J|A|C|S
ARTICLES
Published on Web 10/12/2007

Petasis Borono-Mannich Reaction and Allylation of Carbonyl Compounds via Transient Allyl Boronates Generated by Palladium-Catalyzed Substitution of Allyl Alcohols. An Efficient One-Pot Route to Stereodefined α-Amino Acids and Homoallyl Alcohols

Nicklas Selander, Andreas Kipke, Sara Sebelius, and Kálmán J. Szabó*

Contribution from the Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91, Stockholm, Sweden

Received July 4, 2007; E-mail: kalman@organ.su.se

Abstract: An efficient one-pot procedure was designed by integration of the pincer-complex-catalyzed borylation of allyl alcohols in the Petasis borono-Mannich reaction and in allylation of aldehydes and ketones. These procedures are suitable for one-pot synthesis of α-amino acids and homoallyl alcohols from easily available allyl alcohol, amine, aldehyde, or ketone substrates. In the presented transformations, the active allylating agents are in situ generated allyl boronic acid derivatives. These transient intermediates are proved to be reasonably acid-, base-, alcohol-, water-, and air-stable species, which allows a high level of compatibility with the reaction conditions of the allylation of various aldehyde/ketone and imine electrophiles. The boronate source of the reaction is diboronic acid or in situ hydrolyzed diboronate ester ensuring that the waste product of the reaction is nontoxic boric acid. The regio- and stereoselectivity of the reaction is excellent, as almost all products form as single regio- and stereoisomers. The described procedure is suitable to create quaternary carbon centers in branched allylic products without formation of the corresponding linear allylic isomers. Furthermore, products comprising three stereocenters were formed as single products without formation of other diastereomers. Because of the highly disciplined consecutive processes, up to four-step, four-component transformations could be performed selectively as a one-pot sequence. For example, stereodefined pyroglutamic acid could be prepared from a simple allyl alcohol, a commercially available amine, and glyoxylic acid in a one-step procedure. The presented method also grants an easy access to stereodefined 1,7-dienes that are useful substrates for Grubbs ring-closing metathesis.

1. Introduction

Synthetic application of allyl boronates have received considerable recent attention because of the highly selective and efficient carbon−carbon bond formation performed by these reagents in allylation reactions.[1−7] Allyl boronates are most widely employed for allylation of aldehydes;[1−8] however, allylation of ketones[9−12] and imines[13−19] were also reported. As a consequence, there is a high current demand for new efficient synthetic procedures providing functionalized allyl boronates. However, development of these procedures raises two important synthetic issues: (i) the synthetic procedures have to be highly stereo- and regioselective and have to tolerate many functionalities, and (ii) the prepared functionalized allyl boronates are required to be stable under the purification and isolation procedures, yet sufficiently reactive in the desired allylation reactions.

Several recent procedures have been developed addressing problem i above. The direct methods, based on addition of reactive allylmetal reagents[20,21] (such as allyl lithium and Grignard reagents) to borate esters, are suitable for bulk preparation of allyl boronates. However, a potential draw-back of this approach is the poor stereo- and regiochemical stability of the allylmetal reagents which leads to formation of isomeric mixtures of the allyl boronates. Another problem is the poor

(1) Hall, D. G. *Boronic Acids*; Wiley: Weinheim, Germany, 2005.
(2) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, 4732.
(3) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(4) Otera, J. *Modern Carbonyl Chemistry*; Wiley: Weinheim, Germany, 2000.
(5) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.
(6) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.
(7) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.
(8) Wu, T. R.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.
(9) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909.
(10) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
(11) Pace, R. D.; Kabalka, G. W. *J. Org. Chem.* **1995**, *60*, 4838.
(12) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.
(13) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(14) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182.
(15) Kobayashi, S.; Hirano, K.; Sugiura, M. *Chem. Commun.* **2005**, 104.
(16) Sugiura, M.; Mori, C.; Hirano, K.; Kobayashi, S. *Can. J. Chem.* **2005**, *83*, 937.
(17) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551.
(18) Sebelius, S.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2003**, *5*, 3065.
(19) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000.
(20) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.
(21) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990.

functional group tolerance arising from the high reactivity of the allyl metal species. On the other hand, high selectivity and functional group tolerance can be achieved in transition-metal-catalyzed procedures for generation of allyl boronates,[22−30] which often involves application of diboronates as a source of the boronate functionality. In this respect, palladium-,[22−26] platinum-,[27,28,31] nickel-,[29] and copper-catalyzed[30,32] boronation of allenes, dienes, and substituted allylic substrates represent the most efficient procedures.

Considering the relatively low stability of the functionalized allyl boronates, their isolation and purification often becomes a major issue (ii, above), which may encumber the synthetic application of allyl boronates. Allyl boronic acids are more reactive allylating reagents[17,33] than allyl boronate esters; however, these species rapidly decompose (probably oxidized) under solvent-free conditions.[20,23,34,35] An attractive solution for the above purification issues is the development of one-pot procedures, in which the transient allyl boronates are not isolated but directly reacted with the corresponding allyl acceptors.[18,23,32,34,36−38] Development of these procedures requires highly selective formation of allyl boronates and carefully designed reaction conditions to avoid undesired side products in the multicomponent processes. We[18,34,36] and others[32,37,38] have shown that transition-metal-catalyzed generation of allyl boronates followed by subsequent allylation of aldehydes can be performed in a one-pot sequence. In a couple of recent communications,[23,24,36] we have shown that allyl boronates can be efficiently prepared from simple allylic substrates, such as allyl alcohols, employing palladium pincer complex[39−44] catalysis. This efficient borylation procedure can be integrated in a one-pot sequence[36] for stereo- and regioselective carbon−carbon bond coupling of allyl alcohols and aldehydes. The selective coupling reaction proceeds via generation of transient allyl boronic acids from diboronic acid[45] as boronate source. In this paper, we give a full account of our results with extending the allyl-alcohol-based allylation procedures to new one-pot transformations, new reagents, and catalysts. These new results clearly indicate that complex, highly functionalized, regio- and stereodefined products can easily be prepared from allyl alcohols via catalytic generation of allyl boronates in a one-pot sequence. Furthermore, the cost efficiency of the transformations has been improved by application of a new boronate source and catalyst. The new aspects of the full paper version can be summarized as follows: (a) Extension of the synthetic scope of the reaction to the Petasis borono-Mannich reaction is achieved.[14,16,17,46,47] Using this procedure stereo- and regiodefined α-amino acids[48−55] can be prepared from inexpensive allyl alcohols in a multicomponent one-pot reaction. (b) Allylation of ketones by in situ generated allyl boronic acids in the presence of catalytic amounts of InI takes place.[9] (c) By appropriate choice of the reaction conditions and allyl alcohol substrates, selective carbon−carbon bond formation involving quaternary carbons can be achieved. (d) The reactions are made suitable for one-pot stereoselective synthesis of 1,7-dienes, which are useful precursors for Grubbs-cyclization.[56,57](e) With a slight change of the reaction conditions, the one-pot procedures can be performed using commercially readily available bis-(pinacolato)diboron in place of diboronic acid. (f) A new SCS based pincer complex catalyst was introduced as a complement for the very efficient and easily accessible selenium based SeCSe complex. A new straightforward procedure for synthesis of this latter complex is included in the Supporting Information.

