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Organocatalytic asymmetric 1,4-addition of organoboronic acids to γ-hydroxy α,β-unsaturated aldehyde: facile synthesis of chiral β-substituted γ-lactones

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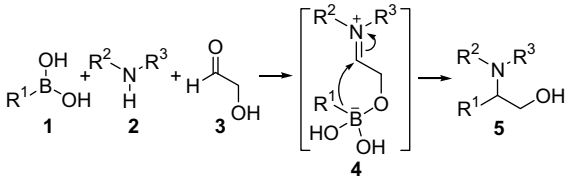
ABSTRACT

Catalytic asymmetric 1,4-addition of arylvinyl- and arylboronic acids to a γ-hydroxy α,β-unsaturated aldehyde, which affords β-substituted γ-lactols, has been established using a diarylprolinol silyl ether as an organocatalyst. The β-substituted γ-lactols have been obtained in good yields and with up to 91% ee, which lead to chiral β-substituted γ-lactones followed by oxidation.

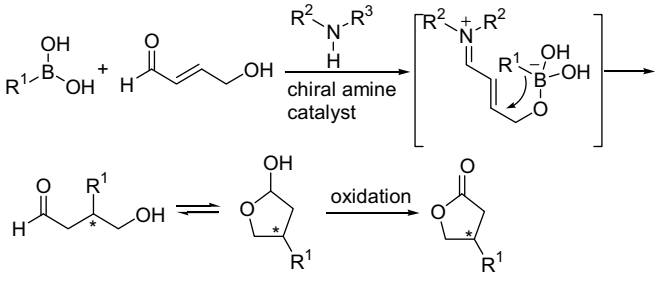
Enantiomerically pure γ-lactones are widely distributed in nature and in many biologically active compounds.[1] In addition, γ-lactone chemistry plays a very important role in the synthesis of natural products.[2] Among them, chiral γ-butyrolactones possessing a β-stereocenter are found in a number of biologically active natural products such as lignans (−)-trachelogenin and (−)-enterolactone.[3] They also serve as key precursors to the synthesis of γ-aminobutyric acid (GABA) derivatives such as (−)-baclofen and pregabalin, which are neurotransmitter inhibitors in the central nervous system.[4]

Owing to the importance of this class of compounds, numerous synthetic approaches to chiral β-substituted γ-lactones have been reported.[5] Some of the strategies include enzymatic resolution,[6] synthesis using a chiral auxiliary,[7] catalytic enantioselective Baeyer–Villiger oxidation,[8] C–H insertion reaction,[9] hydrogenation,[10] 1,4-reduction[11] and 1,4-addition reaction.[12] In this Letter, we describe the facile synthetic strategy of chiral β-substituted γ-lactones by the oxidation of chiral β-substituted γ-lactols, which are prepared by new catalytic asymmetric 1,4-addition of arylvinyl- and arylboronic acids to a γ-hydroxy α,β-unsaturated aldehyde using an organocatalyst.[13,14]

Petasis and co-workers elegantly demonstrated a one-step three-component process involving the condensation of aryl- and vinylboronic acids with amines and α-hydroxy aldehydes leading to β-amino alcohols;[15,16] this mechanism involves a transient species such as **4**, leading to the product **5** (Scheme 1). With this mechanism in mind, we envisioned that 1,4-iminium addition might be possible if a γ-hydroxy α,β-unsaturated aldehyde was used instead of an α-hydroxy aldehyde, wherein an amine component would also be changed from a coupling partner to a catalyst (Scheme 2).



Scheme 1. Petasis one-step three-component coupling.



Scheme 2. Organocatalytic 1,4-addition of organoboronic acid to γ-hydroxy α,β-unsaturated aldehyde.

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In this process, arylvinyl boronic acids are able to perform 1,4-addition on γ-hydroxy α,β-unsaturated aldehydes to give chiral γ-hydroxy β-substituted aldehydes, which are equilibrated or shifted to chiral β-substituted γ-lactols, when chiral amine catalysts are used. The resulting β-substituted γ-lactols might be easily converted to β-substituted γ-lactones by oxidation.

The 1,4-addition of styrylboronic acid **6** to 4-hydroxy-but-2-enal **7**[17] was selected as a model reaction. L-Proline **I** (Fig. 1) was initially examined in this reaction with H_2O (2 equiv)[18] in CH_2Cl_2 at room temperature. The reaction proceeded to furnish the corresponding β-styryl γ-lactol (diastereomeric ratio, 0.6:0.4) without detection of γ-hydroxy β-styryl aldehyde, though the yield was moderate and its enantioselectivity was not as high as desired (Table 1, entry 1).

