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Imine allylation using 2-alkoxycarbonyl allylboronates as an expedient three-component reaction to polysubstituted α-*exo*-methylene-γ-lactams

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ABSTRACT

α-*exo*-Methylene-γ-lactams are key structural units in a wide variety of biologically active natural products. A concise route to the formation of polysubstituted α-*exo*-methylene-γ-lactams is described. In this three-component reaction, an imine is formed from an aldehyde and ammonia in situ, and is subsequently allylated through the use of a 2-alkoxycarbonyl allylboronate. Due to the ester functionality, the addition intermediate subsequently undergoes in situ cyclization to form the observed α-*exo*-methylene-γ-lactam products. This route allows access to highly substituted α-*exo*-methylene-γ-lactams in moderate to excellent yields.

The α-*exo*-methylene γ-butyrolactone and γ-lactam ring is a key structural motif in many natural products,[1–6] most notably the sesquiterpene lactones (Fig. 1). These natural products have proven to be quite useful as DNA polymerase inhibitors, nuclear vitamin D receptor inhibitors, cellular steroidal inhibitors, blockers of tumour necrosis factor-α production, as well as many other uses.[7] The wide inhibitory action of these natural products makes them potential drug candidates due to their cytotoxic, anti-inflammatory, phytotoxic and antimicrobial properties.[8] However, many α-methylene-γ-lactone natural products display toxic side effects when tested in vitro and are thus not suitable for pharmaceutical purposes.[8,9] One closely related class of molecules to the γ-lactones is the corresponding α-*exo*-methylene-γ-lactam scaffold. Even though there are significantly fewer reports compared to the γ-lactones, there are still a considerable number of natural products that contain a γ-lactam moiety as part of their structures (Fig. 1). Furthermore, since the α-*exo*-methylene-γ-lactones are often too toxic to be used for pharmaceutical purposes, it has been suggested that the use of substituted α-*exo*-methylene-γ-lactams in place of the γ-lactone moiety might help to mitigate their promiscuous biological toxicity.[9] Synthetic routes to access γ-lactams have been the focus of several reports in the literature;[8,10,11] however, many of the reported routes are tedious in accessing the γ-lactam core structure. To satisfy the demands of parallel synthesis, more efficient routes to N-unsubstituted α-methylene-γ-lactams are greatly needed.[11a]

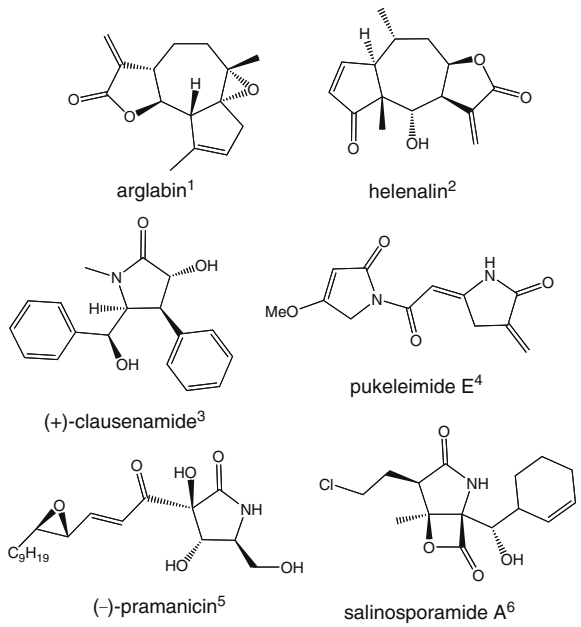

Figure 1. Selected natural products containing α-substituted-γ-lactones or α-substituted-γ-lactam rings.

As a solution to this synthetic problem, it was envisioned that one could simply add 2-alkoxycarbonyl allylboronates to imines and thus form α-*exo*-methylene-γ-lactams in a single step via a tandem allylation/lactamization reaction. Villiéras and co-workers

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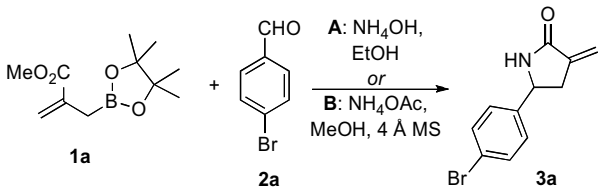
Table 1
Imine allylation using 2-alkoxycarbonyl allylboronate **1a**



Entry	Method	Temperature (°C)	Time (h)	Yield[a] (%)
1	A	20	4	0
2	B	20	16	0
3	A	70	4	48
4	B	70	16	36

