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Organocatalytic Enantioselective Cross-Dehydrogenative Coupling of *N*-Carbamoyl Cyclic Amines with Aldehydes

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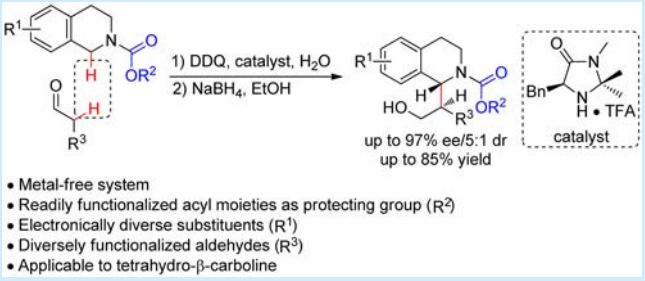
Supporting Information

ABSTRACT: The existing catalytic enantioselective cross-dehydrogenative coupling of cyclic amines predominantly focused on reactive *N*-aryl tetrahydroisoquinolines, which typically suffered from limited substrate generality and synthetic utility, and required the use of metal catalyst. Herein, a metal-free catalytic enantioselective cross-dehydrogenative coupling of *N*-carbamoyl cyclic amines and aldehydes has been reported for the first time. Employing an easily installed and functionalized acyl protecting group rather than the widely adopted aryl moiety endows the enantioselective process with better substrate generality and broader synthetic utility.



The oxidative coupling of two readily accessible C−H reagents has emerged as a straightforward and economical alternative to conventional strategies for new C−C bond construction whereby the only loss is H_2O.[1] Despite significant advances, the development of catalytic enantioselective variants remains a formidable challenge.[2,3] Due to the importance of enantiomerically pure C_1-substituted cyclic amines in modern organic synthesis and pharmacology, several catalytic enantioselective cross-dehydrogenative coupling (CDC) reactions of cyclic amines with different types of C−H components have been established.[4] Despite great innovation, the approaches lack generality and broad synthetic utility. The scope of cyclic amines is predominantly restricted to electron-rich *N*-arylated tetrahydroisoquinolines (THIQs), with THIQs bearing electron-withdrawing substituents and other types of nitrogen heterocycles rarely explored. The aryl protecting group, the crucial element for the reactivity and enantioselectivity, is not easily removed. This problem might result in poor functional group compatibility and, thus, limit the synthetic utility.[5] Additionally, the majority of the enantioselective methods required the use of a transition metal as the catalyst, and the metal-free catalytic enantioselective CDC of cyclic amines remained elusive.

Employing an acyl protecting group to replace the aryl moiety would be an attractive solution for enhancing the generality and utility of the method because the more reactive *N*-acyliminium intermediate would react with a broader range of C−H components and the acyl group should be more easily installed and functionalized. However, even the nonenantioselective CDC of *N*-acyl THIQs proved to be much more challenging because of the reduced substrate reactivity and intermediate stability.[6] Therefore, the catalytic enantioselective variant remains underdeveloped. Sodeoka disclosed the first enantioselective CDC of *N*-carbamoyl THIQs and malonates catalyzed by a palladium complex with moderate enantiocontrol (up to 86% ee).[7a,b] However, the scope of the method was only limited to dimethoxy-substituted electron-rich THIQs, with electron-neutral and -deficient ones intact. Recently, we developed a catalytic enantioselective CDC of *N*-carbamoyl THIQs with terminal alkynes.[7c] A variety of electronically varied *N*-carbamoyl THIQs were tolerated with up to 95% ee, and the synthetic utility was demonstrated in several natural product syntheses. However, metal additives including copper salt and more than a stoichiometric amount of $Yb(OTf)_3$ were always prerequisite. To the best of our knowledge, a metal-free catalytic enantioselective CDC of *N*-acyl amines has not been established to date.

