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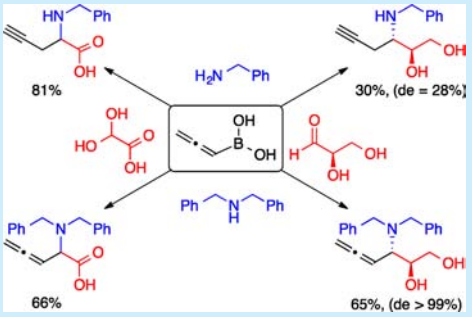
Component-Selective and Stereocontrolled One-Step Three-Component Reaction among Aldehydes, Amines, and Allenyl Boronic Acids or Allenyl Pinacolboronates

Fotini Liepouri,[†] Giovanni Bernasconi,[‡] and Nicos A. Petasis*

Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, California 90089, United States

Supporting Information

ABSTRACT: A one-step, three-component condensation of allenyl boronic acids or allenyl pinacolboronates with amines and aldehydes affords α-allenyl or α-propargyl α-amino acids and *anti*-β-amino alcohols. This process gives the allenyl or propargyl product depending on the amine and boron components. Secondary amines generate exclusively α-allenyl α-amino acids, while primary aliphatic amines lead to α-propargyl α-amino acids. Secondary aliphatic amines react with chiral α-hydroxy aldehydes and allenyl boron derivatives to form stereoselectively allenyl *anti*-β-amino alcohol products.



We previously introduced a one-step, three-component condensation (Scheme 1, reaction A)[1−4] among amines **1**, carbonyl compounds **2**, and alkenyl or aryl boronic acids **3** as a convenient, versatile, and synthetically useful process for the synthesis of multifunctional amine derivatives **4**. This method is very effective for the direct synthesis of a wide range of structurally diverse α-amino acids,[1a,b] *anti*-β-amino alcohols,[1c,e,f,h] and various amine,[1f,g] as well as heterocycles.[1d,i]

We have shown[1,2] that a wide range of amine components (primary or secondary amines,[1] anilines,[1] amino acids,[1f] peptides,[1f] etc.) and a variety of carbonyl components (glyoxylic acid,[1a,b] α-keto acids,[1a] α-hydroxy aldehydes[1c,e,f,h] α-hydroxy ketones,[1f] carbohydrates,[1f] salicylaldehydes,[1f,g] etc.) work effectively in this process under mild conditions. In our initial publications,[1,2] we have reported that alkenyl as well as aryl and heteroaryl boronic acids **3** participate effectively in this multicomponent process by forming a new C−C bond at the site of the C−B bond while incorporating the amine moiety into the product **4**. Numerous examples of this synthetically useful process have been reported by us[1,2] and others.[5]

We now report the use of allenyl boronic acids **5** and allenyl pinacolboronates in this reaction (Scheme 1, reaction B). Following our previous disclosures of the first examples of this chemistry,[6] further detailed studies investigated the remarkable selectivity on the type of product formed, based on the particular components used in this process. Although alkenyl or aryl boronic acids **3** participate in our three-component process (Scheme 1, reaction A) to give only one type of amine product **4**, allenyl boron compounds can generate either α-allenyl **6** or α-propargyl **7** amine products (Scheme 1, reaction B). This process is further complicated by the ability of allenyl nucleophiles to react with carbonyl compounds to form the corresponding homopropargylic alcohol products **8**.[7]

Scheme 1. One-Step Condensation of Amines 1, Carbonyl Compounds 2, and Alkenyl or Aryl Boronic Acids 3 (Reaction A) or Allenyl Boronic Acids 5 (Reaction B)