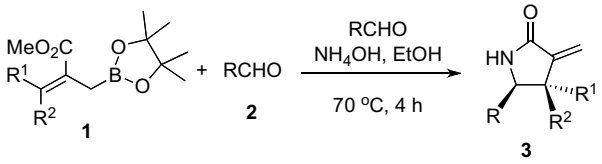
[a] Isolated yield after flash chromatography.

have demonstrated that this chemistry is indeed possible.[12] Their work described the use of highly activated, preformed imines reacting with 2-alkoxycarbonyl allylboronates to form γ-lactams through the same allylation/cyclization process described with aldehydes. Despite the fact that this route provided facile access to the γ-lactam core structure, the imines utilized in this protocol are severely limiting, not to mention the need to first pre-form the imines before carrying out the allylboration reactions. Furthermore, the reaction times are long (14 days at room temperature). In this regard, the Kobayashi[13] and Morken[14] groups have recently shown that imines formed in situ from aldehydes can be allylated to form homoallylic amines. However, both these reports make use of significantly more reactive allylboronates as compared to the less reactive 2-alkoxycarbonyl allylboronates that are required to access γ-lactams. We wondered whether either of these reported conditions would also be suitable with less reactive allylboronates, such as 2-alkoxycarbonyl allylboronate **1a**.[15] Initially, both sets of conditions were attempted on a typical aromatic aldehyde, **2a** (Table 1).

Not surprisingly, under both Kobayashi's conditions (Table 1, entry 1) and Morken's conditions (Table 1, entry 2), none of the desired γ-lactam product **3a** was obtained. The reactions were then repeated, but with a higher reaction temperature of 70 °C. Gratifyingly, this time both method A[16] and method B[17] provided the desired lactam product **3a**. Since the yields of **3a** were similar for these two different sets of reaction conditions, the modified Kobayashi conditions[13] were chosen for further investigation of α-*exo*-methylene-γ-lactam formation. This choice was based on the fact that method A is experimentally easier to perform, the reaction time is shorter and the purification steps are more straightforward.

Various aldehydes were selected and then subjected to the imine allylation conditions, forming a wide variety of γ-substituted α-*exo*-methylene-γ-lactams (Table 2). Not only allylboronate **1a**, but also the corresponding *Z*- and *E*-crotylboronates **1b** and **1c**[18] were used in the investigation of these imine allylation conditions (vide infra). Initially, unsubstituted allylboronate **1a** was used with a number of electron-poor aromatic aldehydes (Table 2, entries 1–3), an electron-rich aromatic aldehyde (entry 4) and even a number of aliphatic aldehydes (entries 7 and 8). The yields were typically good to excellent; however, a few entries displayed less satisfactory results. The lower yield observed for entry 4 can most likely be attributed to poor imine formation. *p*-Anisaldehyde is less reactive towards imine formation, and under the standard reaction conditions would be slow in forming the required imine intermediate. Longer reaction times may help to increase the yield for similarly less reactive aldehydes. Lower yields were also observed for the aldehydes containing an enolizable proton (entries 7 and 8). However, this result could be predicted due to the strongly basic conditions under which the reactions are performed. Enamine formation is expected to be a competing side reaction, and would result in a lower observed yield. Kobayashi and co-workers have shown that modifying the order of reagent addition is advantageous for obtaining the desired products with aliphatic aldehydes.[13] In the typical reaction procedure, the aldehyde is dissolved in a mixture of NH_4OH and ethanol, and the allylboronate is added to this reaction solution and subsequently heated. However, the order of addition was switched for aldehydes containing an enolizable proton (entries 7 and 8), whereby allylboronate **1a** was added first. The aldehyde was then added to the reaction mixture and this was subsequently heated to provide the desired α-*exo*-methylene-γ-lactams **3g** and **3h** (see Supplementary data for a more detailed description).

Table 2
Substrate scope using allylboronate **1** and aldehydes **2** to form α-methylene-γ-lactams **3**



Entry	Allylboronate	R^1	R^2	Aldehyde **2** (RCHO)	Product	Yield[a] (%)
1	**1a**	H	H	4-BrC_6H_4CHO	**3a**	48
2	**1a**	H	H	4-$NO_2C_6H_4CHO$	**3b**	76
3	**1a**	H	H	4-FC_6H_4CHO	**3c**	62
4	**1a**	H	H	4-$MeOC_6H_4CHO$	**3d**	39
5	**1a**	H	H	4-MeC_6H_4CHO	**3e**	90
6	**1a**	H	H	PhCHO	**3f**	53
7[b]	**1a**	H	H	$PhCH_2CH_2CHO$	**3g**	39
8[b]	**1a**	H	H	*n*-$C_{10}H_{21}CHO$	**3h**	35
9	**1b**	CH_3	H	4-BrC_6H_4CHO	**3i**	63
10	**1b**	CH_3	H	4-$NO_2C_6H_4CHO$	**3j**	52
11	**1b**	CH_3	H	4-$CH_3C_6H_4CHO$	**3k**	56
12	**1b**	CH_3	H	2-BrC_6H_4CHO	**3l**	98
13	**1c**	H	CH_3	4-BrC_6H_4CHO	**3m**	73
14	**1c**	H	CH_3	4-$NO_2C_6H_4CHO$	**3n**	66
15	**1c**	H	CH_3	4-$CH_3C_6H_4CHO$	**3o**	95
16	**1c**	H	CH_3	2-BrC_6H_4CHO	**3p**	74