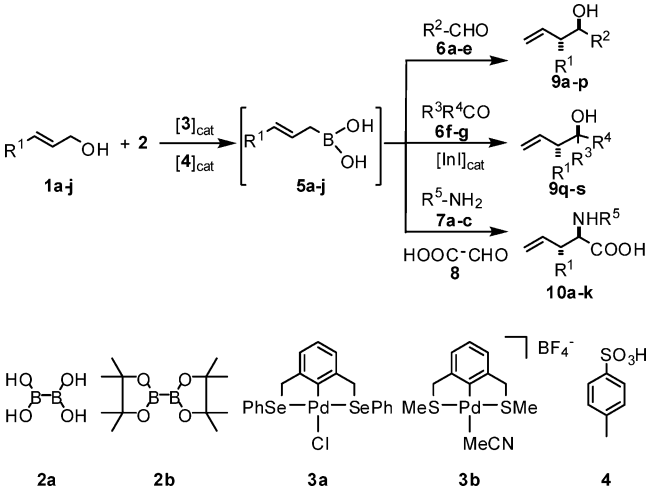


Figure 1. General scheme of the studied one-pot reactions for synthesis of homoallyl alcohols and α-amino acids via catalytic generation of allyl boronates.

2. Results and Discussion

As mentioned above, the present studies (Figure 1) are mostly directed to one-pot synthesis of functionalized homoallyl alcohols (**9**) and α-amino acids (**10**) from inexpensive, easily accessible allyl alcohols (**1**). The reactions proceed via pincer-

(22) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889.
(23) Sebelius, S.; Olsson, V. J.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478.
(24) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588.
(25) Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174.
(26) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761.
(27) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1996**, 2073.
(28) Clegg, W.; Johann, T. R. F.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Paekman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1431.
(29) Suginome, M.; Matsuda, T.; Yoshimoto, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1567.
(30) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034.
(31) Suginome, M.; Nakamura, H.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4248.
(32) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913.
(33) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.
(34) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, 2539.
(35) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150.
(36) Selander, N.; Sebelius, S.; Estay, C.; Szabó, K. J. *Eur. J. Org. Chem.* **2006**, 4085.
(37) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807.
(38) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807.
(39) Albrecht, M.; Koten, G. v. *Angew. Chem., Int. Ed.* **2001**, 3750.
(40) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.
(41) Boom, M. E. v. d.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759.
(42) Singleton, J. T. *Tetrahedron* **2003**, *59*, 1837.
(43) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055.
(44) Szabó, K. J. *Synlett.* **2006**, 811.
(45) Baber, R. A.; Norman, N. C.; Orpen, A. G.; Rossi, J. *New J. Chem.* **2003**, *27*, 773.
(46) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
(47) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
(48) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468.
(49) Zumpe, F. L.; Kazmaier, U. *Synlett.* **1998**, 1199.
(50) Kazmaier, U. *Angew. Chem., Int. Ed.* **1994**, *33*, 998.
(51) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 2012.
(52) Bakke, M.; Ochta, H.; Kazmaier, U.; Sugai, T. *Synthesis* **1999**, 1671.
(53) Mock, M. L.; Michon, T.; Hest, J. C. M. v.; Tirrell, D. A. *ChemBiochem.* **2006**, *7*, 83.
(54) Ellis, T. K.; Ueki, H.; Yamada, T.; Ohfune, Y.; Soloshonok, V. A. *J. Org. Chem.* **2006**, *71*, 8572.
(55) Soloshonok, V. A.; Cai, C.; Hruby, V. C.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688.
(56) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
(57) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693.

complex[58−62] (**3**) catalyzed generation of allyl boronic acids (**5**) using diboronates[45] (**2**) as boronate source in the presence of catalytic amounts of *p*-toluenesulfonic acid (**4**) followed by coupling to the corresponding electrophiles. The presented one-pot procedures are not moisture and air sensitive, and therefore the reactions are conducted without employing inert gas atmosphere or using carefully dried solvents.

Allylation of Aldehydes. Allylation of aldehydes using allyl alcohol as allylating reagent is a highly efficient and attractive synthetic route to functionalized homoallyl alcohols. Allyl alcohols are one of the least expensive and most accessible allylating agents, and therefore carbon−carbon couplings between allyl alcohols and aldehydes represent excellent examples for value-added synthesis. However, a usual problem of these types of reactions is the activation of the allylic carbon−oxygen bond of the alcohol functionality. Many excellent solutions for this problem were presented by using palladium-catalyzed substitution[3,5,7] of the in situ activated hydroxy group of allyl alcohols. The most important strategies for activation of the hydroxy group[63,64] involve application of $SnCl_2$,[65−68] BEt_3,[69−71] Et_2Zn,[72] and various indium salts.[73−75] However, by using these activating reagents, functionalities coordinating to Lewis acids or sensitive to reduction cannot be tolerated in the substrates. Another problem is often the unsatisfactorily low stereoselectivity of the reaction.

As we have shown in our previous communication,[36] the majority of these selectivity problems can be avoided by conversion of the hydroxy group of the allyl alcohol to a boronate. In these reactions the hydroxy group was activated by diboronic acid,[45] which does not affect the usual functional groups, and therefore the reaction tolerates carbonyl, cyano, aromatic halogenide, and nitro groups. As the allylation proceeds via a cyclic six-membered ring transition state (TS),[1,2,6] the stereoselectivity of the coupling of the transient allyl boronate with aldehydes proceeds with a remarkably high stereoselectivity. In fact, all the presented coupling reactions of aldehydes with in situ generated allyl boronates provided a single diastereomer without formation of traces of the other isomer. Considering the allylation reactions of aldehydes with allyl alcohols, we mainly focused on extension of the synthetic scope of the reactions, on application of commercially easily available diboronate **2b**, and on the acceleration of the sluggish reactions by using a new catalyst. Some of the previously communicated[36] reference reactions (entries 1, 2, 4, 8, 9, 13, 14, 16, 17, 18, 21, and 23) are given in Table 1, while the rest of the processes listed in this table are newly developed transformations.

The coupling reaction between the corresponding allyl alcohol and aldehyde can be performed as an operationally simple one-pot, one-step procedure. Accordingly, in a typical reaction, reactants **1**, **2**, and **6** and catalysts **3a**[58,59] (5 mol %) and **4** (5 mol %) were dissolved in a mixture of DMSO and methanol (1:1) at the beginning of the reaction, then after the allotted reaction time the coupling product was isolated (Table 1). We have previously shown that primary (**1a**,**f**,**g**), secondary (**1b**,**e**,**h**), cyclic (**1h**), and acyclic (**1a**−**g**) alcohols react with an excellent regioselectivity to give branched homoallyl products (**9a**−**f** and **9i**−**k**).

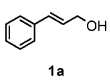
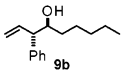
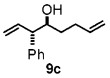
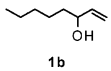
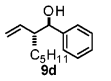
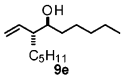
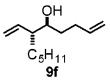
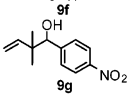
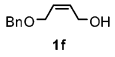
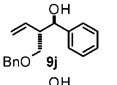
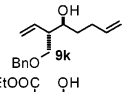
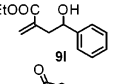
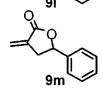
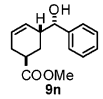
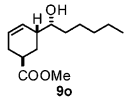
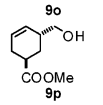
We have now found that the high regioselectivity is maintained even for tertiary alcohols **1c**,**d**. The reaction of these alcohols with aldehydes **6a** and **6d** resulted in exclusively the corresponding homoallyl alcohols (**9g**,**h**) creating a new quaternary carbon center (Table 1, entries 11, 12). Formation of the linear product with a new carbon−carbon bond to a secondary center was not observed at all. Applying 4-pentenal (**6c**) as aldehyde component with alcohols **1a**, **1b**, and **1f** we could perform an operationally simple one-pot formation of stereodefined 1,7-dienes **9c**, **9f**, and **9k** (Table 1, entries 5−7, 10, and 15). These products undergo facile Grubbs ring-closing metathesis (RCM) to give stereodefined cyclohexenes (vide infra).

