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Organocatalyzed Asymmetric Oxidative Coupling of α-Csp^3-H of Tertiary Amines to α,β-Unsaturated γ-Butyrolactam: Synthesis of MBH-Type Products

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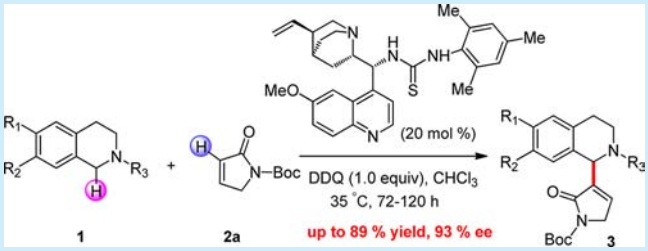
Supporting Information

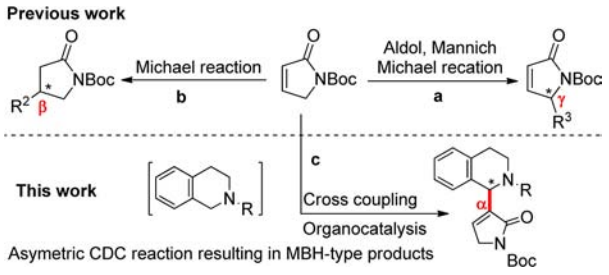
ABSTRACT: A unique organocatalytic asymmetric oxidative cross-dehydrogenative coupling of a α-Csp^3-H bond of tertiary amines with α,β-unsaturated γ-butyrolactams to generate Morita–Baylis–Hillman-type products has been realized for the first time. This method provides an efficient way to access a series of α-heterocyclic optically active tetrahydroisoquinoline scaffolds.



C–H functionalization is a widely utilized method for the efficient and selective construction of C–C bonds.[1] In recent years, the oxidative coupling of two C–H bonds to build new C–C bonds has received increased attention.[2] Among these reactions, the oxidative coupling of a α-Csp^3-H bond of amines, in particular tertiary amines, has made great progress.[3] Various nucleophiles have been employed, successfully intercepting the transient iminium generated and affording the familiar Mannich addition products.[4−10] However, Morita–Baylis–Hillman-type products have rarely been synthesized under this reaction manifold.[11] In 2006, Li and co-workers used DABCO/CuBr promoted oxidative coupling of tertiary amines with methylvinylketone, accessing MBH-type products racemically for the first time.[11a] This work has been extended into asymmetric realm by Wang in 2012 under Cu(OTf)$_2$/Quinine catalysis.[11b] These existing methods all share the same requirement: the addition of transition metals as co-catalysts, bringing additional cost alongside other drawbacks in industrial applications. Therefore, using organocatalysts alone to promote these reactions is highly desirable. Furthermore, these transformations are generally limited to simple unsaturated aldehydes or ketones as coupling reagents. To the best of our knowledge, the coupling of tertiary amines with nitrogen heterocyclic compounds has yet to be reported. Here we present the first coupling of a tertiary amine with α,β-unsaturated γ-butyrolactams to generate the Morita–Baylis–Hillman-type products catalyzed by a bifunctional thiourea.

Chiral butyrolactams are versatile building blocks central to the construction of many biologically and pharmacologically active compounds.[12] Owing to their synthetic significance, intense efforts have been made to extend the structurally diverse substituted butyrolactam between derivatives.[13] Since Shibasaki's group employed the dinuclear nickel catalytic system for the efficient asymmetric vinylogous Mannich reaction and Michael reaction in 2010,[14] a number of studies have investigated the reaction of α,β-unsaturated γ-butyrolactam and various electrophiles. Among them, most of the reactions occurred at the γ-position of α,β-unsaturated γ-butyrolactam[14−19] (Scheme 1a).

