Multicomponent Reactions

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A Four-Component Reaction for the Synthesis of Dioxadiazaborocines**

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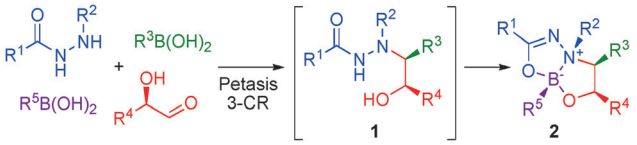
Abstract: *A four-component reaction for the synthesis of heterocyclic boronates is reported. Readily available hydrazides, α-hydroxy aldehydes, and two orthogonally reactive boronic acids are combined in a single step to give structurally distinct bicyclic boronates, termed dioxadiazaborocines (DODA borocines). In this remarkable process, one boronic acid reacts as a carbon nucleophile and the other as a boron electrophile to provide enantio- and diastereomerically pure heterocyclic boronates with multiple stereocenters in high yields.*

Multicomponent reactions are powerful tools for the rapid generation of molecular complexity.[1] In such processes, more than two components are combined in a single reaction, thereby providing an operationally effective and highly modular approach to the synthesis of structurally diverse molecules. The vast majority of reported multicomponent reactions are three-component reactions (3-CRs), and the most well-known examples bear the names of their discoverers, including the Mannich,[2] Passerini,[3] Strecker,[4] Hantzsch,[5] Biginelli,[6] and Petasis[7] reactions. The importance of these reactions is evident from their numerous applications in total synthesis and medicinal chemistry.[1a]

The design of multicomponent reactions beyond three components poses an exceptionally demanding challenge for organic synthesis,[8] with the Ugi reaction[9] being one of the only known synthetically useful four-component reactions (4-CRs). Herein, we report the elaboration of a 3-CR into a 4-CR when the product of the 3-CR contains latently reactive functional groups. We envisioned that a hydrazido variant of the Petasis 3-CR[10] would generate α-hydrazido alcohols containing strategically positioned nucleophilic moieties, represented by the two nitrogen atoms, the hydroxy group, and the carbonyl. Exploration of the pluripotent reactivity of the hydrazido moiety led to the discovery of a novel 4-CR, in which the α-hydrazido alcohol **1** generated in the Petasis 3-CR subsequently undergoes a double condensation with the electrophilic boron moiety of an additional boronic acid, thereby yielding the dihydro-dioxadiazaborocine (DODA borocine) scaffold **2** in a single synthetic operation (Scheme 1). Organoboron heterocycles have found broad



Scheme 1. Combination of Petasis 3-CR and boronic acid condensation in a novel 4-CR for the synthesis of DODA borocines.

use as reagents, catalysts, and chiral auxiliaries,[11] and more recently as chemical biology probes and leads for drug discovery efforts.[12] We therefore set out to investigate the chemistry of this new and structurally unique class of boron-containing heterocycles (**2**), including their formation and reactions.

The substrate scope of the condensation reaction was studied with respect to the boronic acid and it was demonstrated that heteroaromatic, vinyl, aliphatic, and substituted phenylboronic acids successfully underwent the condensation (Table 1). The only limitation was encountered for sterically hindered boronic acids, such as 2,6-dimethyl-phenylboronic acid (**4i**), although both *o*-tolyl-boronic acid and 1-pyrene boronic acid were sufficiently reactive for an effective condensation (**4h** and **4j**). We also demonstrated the condensation of a BINOL-derived bis(boronic) acid with an α-hydrazido alcohol to give the highly sterically encumbered scaffold **4u**, which has potential for application in the field of chiral catalysis.[13]

Initially, the 4-CR of hydrazide, α-hydroxy aldehyde, and two boronic acids was investigated by employing an excess of boronic acid in a hydrazido-Petasis reaction, which satisfyingly furnished the desired DODA borocines (Table 2, **7a–c**). The α-hydroxy aldehyde component of the hydrazido-Petasis reaction was used as its more stable dioxolanol derivative, which facilitated convenient handling and preparation (see the Supporting Information). It was considered plausible that the DODA borocines could be generated in a more controlled fashion by employing two differentially reactive boronic acids. In the 4-CR of hydrazide, α-hydroxy aldehyde, and two such boronic acids, the hydrazido-Petasis reaction proceeds significantly more slowly than the subsequent condensation reaction with any of the two boronic acids. However, the resulting mixture of DODA borocines equilibrates into the

