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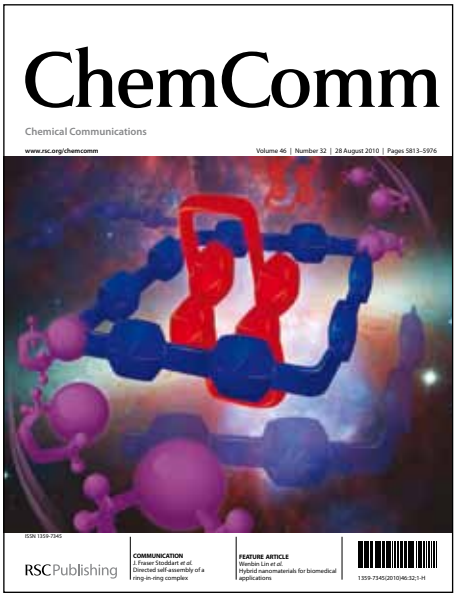

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ARTICLE TYPE

Organocatalyzed asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam

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Highly efficient asymmetric vinylogous 1,6-Michael addition of α,β-unsaturated γ-butyrolactam with 3-methyl-4-nitro-5-alkenyl-isoxazoles and Michael addition to trichloromethyl ketones by using a chiral quinine-derived squaramide organocatalyst were described, giving products with high diastereo- and enantioselectivities (up to >25:1 dr and 96% ee).

The optically active chiral butyrolactams are present in a variety of pharmaceuticals, natural products and versatile building blocks that can undergo synthetically useful transformations.[1] Owing to their synthetic significance, intense efforts have been made on the development of various elegant methods to access the structurally diverse family of 5-substituted butyrolactam derivatives.[2] Not surprisingly, the direct vinylogous additon of α,β-unsaturated γ-butyrolactam is still highly valuable from the standpoint of atom economy which has attracted much research interest.[3] The Shibasaki group has employed their dinuclear nickel catalytic system for the efficient asymmetric vinylogous Mannich reaction and Michael reaction.[4a] Later, asymmetric vinylogous Michael and Aldol reactions were well developed, which use metal-based chiral complex catalysts or organocatalysts.[4] However, to the best of our knowledge, electrophiles have generally been limited to nitroolefins, α,β-unsaturated aldehydes, α,β-unsaturated ketones, alkylidene malonates, imines and aryl α-ketoesters, no reports on catalytic asymmetric Michael reaction to α,β-unsaturated esters. Moreover, there is no example of direct catalytic asymmetric reactions of α,β-unsaturated γ-butyrolactam to the δ-position of electro-deficient olefins. Thus, the development of catalytic asymmetric vinylogous reactions of α,β-unsaturated γ-butyrolactam to a new 1,6-Michael acceptors and a suitably activated carboxylic acid derivatives is highly desirable and particularly attractive. 3-methyl-4-nitro-5-alkenyl-isoxazoles, developed by Adamo and coworkers, are able to be regarded as 1,6-Michael acceptors that show high reactivities toward stabilized nucleophiles.[5] Trichloromethyl ketones not only serve as attractive ester and amide synthetic equivalents, but also enable unique transformations due to trichloromethyl group is a good leaving group with strong inductive effect.[6] Herein, we describe our efforts devoted to the direct asymmetric vinylogous 1,6-Michael addition of α,β-unsaturated γ-butyrolactam with 3-methyl-4-nitro-5-alkenyl-isoxazoles and Michael addition to trichloromethyl ketones by using a chiral quinine-derived squaramide organocatalyst.[7,8]

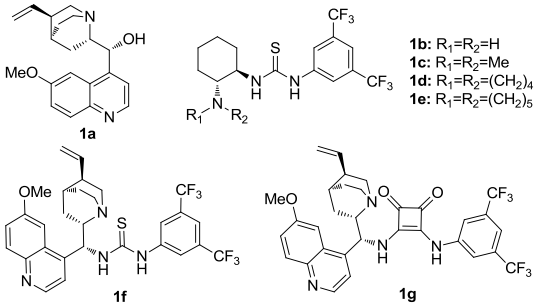

Figure 1: The structures of screened organocatalysts.