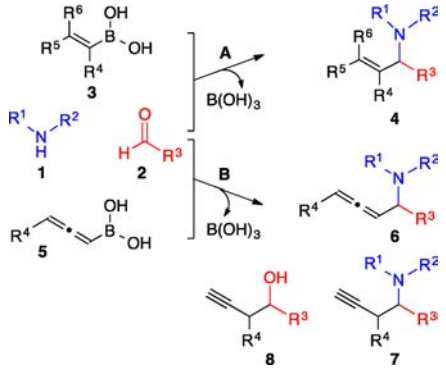


Table 1 summarizes the results of representative examples of the one-step reaction of amines **1** with glyoxylic acid monohydrate **9** and allenyl boronic acid **10**[8] to form α-allenyl **11** or α-propargyl **12** α-amino acid products. Typically, these reactions used either equimolar amounts of the three components or a 1/3 molar excess of the boronic acid and were completed at rt in a variety of solvents over a period of 15−48 h and in most cases gave the pure amino acid products in good to excellent yields (not optimized). The allene to alkyne ratio of the two products was determined by NMR spectroscopy.

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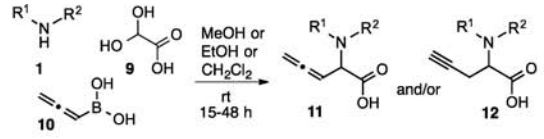
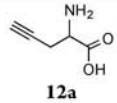
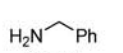
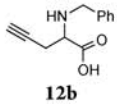
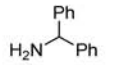
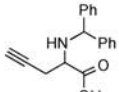
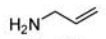
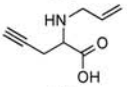
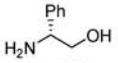
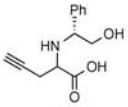
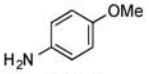
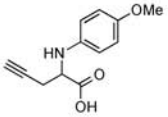
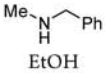
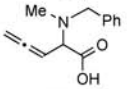
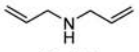
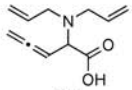
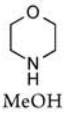
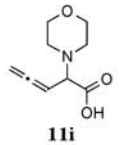
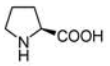
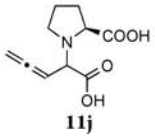
Table 1. One-Step, Three-Component Synthesis of α-Propargyl (11) and/or α-Allenyl (12) α-Amino Acids

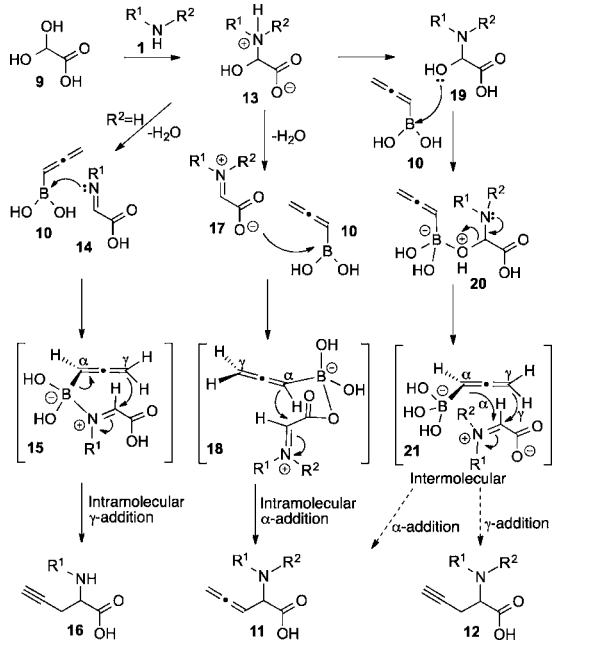


entry	amine **1** conditions	major product	yield (**11** / **12**)
1	NH_3 + **9**, then cat. Et_3N, then **10** MeOH, rt, 15 h	 **12a**	72% (<1:99)
2	 CH_2Cl_2	 **12b**	81% (<1:99)
3	 MeOH	 **12c**	66% (32:68)
4	 MeOH	 **12d**	64% (<1:99)
5	 MeOH	 **12e**	34% (<1:99) (de = 27%)
6	 CH_2Cl_2	 **12f**	56% (<1:99)
7	 EtOH	 **11g**	65% (>99:1)
8	 MeOH	 **11h**	66% (>99:1)
9	 MeOH	 **11i**	70% (>99:1)
10	 MeOH, 48 h	 **11j**	32% (>99:1) (de = 44%)

