128.3, 126.2, 121.1, 113.9, 75.6, 61.5, 57.2, 55.3 (CH), 43.7 [N-$N(CH_3)_2$], 38.8 (OCH_3); MS (ES): *m*/*z*: 430 $[M+Na]^+$, 408 $[M+H]^+$, 390 $[M-H_2O]^+$; HRMS (ES): *m*/*z*: calcd for $C_{23}H_{25}N_3O_4Na$: 430.1743; found: 430.1742 $[M+Na]^+$.

Spectroscopic data for 5e: FTIR ($CHCl_3$ cast): $\tilde{\nu}$ = 3471, 2946, 2817, 2776, 1780, 1705, 1434, 1374, 1279 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50 (dd, J = 1.2, 8.7 Hz, 1H), 7.20 (dd, J = 1.2, 6.8 Hz, 1H), 7.13 (dt, J = 1.5, 7.5 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 5.85 (ddd, J = 1.5, 3.9, 10.5 Hz, 1H), 5.6 (ddd, J = 2.1, 4.7 and 10.5 Hz, 1H), 4.50 (d, J = 8.4 Hz), 4.1 (d, J = 9.9 Hz, 1H), 3.55–3.50 (m, 1H), 3.47–3.39 (m, 1H), 3.05 (s, 3H), 2.50 (s, 6H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 175.0, 138.3, 135.3, 130.4, 130.2, 127.7, 126.6, 126.5, 70.4, 61.4, 57.2, 43.8, 38.7, 25.2, 19.4; HRMS (EI): *m*/*z*: calcd for $C_{18}H_{23}N_3O_3$: 329.1740; found: 329.1741 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{23}N_3O_3$ (329.17): C 65.65, H 6.99, N 12.76; found: C 65.52, H 6.92, N 12.62.

Spectroscopic data for 5f: m.p. 75–78 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 2953, 1777, 1713, 1597, 1499, 1455, 1383, 1180, 751, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.25 (m, 5H), 6.17 (dddd, J = 0.9, 2.2, 4.6, 8.4 Hz, 1H), 6.04 (ddd, J = 2.1, 4.0, 10.5 Hz, 1H), 4.52 (d, J = 8.6 Hz, 1H), 3.54 (m, 1H), 3.24 (m, 2H), 2.52–2.49 (m, 1H), 2.51 (s, 6H), 1.91 (m, 1H), 1.22 (m, 2H), 0.92 (s, 6H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 176.4, 174.1 (CO), 131.6 9 (C), 130.9, 129.2, 129.1, 126.2, 121.2, 70.7, 60.0, 57.3, 56.3, 43.7 (CH), 42.4 (CH_2), 38.6 [N-$N(CH_3)_2$], 24.6, 23.9 (CH_3); MS (ES): *m*/*z*: 380 $[M+Na]^+$, 358 $[M+H]^+$; HRMS (ES): *m*/*z*: calcd for $C_{20}H_{28}N_3O_3$: 358.2131; found: 358.2136 $[M+H]^+$.

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Spectroscopic data for 5g: IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3495, 2927, 2851, 2772, 1781, 1705, 1434, 1376, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.05 (ddd, J = 2.1, 4.8, 10.5 Hz, 1H), 5.94 (ddd, J = 1.2, 3.9, 10.5 Hz, 1H), 4.38 (d, J = 8.7 Hz, 1H), 3.48–3.42 (m, 2H), 3.40–3.36 (m, 1H), 2.95 (s, 3H), 2.60 (d, J = 9 Hz, 1H), 2.48 (s, 6H), 1.78–1.09 (five m's, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 175.1, 130.7, 121.1, 76.1, 56.7, 43.6, 39.1, 38.6, 31.2, 26.8, 26.4, 25.3, 25.2; HRMS (EI): m/z: calcd for $C_{17}H_{27}N_3O_3$: 321.2052; found: 321.2058; elemental analysis calcd (%) for $C_{17}H_{27}N_3O_3$ (321.20): C 63.55, H 8.41, N 13.03; found: C 63.57, H 8.49, N 13.07.