The aldehyde represents an ideal C−H reagent for the catalytic enantioselective CDC with cyclic amines, which would provide an extraordinary opportunity to access C_1-alkylated nitrogen heterocycles with two contiguous stereogenic centers such as γ-amino alcohol/acids for proteomics.[8,9] Chi et al. reported a copper-catalyzed enantioselective CDC of *N*-aryl THIQs and aldehydes with moderate dr and good to excellent ee values.[4c] However, THIQs bearing electron-withdrawing substituents were intact. Moreover, the method dominantly focused on propionaldehyde, and only one isolated example of functionalized aldehyde (3-phenylpropionaldehyde) was studied with moderate efficiency (37%) and ee (67%). Therefore, developing a catalytic enantioselective CDC of electronically varied *N*-acyl THIQs with functionalized aldehydes would be

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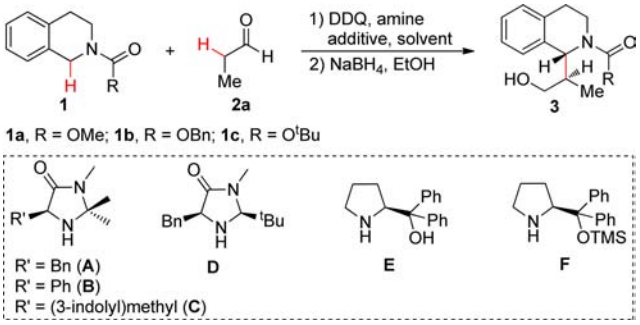
highly desirable. Herein, we report the first metal-free catalytic enantioselective CDC of electronically diverse *N*-carbamoyl THIQs with a broad range of functionalized aldehydes in high efficiency with excellent enantiocontrol. The generality of the method for other types of cyclic amines like *N*-carbamoyl tetrahydro-β-carbolines is also explored.

Initially, we examined the CDC of *N*-carbamoyl THIQ **1a** and propionaldehyde (**2a**) using DDQ as the oxidant and secondary amine as the catalyst (Table 1). An extensive

Table 1. Reaction Condition Optimization[a]



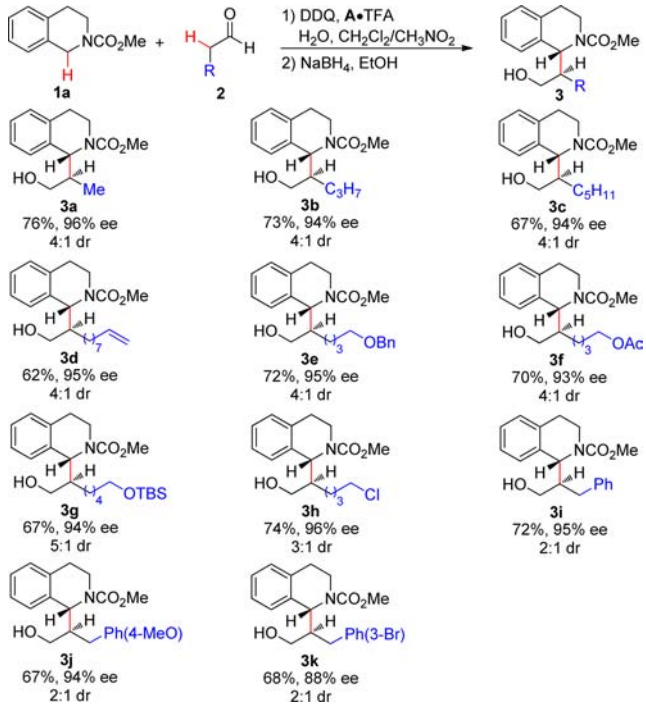
entry	amine	additive	yield (%)[b]	dr[c]	ee[d]
1	**A**·TFA	–	85	2:1	40
2	**A**	–	<5	n.d.	n.d.
3	**B**·TFA	–	80	2:1	30
4	**C**·TFA	–	70	2:1	35
5	**D**·TFA	–	72	1:1	32
6	**E** or **F**	–	<5	n.d.	n.d.
7	**A**·HCl	–	46	1:1	29
8[e]	**A**·TFA	H_2O	80	2:1	70
9	**A**·TFA	H_2O	78	2:1	80
10[f]	**A**·TFA	H_2O	61	2:1	62
11[g]	**A**·TFA	H_2O	<5	n.d.	n.d.
12[h]	**A**·TFA	H_2O	60	3:1	94
13[h,i]	**A**·TFA	H_2O	76	4:1	96