Interestingly, despite the reactivity of allenyl boronates toward carbonyl compounds,[8a−c] that could lead to the hydroxy acid adduct rather than the amino acids, allenyl boronic acid **10** proved to be an effective component in this process. Notably, this chemistry does not involve catalysis by metals[8d] or acids.[8e]

The combination of ammonia and glyoxylic acid (Table 1, entry 1) proved quite efficient in forming free α-propargyl glycine by reacting **10** with preformed hydroxy glycine in the presence of base. Unlike other additions of allenyl boron compounds to

Scheme 2. Mechanistic Hypothesis for the Component Selectivity in the Formation of Allenyl or Alkynyl Products



carbonyls and imines that form propargyl products exclusively,[8] we obtained both the propargyl **12** (Table 1, entries 1−6) as well as the allenyl **11** (Table 1, entries 7−10) products, often with high selectivity.[9]

Notably, *this is a component-selective process* where *the amine component used determines the type of product formed*. Most primary amines including anilines formed exclusively the α-propargyl products (Table 1, entries 2 and 4−6), while a more bulky primary amine was less selective (Table 1, entry 3). Secondary amines gave exclusively the α-allenyl products (Table 1, entries 7−10). However, contrary to other boronic acids,[1a−c,2] phenylglycinol (Table 1, entry 5) or chiral amino acids (e.g., Table 1, entry 10) proceeded with only modest diastereoselectivity. These bulky components (Table 1, entries 5 and 10) give complex mixtures and low isolated yields.

The general trends observed in the above amino acid synthesis from **10** can be attributed to some mechanistic insights regarding this particular process (Scheme 2). Similar to other allenyl nucleophiles, the reactive intermediates are expected to participate in nucleophilic addition to iminium species either from the α- or from the γ-position of the allene moiety. The preferred products formed (Table 1) can be explained via the intramolecular addition processes **15** and **18** due to favorable entropic and electrostatic factors. The preferred formation of α-propargyl products with primary amines can be explained through the formation of an imine **14** and B−N coordination to **10**, which leads to the alkyne **16** via γ-addition to the iminium species **15**. The exclusive formation of allenyl products with secondary amines is consistent with our previously proposed mechanistic hypothesis[2] involving an intramolecular delivery[5c−f] of the allenyl moiety via B−O coordination of **17** to **10**, which leads to the allenes **11** via α-addition to the iminium species **18**.

Table 2 shows representative examples of the one-step reaction of amines **1** with α-hydroxy aldehydes **22** and allenyl boronic acid **10**[8] to form α-allenyl **23** or α-propargyl **24** amino alcohol products. These reactions were run in methanol at rt over a period of 24−48 h and in most cases gave the pure amino alcohol

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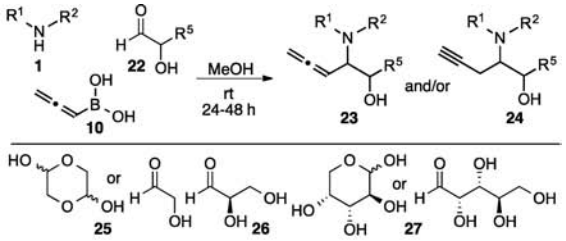
Table 2. One-Step, Three-Component Reaction of Amines 1, α-Hydroxy Aldehydes 22, and Allenyl Boronic Acid 10