As we have shown in recent publications,[23,24] the transient allyl boronic acids can be isolated and fully characterized. Probably, the only exception is the dienyl boronic acid intermediate (**5e**) formed by borylation of **1e** (Table 1, entry 13), which resisted all attempts to isolation. However, because of the one-pot/one-step conditions, the unstable **5e** intermediate was allowed to react directly after formation with **6a**, and thus the corresponding product (**9i**) could be isolated in high yield.

The previously communicated[23,24,35,36] efficient borylation procedures are based on application of diboronic acid **2a**, which is a highly efficient reagent in the pincer-complex-catalyzed transformation of allyl alcohols and other easily accessible substrates. Furthermore, the subsequent coupling reaction is also highly environmentally benign, as the only byproduct is nontoxic boric acid. Nevertheless, the difficult commercial availability of diboronic acid **2a** can be considered as a limiting factor for the widespread use of the above processes. Therefore, we studied the possibility to replace **2a** with commercially easily available bis(pinacolato)diboron **2b**. As we reported before,[23] diboronate **2b** performs much less efficiently in the pincer complex catalyzed boronation reactions, than **2a**. This may be due to destabilizing steric interactions between the pinacolato moiety of **2b** and the pincer ligand of **3a**. Accordingly, it is not surprising that using **2b** in place of **2a** under the standard reaction conditions described above gives only (if at all) traces of homoallyl product **9** and the reaction mixture contains largely unreacted allyl alcohol **1** and aldehyde **6**. We have reasoned that the in situ hydrolysis of **2b** to **2a** could help to improve the performance of the bispinacolato derivative **2b** in the coupling reactions. We have previously reported[24] that addition of water does not inhibit the robust boronation process of allyl

(58) Yao, Q.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997.
(59) Yao, Q.; Sheets, M. *J. Org. Chem.* **2006**, *71*, 5384.
(60) Aydin, J.; Selander, N.; Szabó, K. J. *Tetrahedron Lett.* **2006**, *47*, 8999.
(61) Dupont, J.; Beydoun, N.; Pfeffer, M. *J. Chem. Soc., Dalton Trans.* **1989**, 1715.
(62) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531.
(63) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.
(64) Muzart, J. *Tetrahedron* **2005**, *61*, 4179.
(65) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577.
(66) Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *J. Am. Chem. Soc.* **1998**, *110*, 4473.
(67) Carde, L.; Llebaria, A.; Delgado, A. *Tetrahedron Lett.* **2001**, *42*, 3299.
(68) Banerjee, M.; Roy, S. *J. Mol. Catal. A* **2005**, *246*, 231.
(69) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627.
(70) Mukai, R.; Horino, Y.; Tanaka, S.; Tamaru, Y.; Kimura, M. *J. Am. Chem. Soc.* **2004**, *126*, 11138.
(71) Zhu, S.-F.; Yang, Y.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333.
(72) Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3392.
(73) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847.
(74) Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, *69*, 5054.
(75) Jang, T.-S.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Synthesis* **2003**, 775.

Table 1. Allylation Aldehydes via Transient Allyl Boronates Generated from Allyl Alcohols[a]

entry	alcohol	aldehyde	diboron[b]	cat.[c]	cond.[d]	product	yield[e]
1	 **1a**	 **6a**	**2a**	**3a**	40/16	 **9a**	88
2[f]	**1a**	**6a**	**2a**	**3a**	40/48	**9a**	96
3	**1a**	**6a**	**2b**	**3a**	50/24	**9a**	87
4	**1a**	 **6b**	**2a**	**3a**	50/16	 **9b**	70
5	**1a**	 **6c**	**2a**	**3a**	50/36	 **9c**	74
6	**1a**	**6c**	**2b**	**3a**	50/48	**9c**	62
7	**1a**	**6c**	**2b**	**3b**	50/24	**9c**	87
8	 **1b**	**6a**	**2a**	**3a**	50/16	 **9d**	86
9	**1b**	**6b**	**2a**	**3a**	50/16	 **9e**	76
10[g]	**1b**	**6c**	**2a**	**3a**	50/36	 **9f**	69
11	 **1c**	 **6d**	**2a**	**3a**	50/16	 **9g**	77
12	 **1d**	**6a**	**2a**	**3a**	50/16	 **9h**	82
13	 **1e**	**6a**	**2a**	**3a**	60/16	 **9i**	82
14	 **1f**	**6a**	**2a**	**3a**	40/16	 **9j**	96
15[g]	**1f**	**6c**	**2a**	**3a**	50/36	 **9k**	78
16	 **1g**	**6a**	**2a**	**3a**	40/16	 **9l**	96
17[h]	**1g**	**6a**	**2a**	**3a**	70/16	 **9m**	61
18	 **1h**	**6a**	**2a**	**3a**	50/36	 **9n**	93
19	**1h**	**6a**	**2b**	**3a**	50/48	**9n**	92
20	**1h**	**6a**	**2b**	**3b**	50/6	**9n**	87
21	**1h**	**6b**	**2a**	**3a**	50/36	 **9o**	71
22	**1h**	**6b**	**2b**	**3b**	50/24	**9o**	82
23	**1h**	 **6e**	**2a**	**3a**	50/36	 **9p**	78

[a] In a typical reaction **1**, **2** (1.2 equiv) and **6** (1.2 equiv) were dissolved in a DMSO/MeOH mixture in the presence of catalytic amounts of **3** and **4** (each 5 mol %). [b] When **2b** was applied, also 8.0 equiv of water and 20 mol % of *p*TsOH were employed. [c] Catalyst employed. [d] Temperature/time, °C/h. [e] Isolated yield. [f] *p*TsOH (**4**) was not used. [g] Reaction run using 3.0 equiv. of aldehyde. [h] Reaction run using 50 mol % of *p*TsOH.

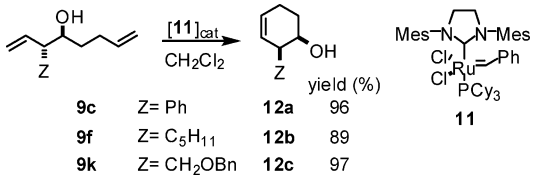
alcohols; however, the catalytic reactions are slightly slowed down. This involves that the in situ hydrolysis of **2b** to **2a** have to be solved by the addition of as small amount of water as possible. Our optimization studies show that the best results can be achieved by the addition of 8 equiv of water per 1 equiv of allyl alcohol and increasing the amount of cocatalyst **4** to 20 mol %. Under these conditions, the coupling reactions with **2b** proceeds with almost as high yield as with **2a** (Table 1, entries 3, 6, 7, 19, 20, and 22). Using catalyst **3a** in these transformations, the required reaction times were usually longer with **2b**, than with **2a** (cf. entries 1 and 3, or entries 18 and 19 in Table 1). This is probably because of the decelerating effect of the water in the borylation process, when **2b** was used as boronate source.