[a] Isolated yields after flash chromatography and are the result of only one run for each reaction.
[b] Reverse order of addition used in reaction procedure (see Refs. 16 and 17, and Supplementary data).

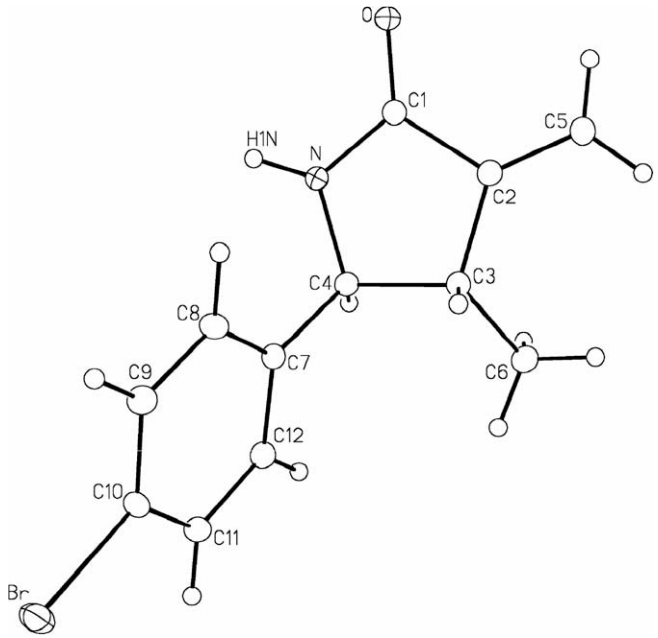


Figure 2. ORTEP diagram of crystal structure for **3i**.

We were also interested in the diastereoselectivity of these imine allylboration reactions. According to the rules set out by Hoffman,[19] allylborations with *E*- and *Z*-crotylboronates and aldehydes provide distinct diastereomers depending on the initial geometry of the crotylboronate. 2-Alkoxycarbonyl 3-methylallylboronates have also been shown to react with the same diastereospecificity, either under thermal conditions,[20] with Lewis acid catalysts[21] and Bronsted acid catalysts.[18,22] Villiéras and co-workers have also shown that imine allylboration reactions carried out at room temperature also proceed in a diastereospecific manner.[12] Although we suspected that the diastereospecific nature of the allylboration reaction would still manifest itself under these new imine allylation conditions, it needed to be verified. Thus, both *Z*-crotylboronate (**1b**) and *E*-crotylboronate (**1c**) were utilized under the same imine allylboration conditions to test the diastereoselectivity of the reaction under these strongly basic conditions. *Z*-Crotylboronate **1b** was reacted with four different aromatic aldehydes and, in each case, the desired *trans* lactam product was obtained as the sole product in moderate to excellent yields after flash chromatography purification (entries 9–12). The X-ray crystallographic structure of **3i** was obtained and allowed us to conclusively assign the relative stereochemistry for this product as being trans with respect to the aldehyde substituent and the methyl group (Fig. 2).[23] The relative stereochemistry of all γ-lactams containing substituents in the β and γ positions were thus assigned as trans or cis based on this result. Similarly, *E*-crotylboronate **1c** (19:1 dr) was reacted with the same four aldehydes and provided the desired *cis* γ-lactam products as the major diastereomers in moderate to excellent yields (entries 13–16). The diastereomeric ratio for the γ-lactam products in these four examples was 19:1, which was identical to the diastereomeric ratio of **1c**. The complete transfer of stereochemistry from starting material to products further demonstrated that the imine allylboration reaction is indeed diastereospecific, even under these harsh, basic reaction conditions. The reaction described thus proceeds in a manner that can be considered to be a three-component reaction. Imines are formed in situ from ammonia and aldehydes, and are subsequently allylated highly diastereoselectively using 2-alkoxycarbonyl allylboronates. After the allylboration step, the intermediate homoallylic amine undergoes in situ lactamization to form the observed γ-lactam products (Fig. 3).

