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Organocatalytic Direct Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactam to α,β-Unsaturated Aldehydes and an Illustration to Scaffold Diversity Synthesis

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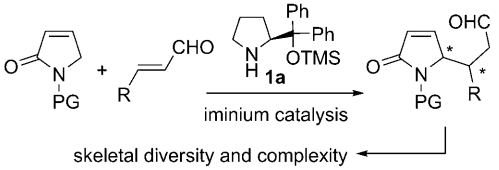
The development of efficient synthetic protocols to access small-molecule libraries that contain structurally and stereochemically diverse scaffolds is highly desirable because of the increasing demand for collections of probe and drug candidates.[1] Therefore, the design of asymmetric reactions from readily available starting materials, which can deliver enantioenriched and multifunctional products and allow subsequent skeletal variation constructions, is extremely attractive. Not surprisingly, the vinylogous reactions of α,β-unsaturated systems, which can supply an additional and versatile olefinic functionality in the products, trigger increasing attention in modern synthetic organic chemistry,[2] and intensive studies have been concentrated on the applications of γ-butenolides and their O-silyl derivatives.[3] Over the past years we have developed a number of asymmetric direct vinylogous-type reactions, which provide facile access to useful chiral materials with structural diversity and complexity.[4] Later we were fascinated by the utilization of the aza analogues of γ-butenolides, α,β-unsaturated γ-butyrolactams, not only because they have been much less explored,[5] but also the associated aza heterocycles might have more potential in the subsequent synthetic transformations and related biological investigation.[2d] In particular, we envisaged that the unprecedented stereoselective direct vinylogous Michael addition of α,β-unsaturated γ-butyrolactams[5a,b] to α,β-unsaturated aldehydes, under the well-established iminium activation of secondary amine **1a**,[6] would afford chiral adducts that have fruitful and orthogonal sets of functional groups in an atom-economic fashion, which would be ideal for the following couple and pair reactions for scaffold diversity synthesis (Scheme 1).[7]



Scheme 1. Direct vinylogous Michael addition to multifunctional adducts for scaffold diversity synthesis.

We initially studied the possible direct vinylogous Michael addition of *N*-Boc α,β-unsaturated γ-butyrolactam **2a** to cinnamaldehyde **3a** catalyzed by **1a** and benzoic acid in toluene at room temperature.[8] Gratifyingly, the reaction proceeded smoothly with high regio- and chemoselectivity, and the desired major *syn* adduct **4a** and its minor *anti* diastereomer **4a′** were obtained in fair yield and stereoselectivity after 43 h (Table 1, entry 1). A few solvents have been tested (Table 1, entries 2–5), and an excellent *ee* value was attained in acetonitrile (Table 1, entry 5). In addition, we found that higher yield could be gained when some H_2O (10% v/v) was added (Table 1, entry 6), and a slight improvement could be reached when more **3a** was applied (Table 1, entry 7). Acid additives also have apparent effects on the outcomes (Table 1, entries 8–10), and finally, we achieved the optimal results in regard to yield, diastereoselectivity, and enantioselectivity in the presence *o*-fluorobenzoic acid (Table 1, entry 10). It was pleasing that the minor diastereomer **4a′** was also afforded in remarkable enantiopurity (Table 1, entry 10).[9]

With the established conditions in hand, the scope of the direct vinylogous Michael addition of *N*-Boc α,β-unsaturated γ-butyrolactam **2a**[10] to an array of α,β-unsaturated alde-

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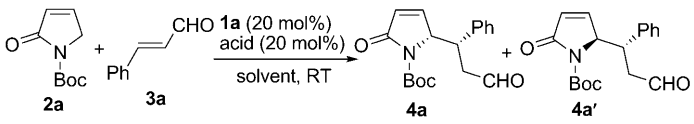
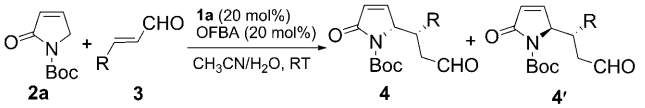
Table 1. Screening studies of the organocatalytic direct vinylogous Michael addition of α,β-unsaturated γ-butyrolactam **2a** to cinnamaldehyde **3a**.[a]



Entry	Solvent	Acid	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	toluene	BA	43	62	2.5:1	76
2	THF	BA	46	60	2.0:1	87
3	DCM	BA	46	55	3.6:1	90
4	$CHCl_3$	BA	46	60	3.0:1	85
5	CH_3CN	BA	46	55	2.0:1	93
6	CH_3CN/H_2O	BA	41	66	2.0:1	93
7[e]	CH_3CN/H_2O	BA	58	76	2.0:1	93
8[e]	CH_3CN/H_2O	AcOH	56	73	2.0:1	73
9[e]	CH_3CN/H_2O	PNBA	56	76	2.0:1	87
10[e]	CH_3CN/H_2O	OFBA	46	80	4.0:1	93 (99)[f]

[a] Unless noted otherwise, reaction conditions were **2a** (0.1 mmol), **3a** (0.15 mmol), **1a** (0.02 mmol), and acid (0.02 mmol) in solvent (0.5 mL) at RT. BA: benzoic acid; PNBA: *p*-nitrobenzoic acid; OFBA: *o*-fluorobenzoic acid. [b] Combined isolated yield of diastereomers. [c] Determined by crude ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis after reaction with $Ph_3PCHCOPh$ for major **4a**. [e] Compound **3a** (0.2 mmol) was used. [f] The data in parenthesis is related to minor **4a′**.