Encouraged by this result, we investigated other organocatalysts for the 1,4-addition of styrylboronic acid **6** to 4-hydroxy-but-2-enal **7** to improve both reactivity and enantioselectivity. (*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole **II** afforded good reactivity (89% yield, entry 2), but a poor level of enantioselectivity was observed. Imidazolidinone catalyst **III** and **IV** showed increased enantioselectivities (88:12 er and 83:17 er, respectively) but in low yields (entries 3 and 4). However, we were pleased to discover that diphenylprolinol silyl ether **V** provided the product in good yield with high enantioselectivity (88% yield, 87:13 er, entry 5). Furthermore, trifluoromethyl-substituted diarylprolinol silyl ether **VI** afforded excellent reactivity and improved enantioselectivity (99% yield, 92:8 er, entry 7).

After the reaction conditions were optimized, we found that the superior levels of enantioselectivity and yield were exhibited by catalyst **VI** in CH_2Cl_2 at 0 °C (98% yield, 95.5:4.5 er, entry 12). An acid additive diminished the reaction efficiency in this reaction, though it slightly increased the enantioselectivity (entry 11).

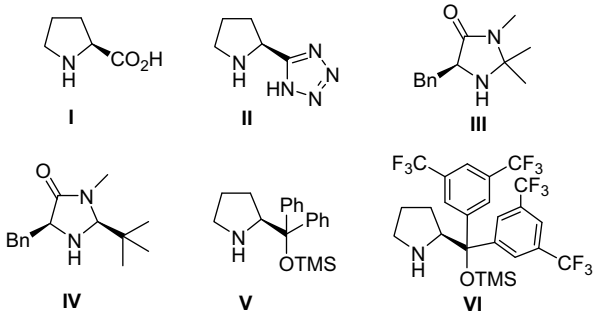
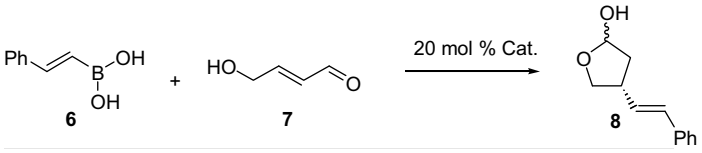


Figure 1. Chiral amine organocatalysts.

Table 1
Asymmetric 1,4-addition of styrylboronic acid to 4-hydroxy-but-2-enal by organocatayst[a]



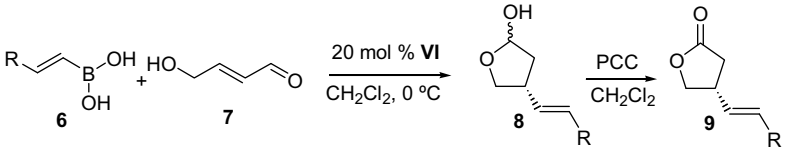
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	er[c]
1	**I**	CH_2Cl_2	rt	24	59	63:37
2	**II**	CH_2Cl_2	rt	24	89	65:35
3	**III** CF_3CO_2H	CH_2Cl_2	rt	24	23	88:12
4	**IV** CF_3CO_2H	CH_2Cl_2	rt	24	28	83:17
5	**V**	CH_2Cl_2	rt	24	88	87:13
6[d]	**V**	CH_2Cl_2	rt	24	64	86:14
7	**VI**	CH_2Cl_2	rt	24	99	92:8
8	**VI**	Toluene	rt	24	53	89:11
9	**VI**	CH_2Cl_2	rt	24	64	92:8
10	**VI**	CH_2Cl_2	rt	24	88	92:8
11[e]	**VI**	CH_2Cl_2	rt	48	60	95:5
12	**VI**	CH_2Cl_2	0	48	98	95.5:4.5

[a] Reactions were carried out in solvent (0.3 M) with 2.0 equiv of H_2O and 2.0 equiv of 4-hydroxy-but-2-enal relative to the styrylboronic acid in the presence of 20 mol % catalyst.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis.
[d] Reactions were carried out with 1.1 equiv of styrylboronic acid relative to the 4-hydroxy-but-2-enal.
[e] 10 mol % of PhCO2H was added.

Having established the optimal reaction conditions, we next probed the generality of this asymmetric catalytic reaction with various arylvinyl- and arylboronic acids to 4-hydroxy-but-2-enal **7**. In the first, arylvinylboronic acids were examined in this reaction (Table 2). The results showed that high levels of enantioselectivity (>93:7 er's) were obtained with arylvinylboronic acids, regardless of electron-donating (4-MeO, entry 2) and electron-withdrawing substituents (4-Cl, 4-F, entries 3 and 4). It was noted that the resulting γ-lactols provided chiral β-substituted γ-lactones with good yields (61-86%) after treatment of pyridium chlorochromate (PCC).