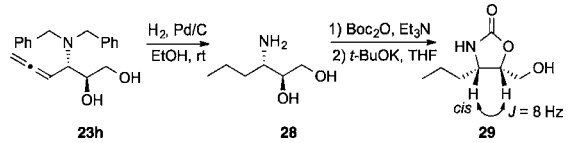


entry	amine **1** conditions	major product	yield (**23** / **24**)
1	**25**, MeOH, 24 h	**23a**	46% (>99:1)
2	**25**, MeOH, 24 h	**24b**	78% (1:1)
3	**25**, MeOH, 24 h	**24c**	61% (<1:99) (de = 63%)
4	**16**, MeOH, 24 h	**24d**	68% (<1:99) (de = 67%)
5	**26**, MeOH, 24 h	**24e**	30% (<1:99) (de = 23%)
6	**25**, MeOH, 24 h	**23f**	90% (>99:1)
7	**26**, MeOH, 24 h	**23g**	70% (>99:1) (de > 99%)
8	**26**, MeOH, 24 h	**23h**	65% (>99:1) (de > 99%)
9	**27**, MeOH, 48 h	**23i**	21% (>99:1) (de > 99%)

products in good to moderate yields (not optimized). The allene **23** to alkyne **24** ratio was determined by NMR.

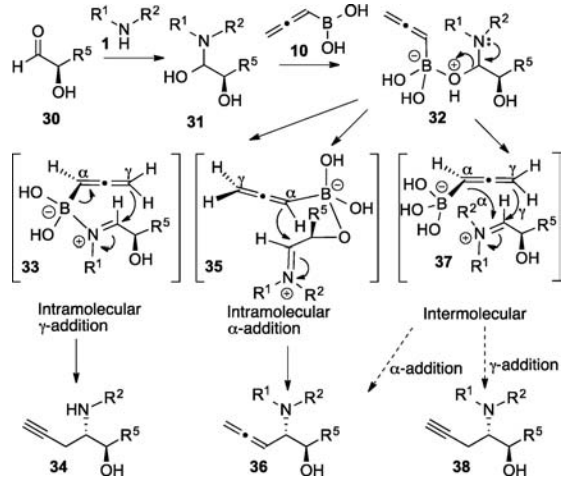
Depending on their substitution patterns, primary amines can favor the formation of allenyl products (Table 2, entry 1) or alkynyl products (Table 2, entries 3−5), while anilines gave equimolar amounts of both products (Table 2, entry 2). Analogously to the synthesis of amino acids (Table 1), secondary amines gave exclusively the allene products (Table 2, entries 6−9). Although the use of chiral amines provided only modest stereocontrol (Table 2, entries 4 and 5), when chiral α-hydroxy aldehydes **26** or carbohydrate components **27** were combined with secondary amines, the resulting products (Table 2, entries 7−9) were obtained as single *anti*-stereoisomers (de >99%).[1c] The *anti* configuration was consistent with that observed for

Scheme 3. Conversion of an Allenyl *anti*-β-Amino Alcohol (Table 2, Entry 8) to the Corresponding Oxazolidinone



23h **28** **29**

Scheme 4. Mechanistic Hypothesis for the Stereoselective Formation of Allenyl *anti*-β-Amino Alcohols 36



other boronic acids and was confirmed for diol **23h** (Table 2, entry 8) by the formation of the *cis*-oxazolidinone **29** (J = 8 Hz) as shown in Scheme 3.

The high degree of stereocontrol in the formation of allenyl *anti*-β-amino alcohols is presumably due to an intramolecular α-addition to the iminium species that is similar to that postulated above (**18**) (Scheme 2) for the amino acid synthesis. As shown in Scheme 4, condensation of the amine **1** with a chiral α-hydroxy aldehyde **30** leads to adduct **31**, which binds to the boronic acid group to form initially adduct **32**, as we had proposed.[2] With primary amines further transformation can lead to the attachment of the boron group to an imine species **33** that leads to alkyne **34**. With both primary and secondary amines the boron group can be attached to the α-hydroxy group that proceeds to the formation of the β-amino alcohol **36** via intramolecular α-addition to the iminium species **35**. For steric reasons, the nucleophilic attach takes place away from substituent R^5, resulting in the exclusive formation of the *anti*-diastereomer **36**. The alternative α- or γ-intermolecular addition of the allene borate to the iminium species is less likely for entropic reasons.