In the coupling reactions we also employ catalytic amounts of *p*-toluenesulfonic acid (**4**). As it was pointed out previously,[23,36,76,77] **4** has a catalytic effect for at least two important procedures of the coupling reactions, such as the borylation reaction[23] and the allylation of aldehyde with the in situ generated allyl boronate.[36,76,77] Although the coupling reactions can be carried out in the absence of **4** (Table 1, entry 2), the reaction proceeds much faster when catalytic amounts of *p*-toluenesulfonic acid is present in the reaction mixture (cf. Table 1, entries 1, 2). Furthermore, *p*-toluenesulfonic acid (**4**) probably has an important catalytic effect even in the in situ hydrolysis of **2b** to **2a**. Accordingly, in the procedures when bis-pinacolato derivative **2b** is employed as borylation agent (Table 1, entries 3, 6, 7, 19, 20, and 22), acid **4** catalyzes three distinct processes under the applied one-pot conditions: hydrolysis of **2b** to **2a** in the presence of water, borylation of **1** to **5**, and allylation of **6** with **5**.

Some structural features in the allyl alcohol substrates, such as the presence of carboxy functionality (**1g**,**h**) and the cyclic topology of the substrate (**1h**), leads to a decrease of the reactivity. As application of **2b** in place of **2a** leads to a further slow down of the processes, some of the reactions required extended reaction times (e.g., Table 1 entries 19 or 21). We attempted to accelerate these reactions by employing other type of catalysts. It was found that application of SCS catalyst **3b**[61,62] (Figure 1) instead of **3a**[58−60] led to much faster coupling reactions without significant decrease of the yields. For example, the coupling reaction of cyclic substrate **1h** with benzaldehyde (**6a**) using **2b** as boronate source required 48 h using **3a** as catalyst (Table 1, entry 19), while the same reaction with **3b** could be completed in only 6 h (Table 1, entry 20).

Considering the above-described coupling reactions of allyl alcohols and aldehydes, it can be concluded that the reaction has a very broad synthetic scope, involving primary, secondary, and tertiary alcohols with both cyclic and acyclic architecture. The reactions are highly regio- and stereoselective and tolerate many substituents. For example, products **9n**,**o** with three stereocenters forms as a single diastereomer without trace of the other stereoisomers (Table 1, entries 18−22). Furthermore, the obtained densely functionalized homoallyl alcohols involve functionalities (such as **9c**,**f**,**i**,**k**) that can be directly employed in further catalytic processes. For example, stereodefined 1,7-dienes (**9c**,**f**,**k**) can easily be cyclized (Figure 2) affording

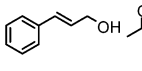
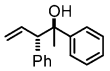
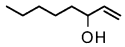
(76) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808.
(77) Elford, T. G.; Arimura, Y.; Yu, S. H.; Hall, D. G. *J. Org. Chem.* **2006**, *72*, 1276.



9c	Z= Ph	**12a**	96
9f	Z= C_5H_{11}	**12b**	89
9k	Z= CH_2OBn	**12c**	97

Figure 2. Synthesis of stereodefined cyclohexenes from the products of the one-pot allylation of **6c** with various allyl alcohols.

Table 2. One-Pot Allylation of Ketones Using InI as Cocatalyst

entry	alcohol	ketone	diboron	cat.[b]	cond.[c]	product	yield[d]
1	 **1a**	 **6f**	**2a**	**3a**	50/16	 **9q**[e]	72
2	**1a**	 **6g**	**2a**	**3a**	50/16	 **9r**	73
3	 **1b**	**6g**	**2a**	**3a**	50/16	 **9s**	86

[a] In a typical reaction, **1** and **2** (1.2 equiv) were dissolved in a DMSO/MeOH mixture in the presence of catalytic amounts of **3** and **4** (each 5 mol %). After the borylation was completed, **6f**/**6g** (1.2 equiv) and InI (20 mol %) were added. [b] Catalyst employed. [c] Temperature/time, °C/h. [d] Isolated yield. [e] Formation of 10% of the syn diastereomer was also observed.

stereodefined cyclohexene derivatives (**12a**−**c**) using Grubbs RCM procedure.[56,57]

Allylation of Ketones. Although allyl boronates do not react directly with ketone substrates,[5,7] these transformations can be performed by activation of one of the reactants.[9−11] In a recent paper, Kobayashi and Schneider[9] reported an operationally simple and elegant way of activation of allyl boronates by using InI as catalyst. We have found that application of InI catalysis can also be employed for activation of allyl boronic acids generated in situ from allyl alcohols (Table 2). The reaction was conducted similarly to the allylation of aldehydes, except that the ketone substrate (**6f**,**g**) and InI (20 mol %) was added after completion of the borylation step. This slight modification was necessary to avoid the deactivation of catalyst **3a** by InI in the borylation reaction. The limited number of reactions we have carried out with alcohols **1a**,**b** and ketones **6f**,**g** suggest a broad synthetic scope. The regioselectivity of the process is excellent, as the branched allylic isomer with a new quaternary carbon center is formed as the only product. The diastereoselectivity of the coupling of **1a** and acetophenone (**6f**) is still high (Table 2, entry 1), as the two diastereomers are formed in a 9:1 ratio. As expected,[5,7,78] this level of stereoselectivity is somewhat lower than in the corresponding reaction with benzaldehyde (Table 1, entry 1).

The high regio- and stereoselectivity and the high yield in the presented reactions clearly shows that the one-pot allylation reactions using alcohols as allyl sources can easily be extended to ketone substrates as well. Although, the above results clearly demonstrate the benefits of the operationally simple coupling of easily available allyl alcohols and carbonyl compounds, we wished to further extend the synthetic scope of the reaction by integrating the multicomponent Petasis borono−Mannich reaction[14,16,17,46,47] as a crucial segment in our one-pot approach.

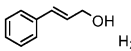
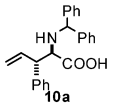
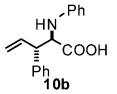
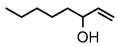
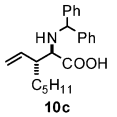
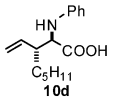
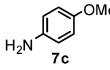
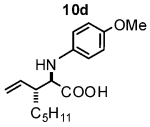
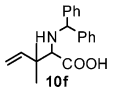
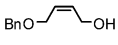
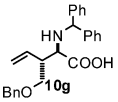
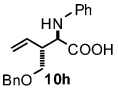
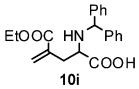
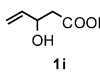
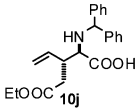
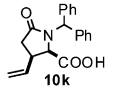
(78) Yashuda, M.; Hirata, K.; Nishio, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442.

α-Amino Acids from Allyl Alcohols via Petasis Borono-Mannich Reaction. Petasis and co-workers[46,47] have reported a new powerful three component method for coupling of alkenyl boronic acids with amines and aldehydes to obtain homoallylic amines, including α-amino acids. This efficient coupling reaction have found many applications,[46,47,79−83] and recently, it was also extended by Kobayashi and Thadani and their co-workers[14,16,17] to coupling of allyl boronates with aldehydes and ammonia. These reactions proceed with high regio- and stereoselectivity, however their synthetic scope is limited by the poor availability of functionalized allyl boronates. Therefore, we decided to extend the three-component Petasis borono-Mannich reaction to a four-component coupling involving in situ generation of the allyl boronate component of the reaction (Figure 1, Table 3). As far as we know, allyl alcohols were not employed previously as reagents to allylate imine substrates, and, furthermore, the Petasis borono-Mannich reactions were not carried out with in situ generated organoborane substrates either. It was found that several elements of the above-described coupling of alcohols and aldehydes can be flexibly employed in combination with the Petasis reaction. The most important difference was that amines **7a**−**c** and glyoxylic acid (**8**) were not added at the beginning of the coupling reaction but after the allotted times required for the borylation process. Addition of the amine component at the beginning of the reaction probably leads to coordination of the nitrogen atom to palladium deactivating catalyst **3** and thus preventing formation of **5**.