We next expanded our substrates to include aromatic boronic acids. However, we discerned that aryl substrates have less reaction efficiency than arylvinylboronic acids in this 1,4-addition reaction. In the case of phenylboronic acid, the reaction was inert even under severe reaction conditions such as high temperature and increased catalyst loading. To circumvent this limitation, we sought reaction conditions which would further accelerate the feasibility of this class of substrates. As such, we determined that catalyst **V**

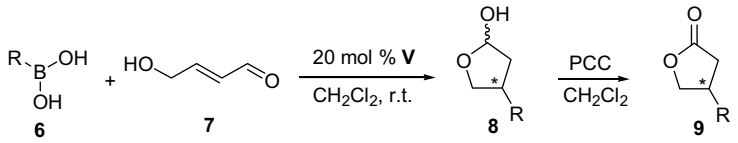
Table 2
Catalytic asymmetric 1,4-addition of arylvinylboronic acids to 4-hydroxy-but-2-enal[a]

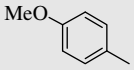
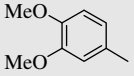
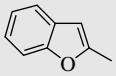
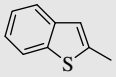
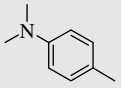


Entry	Time (h)	R	Yield of **8**[b] (%)	Yield of **9**[b] (%)	er[c,d] (%)
1	Ph	48	98	86	95.5:4.5
2	4-$MeOC_6H_4$	48	77	61	93:7
3	4-ClC_6H_4	36	30	75	93:7
4	4-FC_6H_4	24	99	85	93:7

[a] Reactions were carried out in CH2Cl2 (0.3 M) at 0 °C with 2.0 equiv of H2O and 2.0 equiv of 4-hydroxy-but-2-enal relative to the arylvinylboronic acid in the presence of 20 mol% catalyst.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis.
[d] Absolute stereochemistry assigned by chemical correlation.

Table 3
Catalytic Asymmetric 1,4-Addition of Arylboronic Acids to 4-Hydroxy-but-2-enal[a]



Entry	R	Time (h)	Yield of **8**[b] (%)	Yield of **9**[b] (%)	er[c] (%)
1		36	75	65	52:48
2		24	75	60	59:41
3		3	97	84	52:48
4		48	61	74	55:45
5		36	71	80	55:45
6		48	45	65	61:39
7		48	51	83	55:45
8		2	99	—[d]	—

[a] Reactions were carried out in CH_2Cl_2 (0.3 M) with 10 equiv of 0.5 M NaOH in H_2O and 2.0 equiv of 4-hydroxy-but-2-enal relative to the arylboronic acid in the presence of 20 mol % catalyst.
[b] Isolated yield after chromatographic purification.
[c] Determined by HPLC analysis.
[d] The desired product was not obtained.

promoted the 1,4-addition of arylboronic acid to 4-hydroxy-but-2-enal by adding sodium hydroxide. The results are summarized in Table 3. Though phenylboronic acid was still inert under these conditions, electron-donating substituted phenyboronic acids (4-MeO, 3,4-diMeO) provided the corresponding γ-lactol with high efficiency (65% yield and 60% yield, respectively, entries 1 and 2). In particular, 4-*N*,*N*-dimethylamino substituent accelerated the reaction rate and the reaction proceeded to completion (entry 8). We have also found that this process works well with heteroarylboronic acids including furan, benzofuran, thiophen, benzothiophen and *N*-Boc-pyrrole (entries 3–7). However, unfortunately in all cases, poor levels of enantioselection were observed (3–22% ee). Though the resulting γ-lactols did not show high enantioselectivity, the lactols were readily converted to γ-lactones by PCC oxidation, except 4-*N*,*N*-dimethylaminophenyl containing γ-lactol (entry 8).

In summary, we have communicated the catalytic asymmetric 1,4-addition of arylvinyl- and arylboronic acids to γ-hydroxy α,β-unsaturated aldehyde using an organocatalyst to afford β-substituted γ-lactols in good yield with high enantioselectivity although with low enantioselectivity in the case of the arylboronic acids, which readily lead to chiral β-substituted γ-lactones followed by oxidation. The resulting products can also be useful precursors for the synthesis of functionalized γ-lactams and γ-amino alcohols which are currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.025.

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18. We found that reactivity was slightly increased in the case of adding 2 equiv of H_2O without changing the enantioselectivity.