The utilization of hydrogen bonding as an activation force is widespread in organocatalysis. Chiral thioureas and, more recently, squaramides are good hydrogen-bonding donor organocatalysts. Accordingly, Our initial studies were focused on the reaction of α,β-unsaturated γ-butyrolactam **2** and 3-methyl-4-nitro-5-styrylisoxazole **3a** (Table 1), catalyzed by quinine **1a**, thioureas **1b-f** or squaramide catalyst **1g** (Figure 1). Preliminary screening of the catalysts was conducted in CH_2Cl_2 at 50°C using 10 mol% of quinine **1a** (Table 1, entry 1). Pleasingly, the reaction proceeded smoothly to afford the desired product **4a** in good yield albeit with poor diastereo- and enantioselectivity. Considering that chiral amine thioureas have previously been utilized as effective bifunctional organocatalysts for conjugate addition via acid–base cooperative activation. We switched catalysts from quinine to thioureas **1b-f** and led to much better enantioselectivity, though diastereoselectivity was yet satisfactory (Table 1, entry 2-6). Compared with thioureas **1b-e**, quinine derivatived catalyst **1f** gave better result. Encouraged by these results, quinine-derived squaramide catalyst **1g** was then tested (Table 1, entry 7). Improved results in terms of reactivity and selectivity were obtained and catalyst **1g** was identified as the best catalyst. Subsequent screening of solvents displayed that the reaction media had a significant effect on the reaction (Table 1, entries 8-12), and the use of THF was superior to others (Table 1, entry 12). Lowering the reaction temperature to 40°C caused a sharp decrease of the reaction yield (Table 1, entry 13).

Having established the optimal reaction conditions, we explored the scope of the 1,6-Michael additon of α,β-unsaturated γ-butyrolactam. The results are presented in Table 2. Generally, a wide array of 3-methyl-4-nitro-5-alkenyl-isoxazoles compounds containing electron-withdrawing or electron-donating groups were

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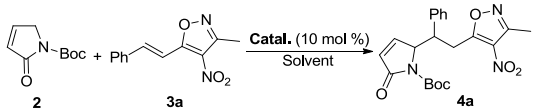
Table1: Screening of the reaction conditions[a]



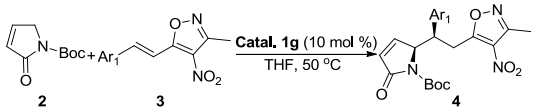
2 3a 4a

Entry	Catal.	Solvent	T (°C)	Yield (%)	d.r.[b]	ee (%)[b]
1	**1a**	CH_2Cl_2	50	70	3:1	19
2	**1b**	CH_2Cl_2	50	23	5:1	59
3	**1c**	CH_2Cl_2	50	78	6:1	73
4	**1d**	CH_2Cl_2	50	75	9:1	55
5	**1e**	CH_2Cl_2	50	71	9:1	67
6	**1f**	CH_2Cl_2	50	75	6:1	79
7	**1g**	CH_2Cl_2	50	82	13:1	91
8	**1g**	Et_2O	50	87	10:1	67
9	**1g**	Toluene	50	85	18:1	93
10	**1g**	CH_3CN	50	trace	—	—-
11	**1g**	$CHCl_3$	50	89	11:1	87
12	**1g**	THF	50	88	19:1	96
13	**1g**	THF	40	63	19:1	96

[a] Reaction were carried out with **2** (0.1 mmol) , **3a** (0.13 mmol), catalyst (0.01 mmol) in solvent (0.2 mL) for 36 h. [b] dr was determined by ^{1}H NMR, and ee by chiral HPLC analysis.