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.6 mmol), amine (0.04 mmol), additive (4.0 mmol), and DDQ (0.2 mmol) in CH_2Cl_2 (2.0 mL) at rt for 48 h. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis on a chiral stationary phase. [e]10 equiv of H_2O were added. [f]**1b** used. [g]**1c** used. [h]Reaction at −20 °C. [i]CH_3NO_2 as solvent. n.d. = not determined.

investigation on the chiral imidazolidinones **A**–**D** and pyrrolidines **E** and **F**, and their combinations with diverse Brønsted acids revealed that catalyst **A**·TFA should be the best choice with respect to ee values and yields (entries 1–7). When 20 equiv of H_2O were employed as the additive, an 80% ee was obtained (entries 8 and 9). The influence of different acyl protecting groups on the reaction was next evaluated. The methyl ester moiety provided the highest level of enantiofacial discrimination, though bulkier moieties gave inferior results (entries 9–11). Optimizations of the temperature and solvent identified the reaction at −20 °C in CH_3NO_2 to be optimal (entries 12 and 13).

The scope of aldehyde components was then explored (Scheme 1). Generally, the metal-free catalytic asymmetric CDC of *N*-carbamoyl THIQ **1a** with diverse aldehydes went smoothly, providing the expected alkylated nitrogen heterocycles **3a**–**3k** with good efficiency (62–76%) with excellent enantiocontrol (94% ee on average) and synthetically useful dr.[10] Notably, the method exhibited excellent functional group

Scheme 1. Scope of Aldehydes[a]

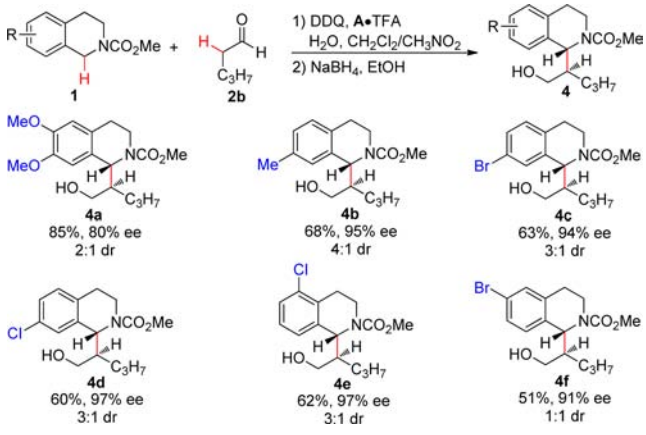


[a]Reaction condition: **1a** (0.2 mmol) and DDQ (0.2 mmol) in CH_2Cl_2 (2.0 mL) at rt for 1 h followed by addition of **2** (0.6 mmol), **A**·TFA (0.04 mmol), H_2O (4.0 mmol) in CH_3NO_2 (2.0 mL) at −20 °C for 48 h.

tolerance, with common moieties such as olefins (**3d**), benzyl ethers (**3e**), acetate (**3f**), silyl ethers (**3g**), halides (**3h**), and aryls (**3i**–**3k**) tolerated without an adverse effect on the efficiency as well as the ee values, demonstrating its capacity in preparing diversely functionalized THIQ-based molecules and thus well solving the scope limitations of aldehyde components in existing methods.

The scope of THIQs **1** was next investigated (Scheme 2). As expected, electron-rich dimethoxy-substituted *N*-carbamoyl THIQ was a suitable substrate, giving **4a** in 85% yield and

Scheme 2. Scope of the THIQs[a]



[a]Reaction condition: **1** (0.2 mmol) and DDQ (0.2 mmol) in CH_2Cl_2 (2.0 mL) at rt for 1–2 h followed by addition of **2** (0.6 mmol), **A**·TFA (0.04 mmol), H_2O (4.0 mmol) in CH_3NO_2 (2.0 mL) at −20 °C for 48 h.

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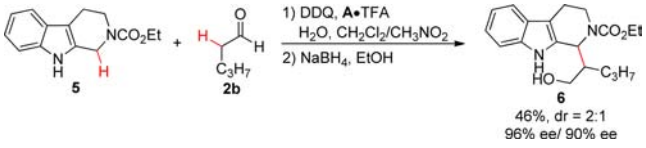
80% ee. 7-Methyl substituted THIQ was also compatible with the process, giving expected **4b** in 68% yield and 95% ee. According to the studies of Chi and Cozzi, the reaction of aldehydes with THIQs bearing electron-withdrawing substituents should be much more challenging.[4c,5] Excitedly, electron-deficient heterocycles bearing bromo (**4c** and **4f**) and chloro (**4d** and **4e**) moieties, which can serve as additional functional handles, were well tolerated with good efficiency with excellent ee values, thus suitably addressing the substrate scope limitation in previous studies.