Spectroscopic data for 5i: m.p. 180–182 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3515, 3028, 2920, 1715, 1600, 1495, 1454, 1384, 1371, 1247, 1195, 1058, 971, 828, 751, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + D_2O$): δ = 7.49–6.92 (m, 15H), 6.23–6.17 (m, 1H), 5.59 (ddd, J = 2.2, 4.4, 10.4 Hz, 1H), 4.61 (d, J = 9.2 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H,), 3.91 (br s, 1H, OH), 3.85–3.71 (m, 2H); ^{13}C (75 MHz, CD_2Cl_2): δ = 173.6, 173.5 (CO), 147.1 139.4, 131.3 (C), 129.6, 129.4, 129.3, 129.1, 128.6, 128.4, 127.1, 126.2, 126.1, 121.1, 114.13, 76.3, 68.1, 68.0, 38.3 (CH); MS (ES): m/z: 448 $[M+Na]^+$; HRMS (ES): m/z: calcd for $C_{26}H_{23}N_3O_3Na$: 448.1637; found: 448.1636 $[M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{23}N_3O_3$ (425.17): C 73.5, H 5.4, N 9.9; found: C 73.2, H 5.2, N 9.6.

Spectroscopic data for 5j: FTIR ($CHCl_3$ cast): $\tilde{\nu}$ = 3464, 3246, 2920, 1958, 1784, 1705, 1617, 1527, 1495, 1431, 1413, 1385, 1275 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.48 (d, J = 8.6, 2H), 7.45–7.21 (m, 5H), 7.16 (d, J = 8.3 Hz, 2H), 6.03 (ddd, J = 1.3, 4.4, 10.4 Hz, 1H), 5.58 (ddd, J = 2.2, 4.4, 10.5 Hz, 1H), 4.50 (d, J = 8.2 Hz, 1H), 4.26 (s, 1H), 4.21 (br s, 1H), 3.75–3.58 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 176.6, 175.3, 151.6, 141.6, 128.8, 128.4, 127.9, 126.9, 123.0, 120.4 (q), 113.3, 113.2, 76.2, 76.1, 62.3, 38.0, 25.1; HRMS (EI): m/z: calcd for $C_{22}H_{20}F_3N_3O_3$: 431.1457; found: 431.1471 $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{20}F_3N_3O_3$ (431.15): C 61.25, H 4.64, N 9.74; found: C 61.1, H 4.51, N 9.64.

Spectroscopic data for 5k: m.p. 210 °C (decomp.); IR (CH_2Cl_2 cast): $\tilde{\nu}$ = 2827, 1771, 1604, 1299, 1205, 1167, 995, 918, 902, 878, 677, 619, 599, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.12 (m, 5H), 6.97–6.92 (m, 2H), 6.82–6.76 (m, 2H), 6.15–6.05 (m, 1H), 5.45 (ddd, J = 2.2, 4.7, 10.4 Hz, 1H), 4.39 (d, J = 8.3 Hz, 1H), 4.09–3.95 (m, 1H), 3.71 (s, 3H), 3.58 (m, 1H), 3.54–3.44 (br s, 1H), 3.00 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ = 174.7 (CO), 154.7 (C), 139.5 (C), 128.5 (CH), 128.3 (CH), 127.1 (CH), 116.0 (CH), 114.9 (CH), 67.3 (CH), 55.7 (CH_3), 37.6 (CH), 25.3 (CH_3); HRMS (ES): m/z: calcd for $C_{22}H_{23}N_3O_4$: 393.1700; found: 393.1704 $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{23}N_3O_4$ (393.44): C 67.16, H 5.89, N 10.68; found: C 66.63, H 5.78, N 10.62.

Spectroscopic data for 5l: m.p. 190–192 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3497, 2921, 1716, 1597, 1496, 1454, 1384, 1371, 1244, 1141, 971, 829, 792, 692, 622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.20 (m, 15H), 6.10 (ddd, J = 1.5, 3.5, 9.0 Hz, 1H), 5.81 (ddd, J = 2.4, 4.1, 10.6 Hz, 1H), 4.41 (d, J = 8.3 Hz, 1H), 4.20 (d, J = 8.9 Hz, 1H), 3.96 (br s, 1H, OH), 3.71–3.62 (m, 2H), 3.01 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ = 175.7, 173.6 (CO), 149.3, 139.8, 131.3 (C), 131.0, 129.5, 129.3, 128.9, 128.5, 128.2, 127.1, 126.0, 120.1, 114.4, 76.6, 66.3, 58.6, 39.5 (CH), 35.6 (CH_3); MS (ES): m/z: 462 $[M+Na]^+$; HRMS (ES): m/z: calcd for $C_{27}H_{25}N_3O_3Na$: 462.1794; found: 462.1792 $[M+Na]^+$.