Table 2. Substrate scope in the organocatalytic direct vinylogous Michael addition reaction.[a]

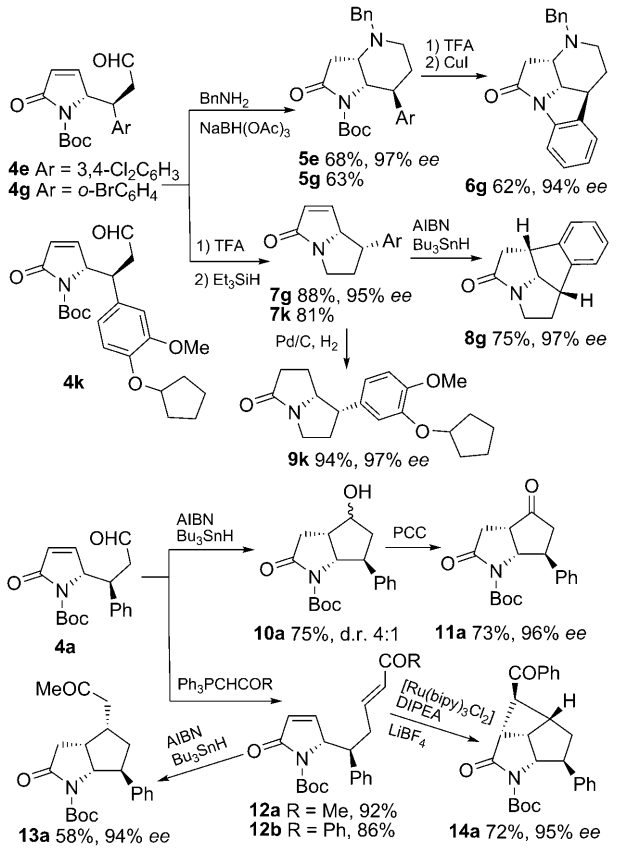


Entry	R	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	46	**4a**, 63 (80)	4:1	93 (99)
2	*p*-ClC_6H_4	58	**4b**, 80	19:1	97
3	*p*-BrC_6H_4	58	**4c**, 73	>20:1	97
4	*p*-$CF_3C_6H_4$	56	**4d**, 78	>20:1	94
5	3,4-$Cl_2C_6H_3$	46	**4e**, 77	>20:1	98[e]
6	*m*-ClC_6H_4	63	**4f**, 72 (79)	13:1	91
7	*o*-BrC_6H_4	64	**4g**, 70	19:1	97
8	*p*-MeC_6H_4	44	**4h**, 66 (85)	5.7:1	97
9	*m*-MeC_6H_4	48	**4i**, 66 (82)	4.9:1	96
10	*p*-$MeOC_6H_4$	46	**4j**, 54 (85)	1.5:1	98 (96)
11	Ar[f]	58	**4k**, 52 (76)	2.3:1	96 (96)
12	2-thienyl	60	**4l**, 39 (61)	1.6:1	98 (96)
13	2-furyl	54	**4m**, 31 (52)	1.5:1	93 (90)
14	3-pyridinyl	38	**4n**, 89[g]	2.4:1	93 (92)
15	Me	68	**4o**, 51[g]	1.1:1	90 (83)
16	Et	64	**4p**, 42[g]	2.0:1	79 (76)
17[h]	*o*-BrC_6H_4	82	**4g**, 62	19:1	97

[a] Unless noted otherwise, reactions conditions were **2a** (0.1 mmol), **3** (0.2 mmol), **1a** (0.02 mmol), and OFBA (0.02 mmol) in CH_3CN/H_2O (0.5 mL/0.05 mL) at RT. [b] Isolated yield of pure isomer **4** (the data in parentheses is related to the combined isolated yield of the diastereomers). [c] Determined by crude ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis after reaction with $Ph_3PCHCOPh$ (the data in parentheses is related to the minor isomer **4′**). [e] The absolute configuration of **4e** has been determined by X-ray crystallographic analysis after conversion to **5e**, see Figure 1.[11] The other products were assigned by analogy. For the structural assessment of the minor **4′**, see the Supporting Information. [f] Ar = 3-cyclopentoxy-4-methoxyphenyl. [g] Combined yield of inseparable diastereomers. [h] At the 1.0 mmol scale.