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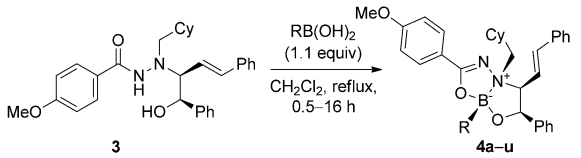
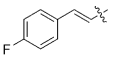
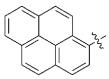
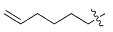
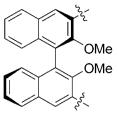
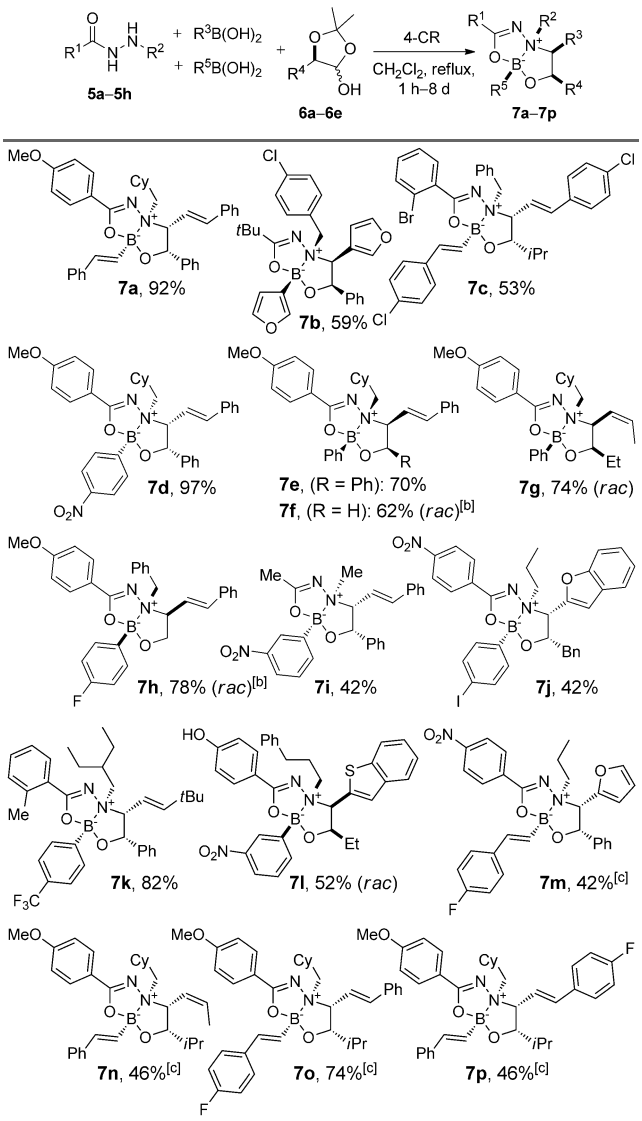
Table 1: Substrate scope for boronic acid condensation.



Product	R	Yield	Product	R	Yield
4a		88%	**4k**		95%
4b		90%	**4l**		78%
4c		95%	**4m**		95%
4d		95%	**4n**		84%
4e		58%	**4o**		95%
4f		90%	**4p**		95%
4g		90%	**4q**		84%
4h		88%	**4r**		89%
4i		0%	**4s**		95%
4j		62%	**4t**		87%
			4u		81%[a]

[a] For this reaction 0.6 equiv of the bis(boronic) acid were used.