Spectroscopic data for 5m: IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3524, 3061, 2937, 1782, 1716, 1598, 1494, 1464, 1387, 1371 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.36 (m, 4H), 7.32–7.18 (m, 7H), 6.94 (dd, J = 7.5, 7.5 Hz, 1H), 6.88–6.82 (m, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.05 (ddd, J = 1.8, 3.9, 10.5 Hz, 1H), 5.80 (ddd, J = 1.8, 4.5, 10.5 Hz, 1H), 4.80 (dd, J = 2.4, 8.1 Hz, 1H), 4.40 (d, J = 8.4 Hz, 1H), 3.79–3.71 (m, 1H), 3.66–3.58 (m, 1H), 3.62 (s, 3H), 3.56 (br d, J = 2.7 Hz, 1H), 3.00 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 175.9, 173.9, 156.2, 149.4, 131.6, 131.0, 129.3, 129.2, 128.8, 128.3, 127.3, 126.3, 120.9, 120.6, 119.7, 114.2, 110.4, 68.8, 65.5, 58.8, 55.2, 39.2, 35.5; HRMS (EI): m/z: calcd for $C_{28}H_{27}N_3O_4$: 469.2002; found: 469.1998 $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{27}N_3O_4$ (469.53): C 71.61, H 5.75, N, 8.95; found: C 71.82, H 5.63, N 8.72.

Spectroscopic data for 5n: m.p. 110–112 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3021, 2960, 2924, 2852, 1593, 1567, 1496, 1455, 1371, 1259, 1186, 1153, 1100, 1026, 920, 867, 793, 730, 667, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.20 (m, 10H), 6.10 (ddd, J = 2.2, 3.0, 10.4 Hz, 1H), 5.98 (ddd, J = 2.4, 3.5, 10.4 Hz, 1H), 5.82 (d, J = 5.5 Hz, 1H), 5.22 (d, J = 9.3 Hz, 1H), 4.75–4.65 (m, 1H), 3.85–3.75 (m, 1H), 1.92 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 174.0, 173.4, 169.6 (CO), 136.9, 136.0 (C), 131.4, 129.1, 128.7, 128.5, 128.4, 127.6, 127.4, 121.0, 77.5, 61.8, 58.7, 39.8 (CH), 21.1 ($COCH_3$); MS (ES): m/z: 414 $[M+Na]^+$; HRMS (ES): m/z: calcd for $C_{22}H_{21}N_3O_4Na$: 414.1430; found: 414.1430 $[M+Na]^+$.

Spectroscopic data for 5o (6): Although compound **5o** shows correct MS data (see HPLC-ESMS chromatogram in Supporting Information), it exists as a mixture of rotamers that complicate NMR spectra. Therefore it was rather characterized as a free hydrazine derivative (**6**) following cleavage of the Boc group: A mixture of trifluoroacetic acid and water (95:5, 10 mL) was added to **5o** (0.327 g, 0.85 mmol) at 0 °C under N_2. The reaction mixture was warmed up to RT and stirred for 2 h. After completion, the reaction mixture was dried with $MgSO_4$, filtered, and benzene (50 mL) was added to the filtrate. The solvents were removed in vacuo (this was repeated twice) to give a brown solid as the crude product (0.300 g). The crude product was purified by flash chromatography with 5% MeOH in CH_2Cl_2 as solvents system, and pure free primary hydrazine compound **6** was obtained (0.126 g, 50%). **Spectroscopic data for 6**: m.p. 178–181 °C; IR (CH_2Cl_2 cast): $\tilde{\nu}$ = 3348, 3059, 2879, 1778, 1602, 1494, 1225, 1198, 1055, 985, 910, 817, 799, 764, 734, 669, 619, 552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 5H), 5.92 (ddd, J = 2.4, 2.6, 10.2 Hz, 1H), 5.32–5.23 (m, 1H), 4.48 (d, J = 8.7, 1H), 3.59 (d, J = 7.5 Hz, 1H), 3.39–3.25 (m, 2H), 3.00 (s, 3H); ^{13}C (100 MHz, $CDCl_3$, APT): δ = 174.9 (C), 140.6 (C), 128.5 (CH), 128.2 (CH), 127.6 (CH), 119.0 (C), 78.7 (CH), 66.7 (CH), 65.1 (CH), 41.3 (CH), 25.1 (CH_3); MS (ES): m/z: 288 $[M+H]^+$; HRMS (ES):: m/z: calcd for $C_{15}H_{17}N_3O_3Na$: 310.1167; found: 310.1660 $[M+Na]^+$.