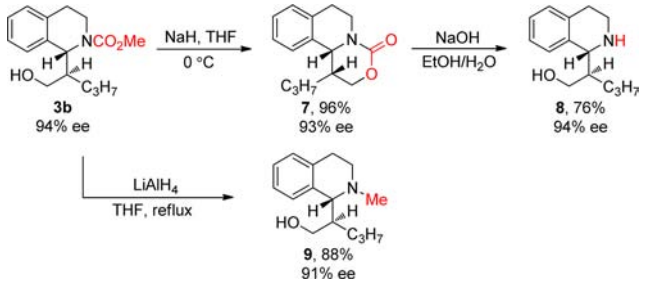
To date, the catalytic enantioselective CDC of carbamates has been limited to THIQ derivatives, leaving other types of *N*-acyl amines untouched. Therefore, the generality of the method for other types of cyclic amines was next explored. Given the prevalence of chiral C_1-substituted tetrahydro-β-carbolines in numerous bioactive molecules, such a heterocycle was selected for study (Scheme 3). Under the standard conditions, *N*-carbamoyl tetrahydro-β-carboline **5** reacted smoothly with aldehyde **2b**, generating expected **6** in moderate yield with excellent ee and moderate dr.

Scheme 3. Enantioselective CDC of *N*-Carbamoyl Tetrahydro-β-Carbolines



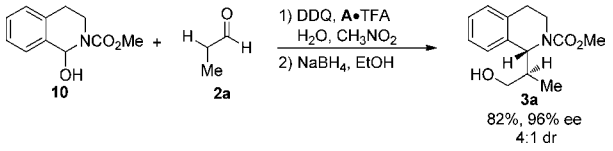
Given the difficult dearylation process for the widely studied *N*-aryl THIQs, we turned to examine the capability of the acyl protecting groups to engage in subsequent cleavage or functionalization (Scheme 4). Treatment of the CDC product **3b** with NaH afforded tricyclic oxazinone **7** in 96% yield and 93% ee, which represents a key scaffold in a variety of bioactive molecules.[11] In addition, oxazinone **7** underwent hydrolysis with NaOH in an EtOH/H_2O mixture, efficiently generating free amino alcohol **8** in 94% ee. Finally, **3b** was reduced with $LiAlH_4$ to provide *N*-methyl THIQ **9** in 88% yield and 91% ee. Notably, all these transformations proceeded smoothly with the ee highly conserved, demonstrating the synthetic utility of the CDC of *N*-carbamoyl amines and aldehydes in creating structurally diverse molecules.

Scheme 4. Manipulations of Acyl Protecting Groups



During the course of the CDC process, TLC analysis suggested the formation of a considerable amount of an intermediate, which was verified to be *N*-acyl hemiaminal **10** (Scheme 5). Subjecting **10** to the standard conditions afforded comparable results to those starting from **1a**, indicating the intermediacy of **10** in the enantioselective CDC process.

Scheme 5. Control Experiment



In summary, the first metal-free catalytic enantioselective CDC of *N*-carbamoyl cyclic amines and aldehydes has been established. The method exhibited good substrate generality with excellent functional group tolerance, allowing for a variety of structurally and electronically diverse *N*-carbamoyl THIQs and functionalized aldehydes to be well tolerated in high efficiency with excellent enantiocontrol. *N*-Carbamoyl tetrahydro-β-carboline proved to be a suitable component for the catalytic enantioselective CDC reaction for the first time, further demonstrating the generality of the method. The acyl protecting group can be facilely removed or functionalized to provide synthetically valuable scaffolds for further manipulations, suggesting that the method should have broader synthetic utilities than those employing *N*-aryl THIQs as substrates. The study on the catalytic enantioselective CDC of other types of carbamates is being pursued and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01625.

Experimental details and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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