Scheme 1. Different Reaction Positions of α,β-Unsaturated γ-Butyrolactam



Meanwhile, the β-position of α,β-unsaturated γ-butyrolactam can conjugate to some nucleophiles[20] (Scheme 1b). In contrast, reaction at the α-position of α,β-unsaturated γ-butyrolactam with electrophiles is rare,[21] especially for the coupling with amines, which still remains a great challenge and has yet to be achieved (Scheme 1c).

The coupling between *N*-aryl tetrahydroisoquinolines with α,β-unsaturated γ-butyrolactam was chosen as the model reaction. Initially, when Mg(OTf)$_2$ and quinine **4a** were employed to promote the reaction, good yield but low enantioselectivity was observed (Table 1, entry 1). Although the reaction could progess in high yield but low enantioselectivity when using Mg(OTf)$_2$ alone (Table 1, entry 2), Cu(OTf)$_2$ failed

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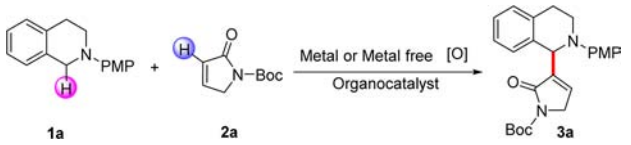
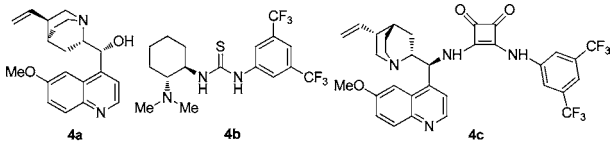
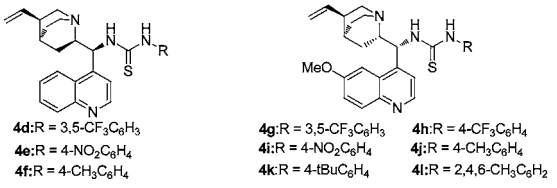
Table 1. Optimization of Reaction Conditions[a]



entry	metal	catalyst	[O]	yield[b] (%)	ee[c] (%)
1	$Mg(OTf)_2$	**4a**	DDQ	91[d]	<5
2	$Mg(OTf)_2$		DDQ	88[d]	<5
3	$Cu(OTf)_2$		DDQ		
4	none	**4a**	DDQ	17	<5
5	none	**4b**	DDQ	26	6
6	none	**4c**	DDQ	29	8
7	none	**4d**	DDQ	69	−55
8	none	**4e**	DDQ	54	−30
9	none	**4f**	DDQ	63	−35
10	none	**4g**	DDQ	51	45
11	none	**4h**	DDQ	78	65
12	none	**4i**	DDQ	68	50
13	none	**4j**	DDQ	81	70
14	none	**4k**	DDQ	71	74
15	none	**4l**	DDQ	72	80
16	none	**4l**	*t*BuOO*t*Bu	68	45
17	none	**4l**	H_2O_2	36	82
18	none	**4l**	$PhI(OAc)_2$	42	7
19	none	**4l**	O_2	39	31
20	none	**4l**	DDQ	68[e]	71

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and **2a** (0.15 mmol) in the presence of organocatalyst **4** (0.02 mmol), oxidant (0.1 mmol), and anhydrous chloroform (1.0 mL) for 72 h at 35 °C. [b]Yield of the isolated product. [c]The ee value was determined by HPLC on a chiral stationary phase. [d]The reaction was carried out in THF (1.0 mL) for 24 h at room temperature. [e]The reaction was carried out at 40 °C for 48 h under standard reaction condition.