Representative examples using the substituted allenyl boronic acid **39** or the pinacol boronate **40** are shown in Table 3. These compounds were prepared and used as the racemates, and due to their axial chirality they exhibited variable degrees of diastereoselectivity. Boronic acid **39** was more diastereoselective but also more labile and gave lower yields (Table 3, entry 1) than pinacol boronate **40** (Table 3, entry 2), which gave higher yields in both the synthesis of amino acid (Table 3, entry 3) and amino alcohols (Table 3, entries 4 and 5).

Overall, the above results have established the ability of allenyl boronic acids to participate effectively in a three-component reaction with amines and aldehydes to form useful alkynyl as well as allenyl amino acids and amino alcohol products. The parent allenyl boronic acid **10** and its boronates have been known for

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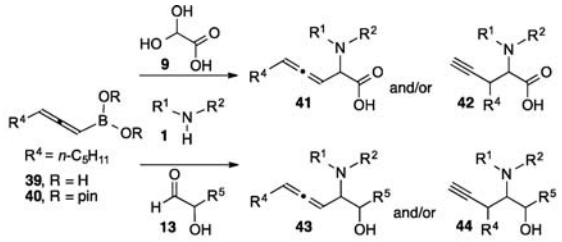
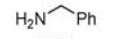
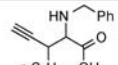
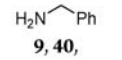
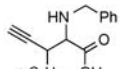
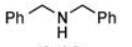
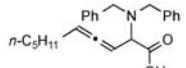
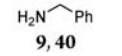
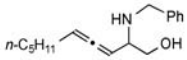
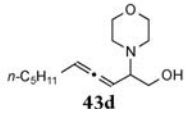
Table 3. Use of a Substituted Allenyl Boronic Acid 39 or Pinacolboronate 40



entry	amine **1** conditions	major product	yield (**41** / **42** or **43** / **44**)
1	 **9**, **39**, MeOH, rt, 72 h	 **42a**	34% (<1:99) (de = 70%)
2	 **9**, **40**, MeOH, rt, 72 h	 **42a**	49% (<33:67) (de = 53 %)
3	 **9**, **39** MeOH, rt, 88 h	 **41b**	28% (<1:99) (de = 59%)
4	 **9**, **40** MeOH, rt, 20 h	 **43c**	36% (<1:99) (de = 30%)
5	 **9**, **40** CH_2Cl_2, rt, 60 h	 **43d**	56% (<1:99)

some time,[7a,8] while the preformed tartrate derivatives were shown to add readily to aldehydes and ketones in a practical and enantioselective manner.[8a−c] Despite their ability to undergo facile γ-intramolecular addition to aldehydes,[8] the reported chemistry demonstrates that allenyl boron compounds can also add preferably to certain in situ adjacent iminium salts to produce allenyl and alkynyl amines and amino acids. The products of this one-step process are multifunctional allenyl and propargyl amine derivatives, which are versatile and valuable building blocks for synthetic and medicinal applications.[10]

In summary, we have developed a new, one-step, three-component methodology to synthesize α-allenyl and α-propargyl α-amino acids in a highly controllable way, just by selecting the boron and amine components used. This chemistry has interesting mechanistic features and can be used to generate novel and potentially valuable molecules, particularly in light of the growing synthetic utility of allenes[10] and the popularity of alkynes in click chemistry.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: petasis@usc.edu.

Present Addresses

†Present address: RAFARM S.A., Pharmaceutical Industry, Agiou Louka Street, Paiania, 19002 Attiki, Greece.
‡Present address: European Chemicals Agency (ECHA), P.O. Box 400, FI-00121 Helsinki, Finland.

Notes

The authors declare no competing financial interest.

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