First we studied the substrate scope of the reactions. It was found that primary (**1a**,**f**,**g**), secondary (**1b**,**i**,**j**) and tertiary (**1c**) alcohols perform equally well in the reactions, and that benzyloxy (**1f**) and carbethoxy/methoxy (**1g**,**i**,**j**) groups are tolerated (Table 3). The four-component coupling reactions proceeded very cleanly, and the crude reaction mixtures indicated formation of a single product with a very high selectivity. The stereo- and regioselectivity of these processes was as high as the analogue coupling reaction of allyl alcohols and aldehydes, as the α-amino acid derivatives (**10a**−**k**) were formed as single regio- and stereoisomers from readily available substrates **1a**−**c**,**f**,**g** and **1i**,**j**. Accordingly, the presented reactions provide an easy access to stereo defined analogues and homologues of natural amino acids, such as phenylalanine (**10a**,**b**), isoleucine (**10c**−**e**), valine (**10f**), serine (**10g**,**h**), glutamic acid (**10i** and **10j**), and pyroglutamic acid (**10k**). In the coupling reactions we have employed benzyl and aryl amines **7a**−**c**, which proved to be beneficial for avoiding the allylic rearrangement of the products. According to Kobayashi and coworkers,[16] branched homoallyl α-amino acids with unprotected amino groups show a tendency for rearrangement to the corresponding linear isomers via aza-Cope rearrangement. This process is the most extensive for products formed with a quaternary carbon center,[16] such as **10f** (Table 3, entry 9); however, even in this case formation of the linear isomer could be completely avoided. The benzhydryl and anilyl derivatives **10a**−**d** and **10f**−**k** could be purified by silica gel chromatography, however, methoxy anilyl derivative **10e** displayed some

(79) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023.
(80) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865.
(81) Jourdan, H.; Gouhier, G.; Hijfte, L. V.; Angibaud, P.; Piettre, S. R. *Tetrahedron Lett.* **2005**, *46*, 8027.
(82) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74.
(83) Southwood, T. J.; Curry, M. C.; Hutton, C. A. *Tetrahedron* **2006**, *62*, 236.

Table 3. One-pot Synthesis of α-Amino Acids from Allyl Alcohols via Petasis Borono-Mannich Reaction of in Situ Generated Allyl Boronates

entry	alcohol	amine	diboron[b]	cat.[c]	cond. A[d]	cond. B[e]	product	yield[f]
1	 **1a**	 **7a**	**2a**	**3a**	40/16	25/16	 **10a**	76
2	**1a**	**7a**	**2b**	**3a**	50/16	25/16	**10a**	67
3	**1a**	 **7b**	**2a**	**3a**	40/16	25/16	 **10b**	78
4	 **1b**	**7a**	**2a**	**3a**	50/16	25/8	 **10c**	75
5	**1b**	**7a**	**2a**	**3b**	50/4	25/16	**10c**	83
6	**1b**	**7a**	**2b**	**3b**	50/4	25/16	**10c**	77
7	**1b**	**7b**	**2a**	**3a**	50/16	25/16	 **10d**	77
8	**1b**	 **7c**	**2a**	**3a**	50/16	25/8	 **10e**	52
9	 **1c**	**7a**	**2a**	**3a**	50/16	25/24	 **10f**	60
10	 **1f**	**7a**	**2a**	**3a**	40/8	25/16	 **10g**	75
11	**1f**	**7b**	**2a**	**3a**	40/8	25/16	 **10h**	77
12	 **1g**	**7a**	**2a**	**3a**	50/16	25/16	 **10i**	68
13	 **1i**	**7a**	**2a**	**3a**	50/16	25/16	 **10j**	78
14	 **1j**	**7a**	**2a**	**3a**	50/16	25/16	 **10k**	80

[a] In a typical reaction, **1** was dissolved in a DMSO/MeOH mixture in the presence of catalytic amounts of **3** and **4** (5 mol %). After the allotted times (cond. A), **7** (2.0 equiv) was added followed by addition of **8** (1.5 equiv) and the reaction was continued for the reaction times and temperatures given in column cond. B. [b] When **2b** was applied, also 8.0 equiv of water and 20 mol % of *p*TsOH were used. [c] Catalyst. [d] Conditions A: temperature/time = °C/h for the boronation reaction. [e] Conditions B: temperature/time = °C/h for the allylation reaction. [f] Isolated yield. All products except **10k** were isolated as the corresponding HCl salts.

tendency for decomposition, and therefore it was purified by recrystallization.

Carbethoxy compound **1g** undergoes a carbon−carbon bond formation reaction followed by lactonization with benzaldehyde (Table 1, entry 17) under forced reaction condition. In contrast, **10i** (also derived from **1g**) did not undergo analogous lactam formation (Table 3, entry 12). When **1g** was reacted with amine **7a** and **8** (Table 3, entry 12) compound **10i** was remained unchanged even under forced reaction conditions. The isomeric homologue of **1g**, allyl alcohol **1i**, showed a somewhat different behavior. Although, when **1i** was reacted under mild, standard conditions coupling product **10j** could be isolated in good yield; compound **10j** showed a clear tendency for lactam formation (**10k**) on heating. Furthermore, when the methoxy analogue **1j** was reacted in similar conditions as **1i** followed by a gentle heating of the crude reaction mixture, the cyclized product, pyroglutamic acid derivative **10k**, could be isolated in a high yield.

Similarly to the coupling reactions of alcohols and aldehydes (Table 1, entries 3, 6, 7, 19, 20, and 22) the four-component coupling reactions proceeds smoothly when diboronic acid **2a** is replaced with **2b** (Table 3, entries 2 and 6). As described above, using **2b** required a slight modification of the reaction conditions, such as the addition of water (8 equiv) and an increase in the catalyst loading of *p*-toluenesulfonic acid (**4**, 20 mol %). However, these changes led only to a slight change of the isolated yields (cf. Table 3, entries 1 and 2, or entries 5 and 6). Use of diboronic acid **2a** (either directly or in situ hydrolyzed from **2b**) to generate transient allyl boronic acids **5** is probably an important factor in obtaining high yield and reactivity in the described coupling reactions with amines **7** and **8**. Thadani and co-workers[17] have pointed out that the analogue coupling reactions of (isolated) allyl boronates with ammonia and aldehydes proceed most efficiently when allyl boronic acid is employed as a substrate instead of allyl boronic esters. This is because allyl boronic acids are more reactive in allylation reactions than the allyl boronic ester analogues.[33] Similarly to the aldehyde coupling reactions (Table 1, entries 7, 20, and 22) SeCSe complex **3a** can be replaced by SCS complex **3b** (Table 3, entries 5 and 6). In this case, we could also observe the acceleration effect by **3b**, which was also significant for coupling of aldehydes and alcohols.