equally good substrates (up to 19:1 dr and 96% ee) (Table 2, entries 1-7). In the cases of **3h-k** as substrates, the corresponding products were obtained in good yields with excellent enantioselectivities and lower diastereoselectivities (Table 2, entries 8-11). In addition, heteroaromatic 3-methyl-4-nitro-5-alkenyl-isoxazoles **3l-m** were readily accommodated to the standard reaction conditions (Table 2, entries 12-13). When 3-methyl-4-nitro-5-(phenylbuta-1,3-dien-1-yl)isoxazole **3n** served as an Michael acceptor, moderate yield and a significant decrease in both enantioselectivity and diastereoselectivity (1.3:1 dr, 84% ee) were observed (Table 2, entry 14). The absolute configuration of the stereogenic centers of **4i** was unambiguously determined by X-ray crystallographic analysis (Figure 1).[9a]

Table 2: Substrate scope for the asymmetric vinylogous 1,6-Michael addition of α,β-unsaturated γ-butyrolactam to 3-methyl-4-nitro-5-alkenyl-isoxazoles[a]



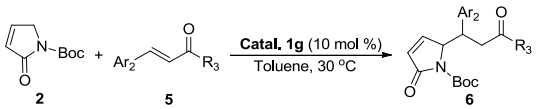
2 3 4

Entry	Ar_1	Product	Yield (%)[b]	d.r.[c]	ee (%)[c]
1	C_6H_5	**4a**	88	19:1	96
2	4-MeC_6H_4	**4b**	90	16:1	95
3	2-ClC_6H_4	**4c**	72	13:1	94
4	3-ClC_6H_4	**4d**	75	19:1	94
5	4-ClC_6H_4	**4e**	84	16:1	96
6	4-FC_6H_4	**4f**	79	16:1	96
7	4-MeOC_6H_4	**4g**	86	13:1	95
8	4-$CF_3C_6H_4$	**4h**	85	7:1	95
9	4-CNC_6H_4	**4i**	87	7:1	92
10	3,4-$Cl_2C_6H_4$	**4j**	82	7:1	96
11	4-$NO_2C_6H_4$	**4k**	77	4:1	91
12	2-furanyl	**4l**	75	13:1	95
13	2-thiopenyl	**4m**	71	16:1	92
14	C_6H_5CH=CH	**4n**	57	1.3:1	84

[a] Reaction conditions: 0.2 mmol (1.0 equiv) of **2**, 0.26 mmol (1.3 equiv) of **3**, and 0.02 mmol (10 mol %) of catalyst **1g** were stirred at 50 °C in THF (0.5 mL); the reaction was monitored by TLC. [b] Isolated yields. [c] dr was determined by ^{1}H NMR, and ee by chiral HPLC analysis.

Further substrate scope was investigated. The reaction of α,β-unsaturated γ-butyrolactam **2** to α,β-unsaturated trichloromethyl ketones proceeded nicely to afford the 1,4-addition products with high diastereo- and enantioselectivities (up to >25:1 dr and 94% ee) under quinine-derived squaramide catalyst in toluene at 30 °C (for the details, see SI). As summarized in Table 3, trichloromethyl ketones **5a-f**, regardless of their electronic and steric properties, underwent efficient reactions affording corresponding adducts in high enantioselectivities and excellent diastereoselectivities (Table 3, entries 1-6). Meanwhile, chalcone **5g** smoothly give rise to the desired 1,4-adduct in high yield, and the ee value of product improved to 99% on the established optimal conditions. Inert aliphatic enone **5h** can also be utilized as a suitable reaction partner to afford the product **6h**. The absolute configuration of **6a** was determined by X-ray crystallographic analysis,[9b] and the relative configuration of **6g-h** was confirmed by comparation with the literature.[4d]

Table 3: Substrate scope for the asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam to α,β-unsaturated ketones[a]