Table 2: The four-component reaction.[a]



[a] The following reagent stoichiometries were used: **5a–5h** (1 equiv), **6a–e** (1–1.2 equiv), $R^3B(OH)_2$ (1–1.1 equiv) and $R^5B(OH)_2$ (1–1.6 equiv). [b] Glycolaldehyde dimer was used instead of the dioxolanol. [c] The boronic acids were added sequentially.

condensation product of the more electron-deficient boronic acid during the course of the reaction. This indicates reversibility of the condensation reaction, thus allowing release of the more electron-rich boronic acid to undergo the irreversible C–C bond forming hydrazido-Petasis reaction.

The novel 4-CR was applicable for a wide range of hydrazides (**5a–h**), dioxolanols (**6a–e**), and boronic acids, and it afforded diastereomerically pure DODA borocines in good to excellent yields (Table 2, **7d–l**). Notably, three new consecutive stereogenic centers are formed during the reaction.

DODA borocines incorporating two boronic acids of similar electronic nature (**7m–p**) could be obtained when the 4-CR was carried out in a sequential fashion to allow complete reaction of one boronic acid in the hydrazido-Petasis reaction before a second boronic acid was added to undergo the double condensation (Table 2, **7m–p**).

The three-dimensional structure of the DODA borocines was determined by single-crystal X-ray crystallography and the results confirmed that all of the substituents were indeed present on the *exo* face of the fused five-membered rings (Figure 1).

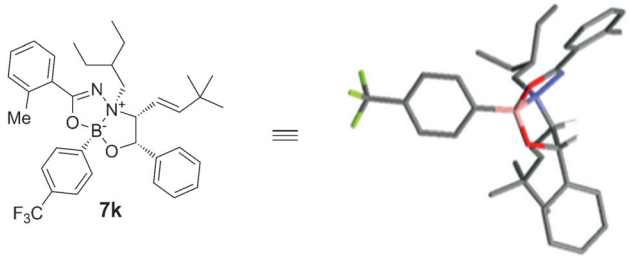
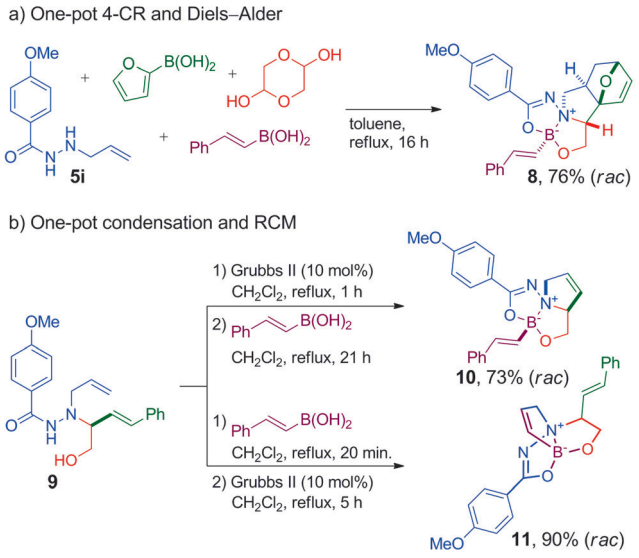


Figure 1. Single-crystal X-ray crystallography of DODA borocine **7k**.

All of the DODA borocines reported herein were stable towards purification by flash column chromatography on silica gel. Furthermore, the products could be stored neat at room temperature without any decomposition for more than a year.

To assess the viability of functional-group manipulation, the DODA borocines were subjected to ring-closing metathesis (RCM) and Diels–Alder reactions (Scheme 2) to yield the structurally complex tri- and pentacyclic boronates **8**, **10** and **11**.



Scheme 2. Complexity-generating reactions.

In conclusion we have developed a novel four-component reaction for the synthesis of DODA borocines. The reaction possesses a high degree of modularity and provides rapid access to chiral and structurally diverse molecules. The reaction process relies on the dual reactivity of the hydrazide moiety in the reaction with an α-hydroxy aldehyde and two differentially reactive boronic acids. Heterocyclic boronates have been the subject of profound interest in recent years and we foresee many applications of these heterocyclic scaffolds in the future, for example, as new bioactive compounds, probes for chemical biology, and catalysts for asymmetric synthesis.

Keywords: boron · cyclization · heterocycles · multicomponent reactions · synthetic methods

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