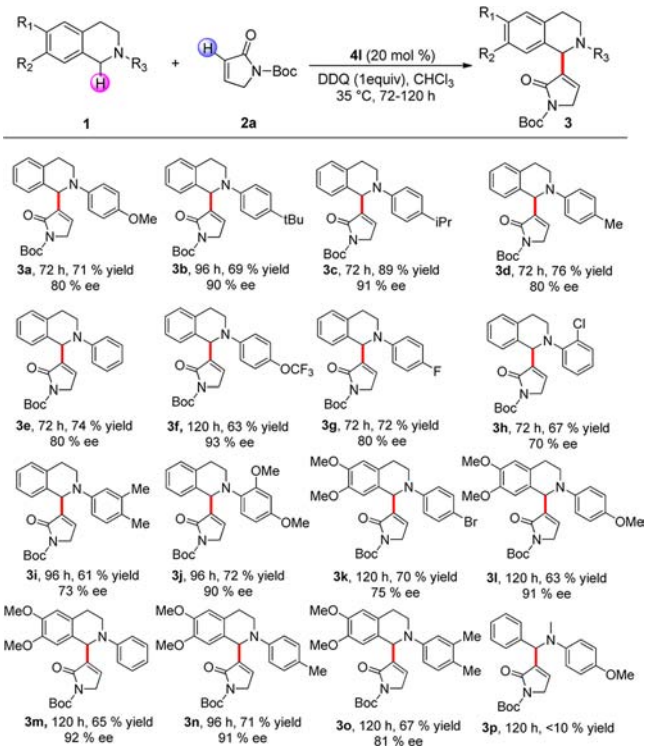




to provide any product (Table 1, entry 3). To our delight, the reaction could also progress in the absence of any metal salt and yield the desired product (Table 1, entry 4). A series of organocatalysts were used to promote the reaction without the addition of any metal salt, and it was noticed that the thiourea derived from quinine **4g**−**4l** provided higher ee values compared with the catalysts **4b**−**4f** derived from diaminocyclohexane, squaramide, and cinchonine (Table 1, entries 5−15). Screening the substitutes on the aryl ring of the catalysts showed that trimethyl-substituted thiourea **4l** was the best catalyst for this reaction. Finally, we investigated a number of oxidants and found that DDQ was the optimal choice (Table 1, entries 16−19). The product can further oxidative cleavage of PMP group to provide α-substituted tetrahydroisoquinoline.[22]

With the optimized reaction conditions in hand, the scope of substrates was then extensively investigated. In general, α,β-unsaturated γ-butyrolactam (**2a**) could react smoothly with various aromatic-substituted tetrahydroisoquinolines to generate the desired products in good yields and good to excellent enantioselectivities. A wide range of aromatic-substituted tetrahydroisoquinolines were examined, and it was observed that with both electron-withdrawing and electron-donating groups on the para and ortho position of the phenyl ring of **1**, the desired oxidative coupling products were obtained in satisfactory yields (63−89%) and good to excellent enantioselectivities (up to 93%, Scheme 2). With double substituents on

Scheme 2. Investigating the Scope of the Procedure[a]



[a]The reaction was carried out with **1** (0.1 mmol) and **2a** (0.15 mmol) in the presence of **4l** (0.02 mmol), DDQ (0.1 mmol) and anhydrous chloroform (1.0 mL) at 35 °C. [b]Yield of the isolated product. [c]Determined by HPLC on chiral stationary phase. The configuration was assigned by comparison of HPLC data and X-ray crystal data of **3n**.

the N-aryl ring of aromatic-substituted tetrahydroisoquinolines, good yield and high enantioselectivities were achieved (61−72% yields and up to 90% ee; Scheme 2). Introduction of electron-donating methoxy to the 6,7-position of the tetrahydroisoquinoline ring led to marginally reduced yields (63−71%) but no influence on the enantioselectivities (up to 92%, Scheme 2). However, attempts to extend this methodology to acyclic tertiary amine (**3p**) proved unsuccessful due to the low reactivity of the substrate (Scheme 2). The absolute configuration of the products were determined to be (*S*) by using a single-crystal X-ray diffraction of compound **3n** (Figure 1)[23]