Mechanistic Aspects. Although the in-depth mechanistic details of the distinct chemical reactions involved in the above one-pot procedures are not fully understood, the consecutive processes and their connectivity can be described (Figures 3 and 4) on the basis of the above studies, our previous communications,[23,24,36] and literature reports on allylation reactions with allyl boronates.[1−7,16,46,47] Accordingly, the coupling reaction of allyl alcohols and aldehydes (Figure 3) is initiated by the activation of the hydroxy functionality of **1** with diboronic acid **2a**.[24] Diboronic acid **2a** is either present as a reactant or it is generated by hydrolysis of **2b**. It was found that under the reaction conditions of application of **2b** (Table 1, entries 3, 6, 7, 19, 20, and 22, or Table 3, entries 2 and 6) as a boronate source (i.e., in the presence of 8 equiv of water and 20 mol % of **4**), immediate formation of free pinacol can be observed. Hydrolysis of **2b** to **2a** under these conditions is probably an equilibrium process (Figure 3), as after extended reaction times the ratio of the boron-bound and free pinacol (3:1) is about constant. We have previously suggested[24] that the activation of the hydroxy group of **1** takes place by formation of boronic ester **13**. This is a very mild way of activation compared to the analogue $SnCl_2$-,[65−68] BEt_3-,[69−71] Et_2Zn-,[72] and indium-based[73−75] methods, which explains the broad synthetic scope and high functional group tolerance of the above presented procedure.

The detailed mechanism of the catalytic formation of **5** from **13** is a subject of ongoing and future studies; however, we strongly suggest that the catalytic transfer of the boronate group from diboronic acid **2a** or its derivatives (such as **13**) proceeds

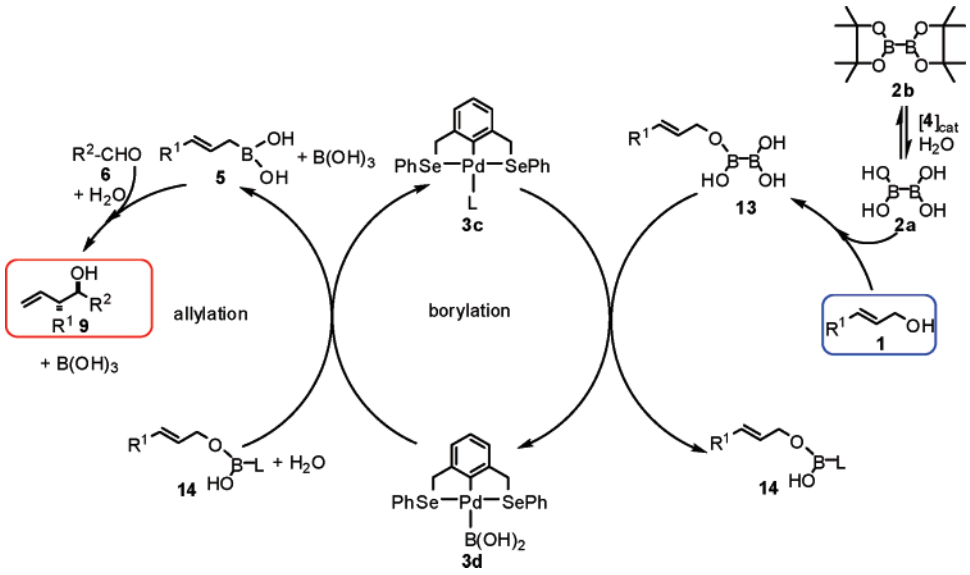


Figure 3. Plausible mechanism for the allylation of aldehydes with allyl alcohols.

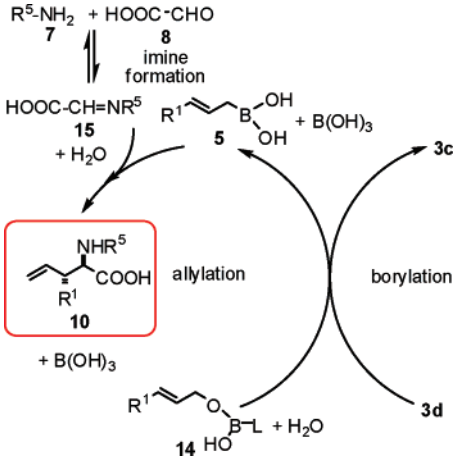


Figure 4. Suggested mechanism for the one-pot four-component coupling reaction.

by a similar mechanism as the analogue stannylation process. Previously, we have shown[84,85] that hexamethylditin (dimetallic analogue of **2a**) readily reacts with pincer complexes under stoichiometric conditions to give an η^1-coordinated monostannyl pincer complex, which is the tin analogue of **3d**. Subsequent DFT modeling studies have shown that the stannyl group is easily transferred from palladium to the allylic position of unsaturated carbons.[84] Accordingly, we suppose that the boronate group is transferred from diboronate **13** to catalyst **3c**, affording η^1-boronato complex **3d**. Subsequently, the boronato group substitutes the activated hydroxy group of **14** to give allyl boronic acid **5** and boric acid. In the absence of aldehydes or other electrophiles, these allyl boronic acid derivatives can also be isolated.[24] Using functionalized allyl alcohols the boronation reaction takes place with an excellent stereo- and regioselectivity,[23,24] which is very important for the subsequent allylation processes.[35,36] The boronation reaction shows a clear preference for the formation of the linear allyl boronates, as both primary (e.g., **1a**) and secondary (e.g., **1b**) allyl alcohols give the corresponding terminally borylated products.[24]

The next step of the process is the allylation of aldehyde **6**, which proceeds with an excellent stereo- and regioselectivity, as the reaction takes place via a six-membered ring TS.[1,5,6,86] The very high stereoselectivity is probably explained by the fact that in the TS the carbonyl oxygen of the aldehyde (**6**) and the boron atom of the allyl boronate comes to a very close proximity.[6,86] As the metal atoms (Si, Sn, Zn, etc.) in other widely used allyl metal species are derived from higher periods of the periodical table, such close proximity between the reactants in the TS of the allylation cannot be realized.[6] Therefore, the stereoselectivity of allylation of electrophiles is much higher with allyl boronates than with any other allylmetal species. Obviously, the high stereoselectivity of formation of **9** is based on the availability of regio- and stereodefined allyl boronic acids (**5**), which is delivered by the efficient pincer-complex-catalyzed borylation reaction.

Using ketones as substrates, Kobayashi and Schneider[9] suggested that allyl boronates are activated by InI followed by electrophilic coupling with the carbon atom of the keto functionality. In the presented reactions involving ketones **6f**,**g** (Table 2) allyl boronic acid **5** is supposed to be activated in a similar way, and the TS geometry of the allylation is probably similar to that of the corresponding reaction with aldehydes.

Allyl boronates are self-activating with aldehydes; however, recent studies revealed[87−90] that Lewis acids accelerate this reaction probably via activation of the allylic component. This activation may be particularly important for allylation of deactivated aldehydes with sterically hindered allyl boronates, such as in the reaction of **6a**,**b** with transient boronate **5h** generated from **1h** (Table 1, entries 18, 19, and 21). For example, the reaction of **1h**, **6a**, and **2b** catalyzed by **3a** requires 48 h to provide product **9n** (Table 1, entry 19). On the other hand, in the replacement of **3a** with catalyst **3b**, in which the counterion is loosely coordinated, the reaction is completed in only 6 h (Table 1, entry 20). This acceleration effect can

(84) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 1787.
(85) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 474.
(86) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692.
(87) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518.
(88) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160.
(89) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586.
(90) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414.

probably be ascribed to the participation of **3b** in the allylation process, as for example a Lewis-acid catalyst.[87−89] Another beneficial effect of the accessible palladium atom in **3b** might be a facile transmetallation of **3c** to **3d**.