Preparation of 7: Compound **5b** (0.16 g, 0.51 mmol) dissolved in EtOH (2 mL) was added under an H_2 atmosphere to a suspension of 10% Pd on carbon (0.16 g) in EtOH (3 mL). After 18 h of stirring at RT, the catalyst was filtered out. The solution was concentrated and purified by chromatography on silica gel (5% MeOH in dichloromethane) affording **7** as pale yellow solid (0.12 g, 75%), which was crystallized from dichloromethane (RT).

Spectroscopic data for 7: m.p. 138–140 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3018, 2916, 2848, 1704, 1434, 1383, 1282, 1215, 1130, 1062, 967, 754, 702, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5H), 4.36 (d, J = 8.8 Hz, 1H), 3.98 (d, J = 7.2 Hz, 1H), 3.08–2.95 (m, 5H), 2.45 (s, 6H), 2.03–1.89 (m, 1H), 1.70–1.60 (m, 1H), 1.25–1.14 (m, 1H), 0.95–0.80 (m, 1H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 178.6, 178.3 (CO), 142.1 (C), 128.2, 127.5, 126.9, 78.7, 65.2, 51.8, 42.1 [N-N(CH_3)$_2$], 40.4 (CH), 25.2 (NCH_3), 22.8, 21.7 (CH_2); MS (ES): m/z: 340 $[M+Na]^+$, 318 $[M+H]^+$; HRMS (ES): m/z: calcd for $C_{17}H_{23}N_3O_3Na$: 340.1637; found: 340.1635 $[M+Na]^+$.

Procedure for the preparation of diene 10: A catalytic amount of glacial acetic acid (1 drop) followed by SADP (0.60 g, 3.8 mmol, 2 equiv) was added to a solution of aldehyde **4** (0.35 g, 1.90 mmol, 1 equiv) in anhydrous Et_2O (20 mL). After vigorous stirring for 1 h at reflux, the mixture was extracted with water (2 × 10 mL). The organic layer was washed once with a saturated aqueous solution of sodium chloride, then dried with anhydrous magnesium sulfate, filtered and concentrated to give the chiral heterodiene **10** as a pale yellow solid in a 93% crude yield (0.57 g). The crude material was subjected immediately to the tandem [4+2]/allylboration reaction.

Spectroscopic data for 10: IR ($CHCl_3$ cast): $\tilde{\nu}$ = 2975, 2933, 2826, 1468, 1213, 924, 667, 647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (dd, J = 9.1, 17.9 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 5.46 (d, J = 17.9 Hz, 1H), 3.34–3.31 (m, 1H), 3.21 (s, 3H), 2.50–2.20 (m, 2H), 1.91–1.53 (m, 4H), 1.23 (s, 12H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 149.4 (CH), 148.9 (CH), 135.1 (CH), 83.3 (C), 82.3 (C), 76.0 (CH), 48.9 (CH_2), 26.7 (CH_2), 23.2, 22.1 (CH_3), 22.0 (CH_3), 21.7 (CH_2), 19.4 (CH_3); MS (ES): m/z: 323 $[M+H]^+$; HRMS (ES): m/z: calcd for $C_{17}H_{32}BN_2O_3$: 323.2506; found: 323.2500 $[M+H]^+$.