In order to clarify the possible reaction pathways of *N*-aryl tetrahydroisoquinolines with α,β-unsaturated γ-butyrolactam, various radical trapping agents (TEMPO or 2,6-di-*tert*-butyl-4-methylphenol, BHT) were added to the reaction system. With addition of TEMPO, the yield and stereoselectivity of the

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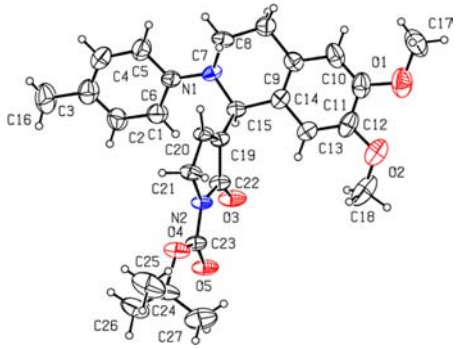
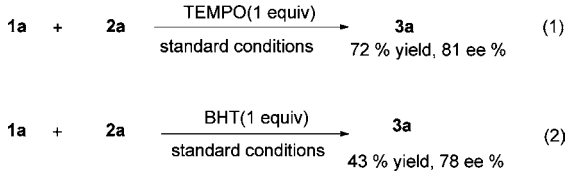


Figure 1. X-ray crystal structure of compound **3n**.

coupling product remained unchanged (eq 1, Scheme 3). However, when the BHT was added, the yield of the coupling product decreased significantly from 74% to 43%, but little change in stereoselectivity was observed (eq 2, Scheme 3). These results show that an ion pair might be involved, but the irreversible hydrogen transfer is sufficiently rapid that TEMPO cannot capture this radical cation.

Scheme 3. Mechanistic Experiments for Organocatalytic Asymmetric Oxidative Coupling



A possible reaction pathway involving single-electron transfer (SET) is outlined in Figure 2. Under the oxidative condition

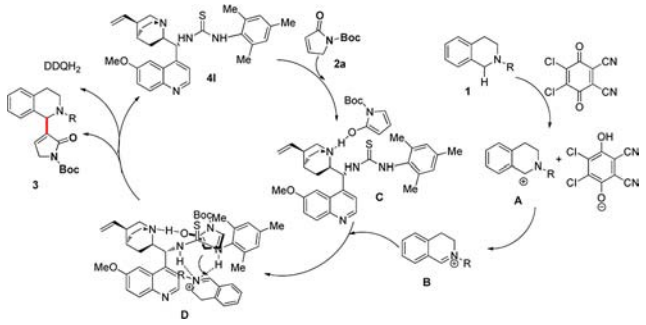


Figure 2. Strategy for asymmetric oxidative coupling of amines via bifunctional thiourea catalysis.

using DDQ as the oxidant, a single-electron transfer from the α-Csp^3-H bond of a tertiary amine would occur to afford the ion pair **A**, which is subsequently transformed to an iminium cation **B** quickly as a key intermediate. Meanwhile the thiourea catalyst **4l** activated α,β-unsaturated γ-butyrolactam through hydrogen bond to generate **C** and captured iminium cation **B** to give the final intermediate **D**. Finally, electrophilic attack of the iminium to the coordination sphere of the enamine occurs, to eventually afford the final product and regenerate the bifunctional thiourea catalyst.

In summary, we have disclosed the first example of an asymmetric oxidative coupling reaction of a α-Csp^3-H bond adjacent to a nitrogen atom of tertiary amines with α,β-unsaturated γ-butyrolactam to construct MBH-type products with the help of a bifunctional thiourea catalyst under mild conditions. A series of α-heterocyclic optically active tetrahydroisoquinoline scaffolds was easily obtained in good yields (61–89%) and good to excellent enantioselectivities (up to 93% ee). The development of this environment-friendly bifunctional thiourea catalysis system in other asymmetric oxidative coupling reactions is being pursued.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **3n**. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(23) CCDC 998433 (**3n**) 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/cgibin/catreq.cgi.