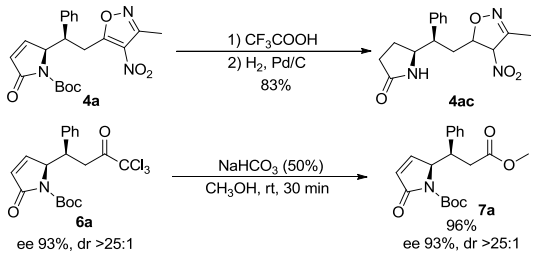


2 5 6

Entry	Ar_2, R_3	Product	Yield (%)[b]	d.r.[c]	ee (%)[c]
1	C_6H_5, CCl_3	**6a**	91	>25:1	93
2	4-MeC_6H_4, CCl_3	**6b**	93	>25:1	93
3	4-ClC_6H_4, CCl_3	**6c**	85	>25:1	90
4	4-BrC_6H_4, CCl_3	**6d**	79	>25:1	91
5	4-FC_6H_4, CCl_3	**6e**	82	>25:1	93
6	4-MeOC_6H_4, CCl_3	**6f**	80	15:1	86
7	C_6H_5, C_6H_5	**6g**	88	>25:1	99
8	C_6H_5, CH_3	**6h**	73	>25:1	93

[a] Reaction conditions: 0.2 mmol (1.0 equiv) of **2**, 0.26 mmol (1.3 equiv) of **5**, and 0.02 mmol (10 mol %) of catalyst **1g** were stirred at 30 °C in toluene (0.5 mL); the reaction was monitored by TLC. [b] Isolated yields. [c] dr was determined by ^{1}H NMR, and ee by chiral HPLC analysis.

The synthetic utility of the current reaction was demonstrated by the transformation shown in Scheme 1. The highly enantiomerically enriched compound **4a** can be easily converted into 5-substituted pyrrolidin-2-one derivative **4ac**. The ester derivative **7a** was smoothly prepared from **6a** without epimerization, by treatment with $NaHCO_3$ in MeOH for 30 min.



Scheme 1: Transformations of the corresponding Michael products.

In summary, we have developed an efficient quinine-derived squaramide catalyzed direct asymmetric vinylogous 1,6-Michael addition of α,β-unsaturated γ-butyrolactam with 3-methyl-4-nitro-5-alkenyl-isoxazoles and Michael addition to trichloromethyl ketones. The reactions with 10 mol% of squaramide **1g** proceeded well to furnish the corresponding adducts in high yields with high diastereoselectivities and enantioselectivities (up to >25:1 dr and

96% ee). This approach provides easy access to highly functionalized 5-substituted butyrolactam derivatives. The versatility of the N-acylpyrrole moiety makes this protocol a powerful tool for synthetic chemistry as well as new drug discovery. Further studies on asymmetric vinylogous reactions are underway in our laboratory.

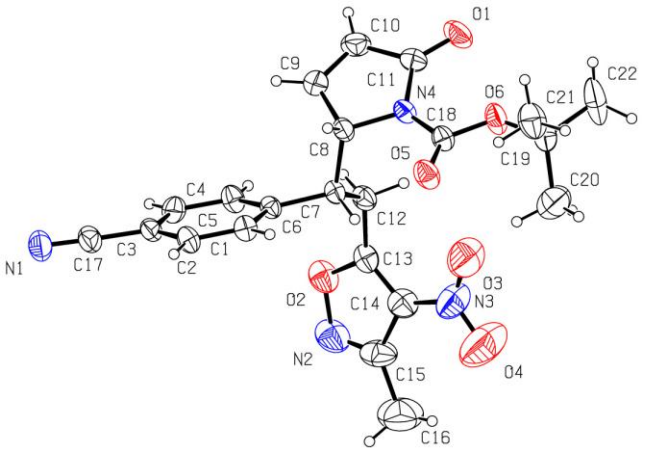


Figure 1. X-ray structure of enantiopure **4i.**

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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9 (a) CCDC 941171 (**4i**); (b) CCDC 941172 (**6a**). contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif