Synthetic Methods

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Organocatalytic Enantioselective Oxidative C–H Alkenylation and Arylation of *N*-Carbamoyl Tetrahydropyridines and Tetrahydro-β-carbolines**

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Abstract: *The first organocatalytic enantioselective C–H alkenylation and arylation reactions of N-carbamoyl tetrahydropyridines and tetrahydro-β-carbolines (THCs) are described. The metal-free processes represent an efficient and straightforward approach to a variety of structurally and electronically diverse α-substituted tetrahydropyridines and THCs in good yields with excellent regio- and enantioselectivities. Preliminary control experiments provide important insights into the reaction mechanism.*

Substituted piperidines and more complex indolopiperidine tetrahydro-β-carbolines (THCs) are key units in numerous bioactive molecules and have been used for many pharmaceutical applications (Figure 1).[1] The catalytic enantioselective addition of carbon-centered nucleophiles to cyclic imine or iminium electrophiles represents a particularly attractive approach to synthesize these structural motifs. However, existing catalytic asymmetric methods that proceed with high efficiency require the use of stabilized precursors derived from isoquinolines and quinolines.[2] Substituted pyridinium ions have been shown to be ideal intermediates for piperidine synthesis, but the employment of transition metals is always a prerequisite.[3] With respect to the synthesis of α-substituted THCs, aside from the enantioselective hydrogenation of cyclic imines,[4] the organocatalytic asymmetric Pictet–Spengler reaction has recently emerged as an elegant approach providing the scaffolds with excellent enantioselectivity.[5] However, this transformation requires the involvement of electron-rich tryptamines, leaving electron-deficient THCs inaccessible. Moreover, enals and electron-rich aromatic aldehydes also cannot be employed as substrates, rendering α-alkenyl and electron-rich aryl-substituted THCs unavailable. The organocatalytic enantioselective addition of boronates to cyclic iminium ions provides an impressive solution to the above limitations by the umpolung of the two components.[6] To the best of our knowledge, organocatalytic asymmetric couplings of boronates with tetrahydropyridine- or THC-derived iminium intermediates have not been established to date.[7]

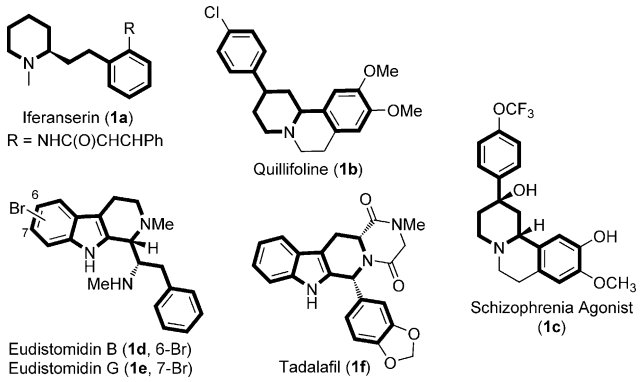

Figure 1. Representative α-arylethyl and α-aryl piperidines and THCs.

Cyclic iminium intermediates can be generated through the selective C–H oxidation of N-heterocyclic precursors.[8] This strategy provides an effective alternative to conventional methods that rely on the manipulation of functional groups. Several impressive catalytic asymmetric variants have been reported, but they still suffer from a limited scope.[9] *N*-Aryl tetrahydroisoquinolines have always been selected as the substrates, and Chi et al. reported that for *N*-aryl piperidines, no reactivity was observed.[9c] To the best of our knowledge, there have been no reports on a catalytic enantioselective C–H functionalization of tetrahydropyridines or THCs to date. Moreover, the synthetic utility of the existing methods is limited because removal of the *N*-aryl group in the presence of other functional groups proved to be difficult.[2g,10] Herein, we report the first organocatalytic asymmetric C–H alkenylation and arylation reactions of *N*-carbamoyl tetrahydropyridines and THCs with excellent enantiocontrol.

Seminal work from the groups of Chong and Schaus established the possibility of using chiral biphenols to promote asymmetric boronate addition reactions.[7] Moreover, Schaus et al. also reported innovative examples using an tartaric acid derived chiral Brønsted acid as an effective catalyst.[7e,f] Therefore, these two types of catalysts were explored for our boronate addition process. The regioselective functionalization of the C1–H bond of *N*-carbamoyl THC **2a** might be challenging given that the C4–H bond adjacent to the enamine moiety can be easily oxidized (Table 1).[9a,11] Careful optimization of catalyst, oxidant, and solvent unearthed promising results: Excellent regioselectivity with

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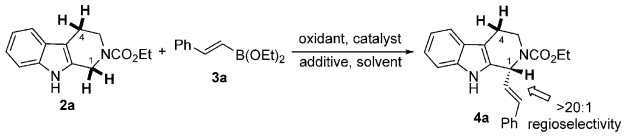
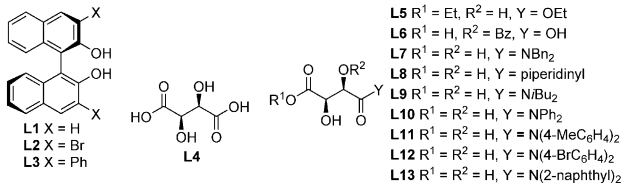
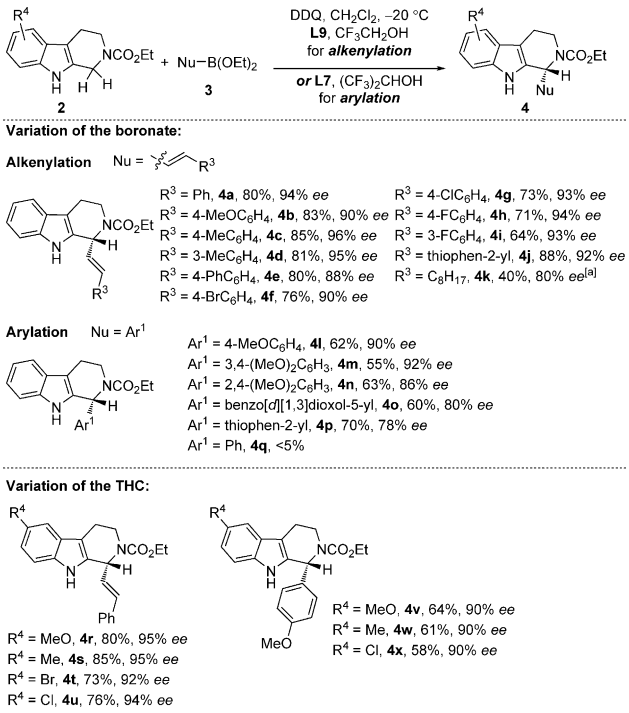
Table 1: Optimization of the reaction conditions.[a]





Entry	Catalyst	Additive	Yield [%][b]	*ee* [%][c]
1	**L1**–**L3**	–	< 5	n.d.
2	**L4**	–	33	36
3	**L5** or **L6**	–	< 5	n.d.
4	**L7**	–	38	38
5	**L9**	–	42	51
6	**L13**	–	28	36
7	**L9**	Lewis acid[d]	< 40	< 5
8	**L9**	CF_3CH_2OH	80	94

[a] Reactions conditions, unless otherwise specified: **2a** (0.1 mmol), **3a** (0.2 mmol), DDQ (0.1 mmol), catalyst **1** (0.015 mmol), CH_2Cl_2 (2.0 mL), −20 °C, 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $Yb(OTf)_3$ or $Sc(OTf)_3$. Bn = benzyl, Bz = benzoyl.



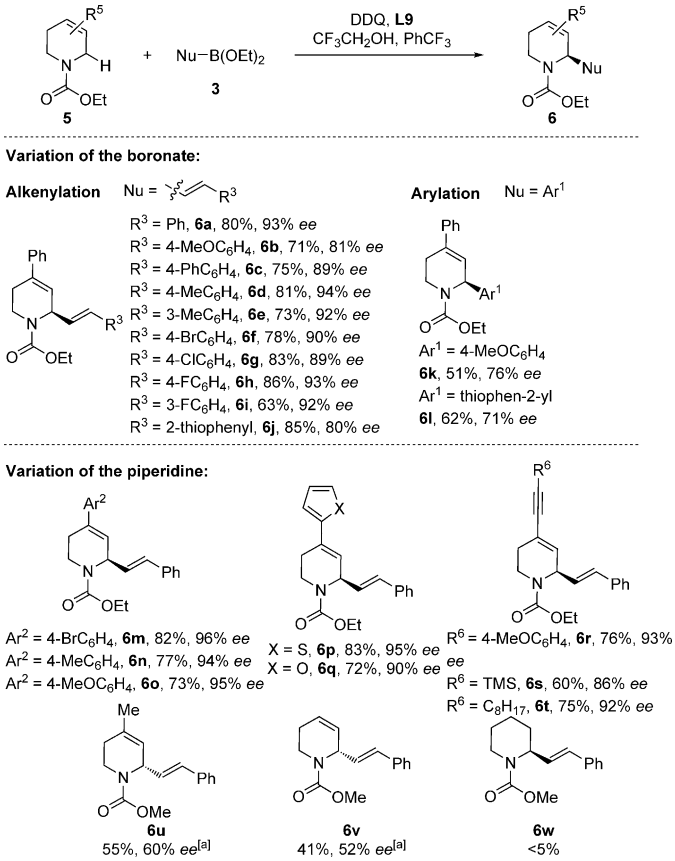
Scheme 1. C–H alkenylation and arylation of *N*-carbamoyl THCs. [a] **L2** (30 mol%), $T^+BF_4^-$ (2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, 1.0 equiv), and the dimethyl boronic ester (2.0 equiv).

functionalization of the C1–H bond was observed, and **4a** was afforded in 36% *ee* when **2a** was reacted with **3a** in the presence of tartaric acid (**L4**) and DDQ at −20 °C (entries 1 and 2; see also the Supporting Information). The catalyst optimization using the modular structure of **L4** implied that the carboxylic acid and diol moieties were essential for the reaction, and that the steric properties of the amide exerted a pronounced effect on the enantioselectivity, and *N*,*N*-diisobutyl-substituted **L9** was found to be optimal (entries 3–6). CF_3CH_2OH as an additive was established to be beneficial to the reaction (entries 7 and 8).