While the coupling of allyl alcohols with aldehydes is based on three stoichiometric components and involves two core processes (Figure 3), application of allyl alcohols as input reagents in the Petasis reaction (Figure 4) is a four-component (**1**, **2a**/**b**, **7**, and **8**) reaction in at least three different processes: the borylation (**1** → **5**), imine formation (**7** + **8** → **15**), and allylation (**5** → **10**). The borylation process takes place similarly to the above-described mechanism; however, as mentioned above, the amine component **7** and glyoxylic acid **8** cannot be added to the reaction mixture at the beginning of the process. Addition of **7** inhibits the boronation process probably by coordination to the palladium atom of pincer complex **3c**. This coordination hinders the transmetallation of diboronate **13** to form **3d**, which prevents formation of **5**. On the other hand, addition of **8** alone leads to allylation of the aldehyde functionality providing homoallyl alcohol as product.

Formation of imine **15** and its addition to organoboronates is still a subject of mechanistic studies.[1,79] Similarly to the studies with isolated vinyl and allyl boronates, we have also observed that addition of **7** and **8** separately gives higher yields than addition of imine **15** formed in a separate process. This suggests precoordination of **7** to the boron atom of **5**, which is probably important for the in situ formation of imine **15**. Then, this imine−boronate complex undergoes the allylation process affording product **10**. Coordination of **7** to **5** may also explain the fact that in the presented reactions we could not observe allylation of aldehyde **8**, whereas the in situ formation of **15** is an equilibrium process. Considering that the regio- and stereoselectivity of formation of amino acids (**10**) is similar to the allylation of aldehydes, we suppose a similar type of TS structure in both processes. When allyl alcohol **1j** was employed as reagent, the reaction is not terminated by formation of an α-amino acid derivative (such as **10j**), but the primarily formed amino carboxylate intermediate underwent lactam formation affording **10k**. Accordingly, the reaction of **1j**, **2a**, **7a**, and **8** triggers a spectacular four-step cascade, which can be performed as a one-pot reaction (Table 3, entry 14).

Considering the fact that the employed reactants, catalysts, transient allyl boronic acids, and catalytic intermediates are moisture and air stable species, the reactions can be performed without using inert atmosphere, and the applied solvents do not require careful drying. These features further increase the operational simplicity of the presented one-pot procedures.

3. Conclusions

In this study we have demonstrated that homoallyl alcohols and amino acids can efficiently be prepared from allyl alcohols via transient allyl boronates in a one-pot sequence. The reactions have a very broad synthetic scope involving cyclic and acyclic alcohols, aromatic and aliphatic aldehydes, and various amines. The mild conditions for activation of the allyl alcohols allow the application of a wide range of functionalities involving ethers, carboxylates, nitro, and other[36] groups. The reaction proceeds with an excellent regio- and stereoselectivity even for problematic substrates, which is due to the high regio- and stereoselectivity both in the formation of allyl boronates (**5**) and in the allylation reaction. For example, products with quaternary carbon, such as **9g**,**h**, and **10f** formed as single branched regioisomers, although formation of the corresponding linear form would have been favored by steric factors. Furthermore, products **9n**,**o** comprising three stereocenters were afforded as single diastereomers in high yields.

The high level of compatibility of the boronation procedure with allylation of various electrophiles forms the basis of the above-described reactions. This compatibility relies on three main factors: (a) the high selectivity of the employed pincer-complex catalyst, which does not undergo further reactions with the other components and allyl boronic acid products; (b) application of **2a**/**b** as boronate source allowing that the only byproduct of the borylation reaction is unreactive (and nontoxic) boric acid; (c) the high reactivity of the in situ formed allyl boronic acids,[33] which is accompanied with a fairly high chemical inertness, such as their acid (**4**), base (**7**), water, and air stability and tolerance of alcohol as cosolvent. As demonstrated above, the presented one-pot procedures are suitable for synthesis of densely substituted stereodefined homoallyl alcohols and amines from commercially available inexpensive starting materials in a benign and operationally simple one-pot procedure. These products are useful drug intermediates[48−55] (**10a**−**k**) or building blocks in advanced organic synthesis (i.e., Figure 2).

Considering the above, the one-pot procedure described here provides a simple, benign and cost efficient access to regio- and stereodefined α-amino acids and homoallyl alcohols. The reaction has a broad synthetic scope and the principal element of the transformations, the efficient pincer-complex-catalyzed generation of allyl boronic acids, can easily be integrated in further one-pot allylation reactions of electrophiles.

4. Experimental Section

Further detailed experimental procedures and characterization of the products are given in the Supporting Information.

General Procedure for Allylation of Aldehydes (Table 1). The corresponding allyl alcohol **1** (0.15 mmol) was dissolved in a mixture of DMSO and MeOH (0.2/0.2 mL) followed by the addition of tetrahydroxydiboron **2a** or bis(pinacolato)diboron **2b** (0.18 mmol), pincer complex **3** (0.0075 mmol, 5 mol %), *p*-toluenesulfonic acid **4** (0.0075 mmol, 5 mol %), and aldehyde **6** (0.18 mmol). This reaction mixture was stirred for the allotted temperatures and times listed in Table 1. Thereafter, the reaction mixture was quenched by water and extracted with ether. After evaporation of the organic phase, product **9** was purified by silica gel chromatography. In the case of using **2b** as boronate source, 20 mol % of **4** (0.03 mmol) and 8.0 equiv of water (1.20 mmol) were also employed. These reactions were performed without using inert atmosphere or application of carefully dried solvents.

3-Phenyl-1,7-octadien-4-ol (9c). ^{1}H NMR ($CDCl_3$): 7.32 (m, 2H), 7.22 (m, 3H), 6.13 (ddd, J = 9.0, 10.3, 17.0 Hz, 1H), 5.76 (dddd, J = 6.7, 6.7, 10.2, 17.0 Hz, 1H), 5.23 (d, J = 10.3 Hz, 1H), 5.21 (d, J = 17.0 Hz, 1H), 4.99 (d, J = 17.0 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 3.82 (tt, J = 3.3, 7.6 Hz, 1H), 3.25 (dd, J = 7.6, 9.0 Hz, 1H), 2.23 (m, 1H) 2.11 (m, 1H), 1.83 (d, J = 3.3 Hz, 1H), 1.43 (m, 2H). ^{13}C NMR ($CDCl_3$): 141.9, 138.8, 138.6, 129.1, 128.3, 127.1, 118.3, 115.1, 73.7, 57.8, 33.9, 30.4. HRMS (ESI): calcd for $[C_{14}H_{18}O + Na]^+$, *m*/*z*, 225.1250; found, 225.1248.

Methyl 5-[hydroxy(phenyl)methyl]-3-cyclohexene-1-carboxylate (9n). This compound was prepared according to the above general procedure except that 0.30 mmol of **2a** or **2b** was used. ^{1}H NMR ($CDCl_3$): 7.32 (m, 5H), 5.79 (m, 1H), 5.30 (m, 1H), 4.56 (d, J = 7.1 Hz, 1H), 3.68 (s, 3H), 2.76 (dtd, J = 3.7, 7.1, 10.2 Hz, 1H), 2.57, (m,

1H), 2.26 (m, 2H), 2.14 (dt, $J = 3.7$, 13.5 Hz, 1H), 2.02 (bs, 1H), 1.81 (ddd, $J = 6.0$, 10.2, 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): 176.4, 143.0, 128.7, 128.3, 128.0, 127.7, 126.8, 77.0, 52.0, 41.3, 36.5, 27.6, 26.1. HRMS (ESI): calcd for $[C_{15}H_{18}O_3 - OH]^+$, *m*/*z*, 229.1223; found, 229.1223.

General Procedure for Allylation of Ketones (Table 2). The corresponding allyl alcohol **1** (0.15 mmol) was dissolved in a mixture of DMSO/MeOH (0.2/0.2 mL) followed by addition of **2a** (0.18 mmol), **3a** (0.0075 mmol, 5 mol %), and **4** (0.0075 mmol, 5 mol %). This reaction mixture was stirred for 16 h at 50 °C. Thereafter, ketone **6** (0.165 mmol) and InI (0.03 mmol, 20 mol %) were added, and the mixture was stirred for a further 16 h at 50 °C. Then, the reaction mixture was quenched with water and extracted with ether. After evaporation of the organic phase, product **9** was purified by silica gel column chromatography. These reactions were also performed without using inert atmosphere or application of carefully dried solvents.

2,3-Diphenyl-4-penten-2-ol (9q). This product was formed as a 9:1 mixture of two diastereomers. The obtained NMR data are identical with the literature[78] values. NMR data for the major isomer is as follows. ^{1}H NMR ($CDCl_3$): 7.28 (m, 10H), 6.14 (ddd, $J = 8.6$, 10.3, 17.1 Hz, 1H), 5.07 (d, $J = 10.3$ Hz, 1H), 4.95 (d, $J = 17.1$ Hz, 1H), 3.65 (d, $J = 8.6$ Hz, 1H), 2.01 (s, 1H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$): 146.7, 140.5, 137.7, 130.0, 128.5, 128.1, 127.2, 126.9, 125.9, 118.4, 76.6, 62.2, 28.9. HRMS (ESI): calcd for $[C_{17}H_{18}O + Na]^+$, *m*/*z*, 261.1250; found, 261.1247.

1-(1-Pentylpropen-2-yl) cyclohexane-1-ol (9s). ^{1}H NMR ($CDCl_3$): 5.60 (ddd, $J = 10.1$, 10.1, 17.1 Hz, 1H), 5.14 (d, $J = 10.1$ Hz, 1H), 5.03 (d, $J = 17.1$ Hz, 1H), 1.89 (m, 1H), 1.40 (m, 18H), 1.32 (s, 1H), 0.87 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$): 139.5, 118.1, 72.8, 56.0, 35.2, 35.1, 32.2, 28.2, 28.0, 26.3, 23.0, 22.2, 22.1, 14.4. HRMS (ESI): calcd for $[C_{14}H_{26}O + Na]^+$, *m*/*z*, 233.1876; found, 233.1872.

General Procedure for One-Pot Synthesis of α-Amino Acids (Table 3). To the corresponding allyl alcohol **1** (0.15 mmol) in a mixture of DMSO/MeOH (0.2/0.2 mL) **2** (0.18 mmol), pincer complex **3** (0.0075 mmol, 5 mol %), and **4** (0.0075 mmol, 5 mol %) were added. The resulted solution was stirred for the allotted temperatures and times listed in column conditions A in Table 3. Thereafter, amine **7** (0.30 mmol) was added, and the mixture was stirred for a further 10 min at room temperature followed by the addition of glyoxylic acid **8** (0.23 mmol). Subsequently, this reaction mixture was stirred for the allotted temperatures and times given in column conditions B in Table 3. After filtration of the reaction mixture through a cotton plug, the solvent was removed, and the residue was dissolved in a mixture of dichloromethane, methanol, and 37% aq HCl (450:50:1). This solution was acidified by addition of a few drops of 37% aq HCl and evaporated. The crude products were purified by silica gel column chromatography using a mixture of dichloromethane, methanol, and 37% aq HCl (450:50:1) as eluent. In the case of using bis(pinacolato)diboron (**2b**), 20 mol % of **4** (0.03 mmol), and 8.0 equiv of water (1.20 mmol) were also added at the beginning of the reaction. As above, these reactions were also performed without using inert atmosphere or carefully dried solvents.

2-(Benzhydrylamino)-3-[(benzyloxy)methyl]-4-pentenoic Acid (10g) ^{1}H NMR (CD_3OD): 7.44 (m, 5H), 7.37 (m, 8H), 7.28 (m, 2H), 5.68 (ddd, $J = 8.7$, 10.3, 17.1 Hz, 1H), 5.54 (s, 1H), 5.36 (d, $J = 17.1$ Hz, 1H), 5.30 (d, $J = 10.3$ Hz, 1H), 4.52 (m, 2H), 4.12 (d, $J = 5.6$ Hz, 1H), 3.71 (m, 2H), 3.22 (m, 1H). ^{13}C NMR (CD_3OD): 169.2, 138.6, 136.6, 135.4, 132.1, 130.8, 130.5, 130.4, 129.7, 129.3, 129.0, 129.0, 121.9, 74.7, 72.5, 67.2, 62.2, 45.7. HRMS (ESI): calcd for $[C_{26}H_{27}NO_3 + H]^+$, *m*/*z*, 402.2064; found, 402.2062.

1-Benzhydryl-5-oxo-3-vinyl-2-pyrrolidine Carboxylic Acid (10k) ^{1}H NMR (CD_3OD): 7.28 (m, 10H), 7.25 (s, 1H), 6.05 (ddd, $J = 6.8$, 10.6, 17.3 Hz, 1H), 5.23 (m, 2H), 4.00 (d, $J = 1.5$ Hz, 1H), 2.99 (dddd, $J = 1.5$, 1.5, 6.8, 8.1 Hz, 1H), 2.89 (m, 1H), 2.38 (m, 1H). ^{13}C NMR (CD_3OD): 177.3, 174.4, 141.0, 139.8, 139.2, 131.5, 129.4, 129.2, 128.7, 128.4, 116.7, 66.6, 62.3, 41.8, 36.4. HRMS (ESI): calcd for $[C_{20}H_{19}NO_3 + H]^+$, *m*/*z*, 322.1438; found, 322.1437.

Ring-Closing Metathesis of Dienes 9c, f, and k. Dienes **9c**,**f** or **k** (0.08 mmol) and catalyst **11** (5 mol %, 0.004 mmol) were dissolved in freshly distilled dichloromethane (8.5 mL) under Ar atmosphere. This reaction mixture was stirred at 40 °C for 2 h, evaporated, and purified by column chromatography.

2-[(Benzyloxy)methyl]-3-cyclohexen-1-ol (12c) ^{1}H NMR ($CDCl_3$): 7.32 (m, 5H), 5.78 (m, 1H), 5.43 (m, 1H), 4.55 (s, 2H), 4.15 (m, 1H), 3.62 (m, 2H), 2.99 (d, $J = 5.0$ Hz, 1H), 2.65 (m, 1H), 2.21 (m, 1H), 2.05 (m, 1H), 1.79 (m, 2H). ^{13}C NMR ($CDCl_3$): 138.1, 129.3, 128.8, 128.2, 128.1, 125.2, 73.8, 71.8, 68.5, 40.6, 28.3, 22.7. HRMS (ESI): calcd for $[C_{14}H_{18}O_2 + Na]^+$, *m*/*z*, 241.1199; found, 241.1200.

Acknowledgment. This work was supported by the Swedish Natural Science Research Council (VR). A.K. is grateful for an Erasmus stipend funded by the EU.

Supporting Information Available: Detailed experimental procedures; characterization and ^{1}H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA074917A