Spectroscopic data for 11: m.p. 80–82 °C; IR ($CHCl_3$ cast): $\tilde{\nu}$ = 3853, 2932, 1715, 1651, 1597, 1499, 1455, 1382, 1179, 1142, 753, 692, 667, 621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.22 (m, 10H), 6.01 (ddd, J = 1.6, 3.7, 10.6 Hz, 1H), 5.70 (ddd, J = 2.3, 4.5, 10.5 Hz, 1H), 5.38 (s, 1H), 4.80 (d, J = 8.5 Hz, 1H), 4.01 (d, J = 9.6 Hz, 1H), 3.63–3.60 (m, 1H), 3.38–3.28 (m, 2H), 3.36 (s, 3H), 2.92–2.88 (m, 1H), 2.65–2.61 (m, 1H), 1.78–1.71 (m, 1H), 1.68–1.57 (m, 3H), 1.37 (s, 3H), 1.18 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, APT): δ = 175.2, 174.1 (CO), 140.7, 131.7, 130.8, 129.3, 128.8, 128.4, 128.1, 127.2, 126.3, 122.1, 78.5 (C), 76.1, 67.9, 63.2, 60.0, 50.7, 49.1 (CH), 38.4, 25.8, 22.7 (CH_2), 21.9, 20.6 (CH_3); MS (ES): m/z: 475 $[M+H]^+$.

Spectroscopic data for 14a (62% crude weight yield): ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 10.8$ (br s, 1H), 8.12 (d, $J = 9$ Hz, 2H), 7.55 (d, $J = 9$ Hz, 2H), 7.60–7.50 (m, 2H), 7.40–7.25 (m, 3H), 6.20 (ddd, $J = 11$, 4, 1.5 Hz, 1H), 6.02 (ddd, $J = 11$, 5, 2 Hz, 1H), 5.23 (d, $J = 9$ Hz, 1H), 4.54 (d, $J = 6$ Hz, 1H), 4.16 (m, 1H), 4.03 (m, 1H), 2.98 (s, 6H); ^{13}C (75 MHz, $(CD_3)_2CO$, APT): $\delta = 175.0$, 174.1, 166.8, 160.1, 142.1, 137.5, 131.0, 130.1, 128.7, 128.5, 128.2, 127.6, 122.9, 75.8, 61.4, 57.3, 43.1 [N-N$(CH_3)_2$], 38.7; HRMS (ES): m/z: calcd for $C_{23}H_{23}N_3O$: 422.1711; found: 422.1708 $[M]^+$.

Spectroscopic data for 14b (54% crude weight yield): ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 8.15$ (d, $J = 9$ Hz, 2H), 7.60–7.45 (m, 6H), 6.30 (ddd, $J = 11$, 4, 2 Hz, 1H), 6.19 (ddd, $J = 11$, 5, 2 Hz, 1H), 5.23 (dd, $J = 9$, 1 Hz, 1H), 4.71 (d, $J = 4$ Hz, 1H), 4.28 (m, 1H), 4.05 (m, 1H), 2.90 (s, 6H); ^{13}C (75 MHz, $(CD_3)_2CO$, APT): $\delta = 173.9$, 166.9, 141.7, 137.5, 131.7, 131.2, 131.0, 130.4, 129.2, 127.7, 123.3, 121.9, 74.6, 60.8, 56.8, 43.0 [N-N$(CH_3)_2$], 38.0; HRMS (ES): m/z: calcd for $C_{23}H_{22}N_3O_3Br$: 500.0816; found: 500.0812 $[M]^+$.

Spectroscopic data for 14c (60% crude weight yield): ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 8.25$–8.10 (m, 2H), 8.02 (m, 1H), 7.80 (d, $J = 9$ Hz, 1H), 7.70–7.00 (several m, 9H), 6.76 (tt, $J = 7$, 1, 1H), 6.14 (ddd, $J = 10$, 4, 1 Hz, 1H), 5.66 (ddd, $J = 10$, 5, 2 Hz, 1H), 4.73 (dd, $J = 9$, 1 Hz, 1H), 4.42 (d, $J = 9$ Hz, 1H), 3.90 (m, 1H), 3.75 (m, 1H); ^{13}C (75 MHz, $(CD_3)_2CO$, APT): $\delta = 174.6$, 166.8, 148.6, 141.8, 137.3, 131.3, 131.2, 131.1, 129.8, 129.3, 129.0, 128.6, 128.1, 127.5, 120.3, 114.5, 76.4, 68.4, 62.3, 39.1; HRMS (ES): m/z: calcd for $C_{27}H_{23}N_3O_5$: 470.1711; found: 470.1701 $[M]^+$.

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