In conclusion, we have optimized a new procedure for accessing highly substituted α-*exo*-methylene-γ-lactams through the use of a diastereospecific, three-component reaction. The reaction is quite general in that a wide variety of aromatic aldehydes and aliphatic aldehydes are suitable substrates, providing the corresponding α-*exo*-methylene-γ-lactams in moderate to excellent yields. One should note that this protocol furnishes polysubstituted α-methylene-γ-lactams that lack any activating or protecting groups on the nitrogen, which allows for immediate functionalization of the γ-lactam nitrogen without an extra deprotection step. Very few examples are found in the literature where this is the case.[11a,24] Further studies are currently being carried out to expand this work to include other types of aldehydes, as well as investigations into the functionalization of these substituted α-*exo*-methylene-γ-lactams. As mentioned earlier, the lactam sub-unit is a key component in a wide variety of bioactive natural products and synthetic drugs. Additional modifications of the α-*exo*-methylene-γ-lactam sub-unit would allow for analogues to be made in a convergent fashion. Studies towards this end are ongoing in our laboratories.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.112.

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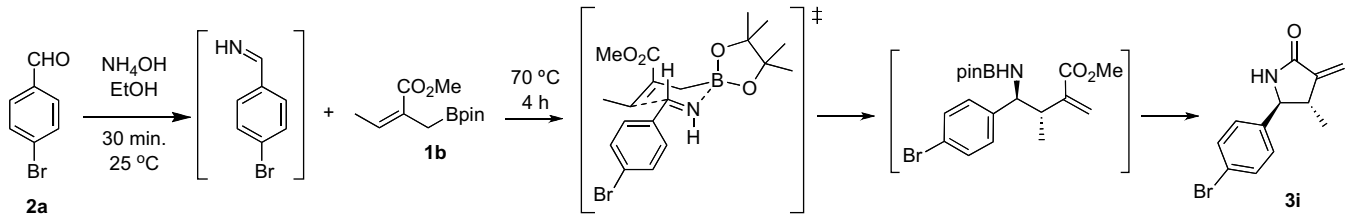

Figure 3. Proposed mechanism for the three-component imine allylation/lactamization reaction.

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16. Method A: Aldehyde **2a** (0.5 mmol) was dissolved in 1 mL EtOH in a high-pressure glass vessel under Ar. Ammonium hydroxide (30%, 0.75 mL) was added and the mixture was stirred at room temperature for 30 min. Allylboronate **1a** (113 mg, 0.5 mmol) was diluted in 0.5 mL EtOH and added to the reaction mixture. An additional 0.5 mL EtOH was used as rinse and added to the reaction mixture. The mixture was heated to 70 °C for 4 h. The reaction mixture was then allowed to cool to room temperature, and 1 N HCl was added to quench the reaction and to bring the pH of the solution to ~1. The mixture was extracted four times with diethyl ether, and the organics were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (70% ethyl acetate/hexanes) to provide the desired α-*exo*-methylene-γ-lactam **3a**. *5-(4-Bromophenyl)-3-methylene-pyrrolidin-2-one* (**3a**): Obtained as a white solid in a yield of 48% (method A) or 36% (method B). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.46 (m, 2H), 7.17–7.12 (m, 2H), 6.09–6.04 (m, 1H), 6.00–5.92 (br s, 1H), 5.43–5.38 (m, 1H), 4.73 (dd, 1H, *J* = 8.4, 4.7 Hz), 3.31 (app. ddt, 1H, *J* = 17.2, 8.2, 2.3 Hz), 2.63 (ddd, 1H, *J* = 17.2, 4.5, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 141.9, 138.3, 132.4, 127.7, 122.2, 117.3, 54.5, 37.0. IR (CH_2Cl_2, microscope, cm^{-1}): 3177, 1697. HRMS (EI, *m*/*z*) calcd for $C_{11}H_{10}ON^{81}Br$: 252.99252, found: 252.99272.
17. Method B: In a flame-dried high pressure glass vessel, ammonium acetate (128 mg, 1.7 mmol) was added to activated 4 Å molecular sieves in 1.5 mL MeOH under Ar. Aldehyde **2a** (0.33 mmol) was added to the mixture and stirred for 2 h at room temperature. Allylboronate **1** (0.22 mmol) was dissolved in 0.5 mL MeOH and added to the reaction, which was subsequently heated to 70 °C for 16 h. The reaction was quenched with saturated NH_4Cl and 1 N HCl to bring the pH to ~5. The mixture was extracted three times with diethyl ether, and the combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (70% ethyl acetate/hexanes) to provide the desired α-*exo*-methylene-γ-lactam **3a**.
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23. Crystallographic data (excluding structure factors) for the structure of compound **3i** in this Letter have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 695506. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif).
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