hydes **3** was explored by the catalysis of 20 mol% of **1a** and OFBA in a mixture of CH_3CN/H_2O (10:1) at room temperature. In general, the pure *syn*-**4** and *anti*-**4′** could be directly separated. As summarized in Table 2, excellent diastereo- and enantioselectivities have been obtained for enals with various electron-withdrawing aryl groups (Table 2, entries 2–7). Outstanding *ee* values were also attained for enals that have electron-donating aryl substitutions (Table 2, entries 8–11). The diastereocontrol was less satisfying, especially for substrates with alkyloxy-substituted aryl groups; nevertheless, the *ee* data of the separable minor diastereomers were outstanding (Table 2, entries 10 and 11). The diastereoselectivity was also low for heteroaryl-substituted enals, but the enantiocontrol for both diastereomers was still remarkable (Table 2, entries 12–14). The linear alkyl-substituted enals could be applied, and moderate to high enantioselectivity with low d.r. ratios was gained (Table 2, entries 15 and 16). Unfortunately, enals with β-branched alkyl groups failed to give the desired adducts, and nonclean reactions were observed. The catalytic reaction could proceed smoothly at a larger scale, and the similar results were attained (Table 2, entry 17).

Because the vinylogous adducts have multifunctional properties, we devoted much effort to exemplify the constructions of natural-product-like or drug-like libraries with versatile skeletal diversity through branching pathways.[7] As outlined in Scheme 2, a domino reductive amination–intramolecular aza Michael addition with **4e** or **4g** could be efficiently performed to afford diaza bicycles **5e** or **5g**, respectively, in excellent diastereocontrol. The relative and absolute configuration of **5e** was unambiguously determined by X-ray crystallographic analysis (Figure 1).[11] Moreover, an indoline derivative **6g** was smoothly prepared from **5g** through a copper-catalyzed intramolecular N-arylation reaction, the analogues of which have exhibited significant biological activities.[12] In addition, another tandem *N*-Boc deprotection–hemiaminal formation–dehydroxylation reaction with **4g** successfully delivered the N-fused bicycle **7g**,[13] which could be further converted to a polycyclic framework **8g** through Bu_3SnH-mediated radical addition, also in excellent diastereoselectivity. The similar tandem reaction was conducted with **4k**, and a *c*AMP-specific phosphodiesterase (PDE IV) inhibitor **9k** was produced, following a simple hydrogenation.[14] On the other hand, the aldehyde functionality could actively contribute to more scaffold diversity in different ways. A Bu_3SnH-mediated direct reductive radical conjugate addition with **4a** afforded a diastereomeric mixture **10a**, which was easily converted to a single ketone product **11a** in good yield after oxidation.[15] Moreover, **4a** was coupled with functionalized ylides to give **12a** and **12b**, respectively, which have two activated olefin systems. A separable major diastereomer **13a** was obtained via a Bu_3SnH-mediated intramolecular ketyl addition reaction of **12a**.[16] Interestingly, we found that Yoon's Ru-based photoredox catalysis[17] could be successfully applied to the pair reaction of intermediate **12b**, and a tricyclic alkaloid **14a** with six



Scheme 2. Synthetic transformations of some vinylogous adducts for scaffold variation constructions.

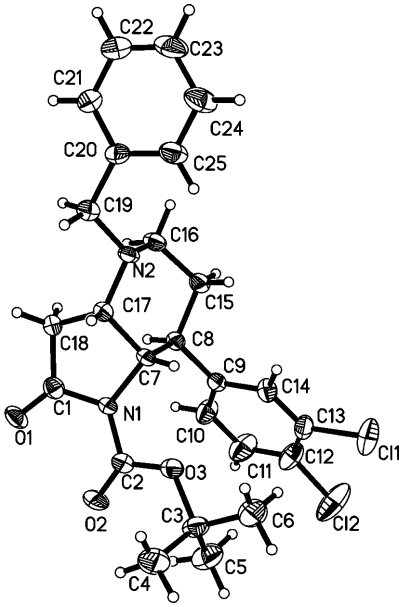


Figure 1. X-ray structure of enantiopure **5e**.

contiguous stereogenic centers was generated with high efficiency.

In conclusion, we have presented the first organocatalytic regio- and chemoselective direct vinylogous Michael addition of *N*-Boc α,β-unsaturated γ-butyrolactam to α,β-unsaturated aldehydes. The desired adducts with multiple orthogonal sets of functionalities were obtained in excellent enantioselectivity (up to 98% *ee*) with low to outstanding diastereoselectivity (d.r. up to > 20:1).[18] Moreover, we have demonstrated that the products were quite valuable for scaffold diversity synthesis. A number of enantioenriched natural-product-like or drug-like molecules with fused bi-, tri-, and polycyclic structures have been efficiently constructed, which might have potentials in the later explorations for the biologically related studies. More synthetic explorations are underway in our laboratory.

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Keywords: aldehydes · lactams · Michael addition · organocatalysis · scaffold diversity synthesis

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