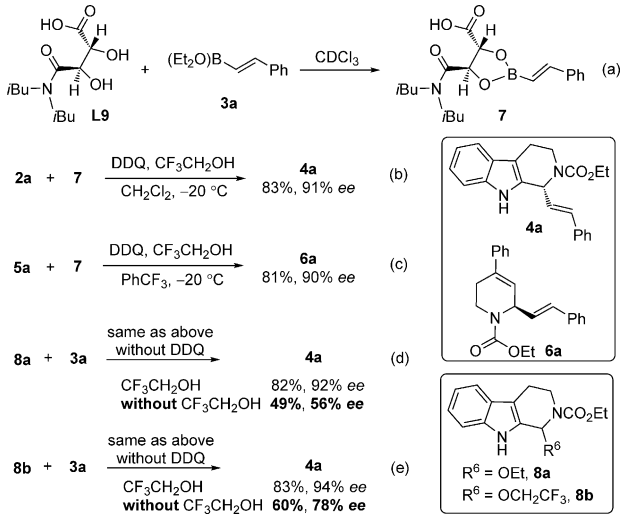
A wide range of electronically varied styrenyl boronates with different substitution patterns participated in the highly regioselective oxidative C–H alkenylation of **2a**, providing the corresponding vinyl-substituted THCs **4a**–**4i** with excellent *ee* values (Scheme 1). Heteroaryl- (**3j**) and alkyl-substituted (**3k**) vinyl boronates were also competent nucleophiles. The C–H arylation process was also effective with electron-rich aryl boronates **3l**–**3o** and heteroaryl boronate **3p**, whereas electron-deficient **3q** failed to deliver **4q**. Many different THCs could also be employed as substrates in this transformation. Both electron-rich and -deficient THCs were well tolerated, affording vinyl-substituted **4r**–**4u** and aryl-substituted **4v**–**4x** with excellent enantioselectivities. It is noteworthy that the products shown in Scheme 1 are inaccessible by catalytic asymmetric Pictet–Spengler reactions.[5]

The C–H functionalization of *N*-carbamoyl tetrahydropyridines was next studied. 2,4-Substituted piperidines are core scaffolds of a number of synthetic drugs, such as quillifoline (**1b**; Figure 1) and **1c**. However, practical catalytic asymmetric methods that provide access to these structures have not been well established. Olsson and Almqvist disclosed an enantioselective addition of aryl Grignard reagents to 4-phenylpyridine *N*-oxides with up to 80% *ee*.[3h] However, a stoichiometric amount of a chiral lithium binolate reagent was required. Therefore, 4-phenyl-substituted **5a** was initially explored. A similar boronate scope as for the THCs was observed, and a broad range of electronically diverse vinyl and electron-rich aryl boronates were well tolerated (Scheme 2). The influence of the substituents on the tetrahydropyridine scaffold was next studied. Electronically varied 4-aryl- and 4-heteroaryl-substituted tetrahydropyridines were effective substrates, affording **6m**–**6q** with excellent *ee* values. At the C4 position, alkynyl moieties were also tolerated, and the corresponding products (**6r**–**6t**) were obtained with high enantiocontrol, demonstrating the capability of the method to prepare structurally diverse 2,4-substituted piperidines through manipulation of the alkyne moieties. 4-Alkyl-substituted **5u** and non-substituted **5v** could also be converted with moderate yield and *ee* values. Unfortunately, with piperidine **5w**, the desired product was not detected.

Schaus and co-workers have demonstrated that tartaric acid catalyzed boronate addition reactions should proceed via the transesterification of the boronate with the catalyst to form a chiral nucleophile.[7e,f] In consistency with the study by Schaus et al., ^1H NMR and ESI-MS analysis of a mixture of **L9** and **3a** implied the generation of dioxaborolane **7** (Scheme 3a).[12] Moreover, the reaction of **7** (1 equiv) with **2a** or **5a** proceeded with comparable efficiency and enantiocontrol to the corresponding catalytic reaction (Scheme 3b,c), implying the involvement of **7** in the catalytic process. During the course of the reaction of **2a** with **3a**,



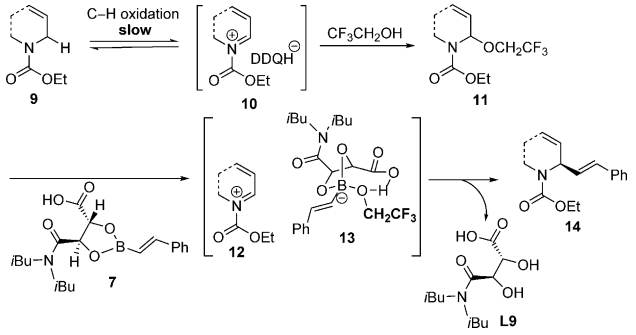
Scheme 2. C–H alkenylation and arylation of *N*-carbamoyl tetrahydropyridines. [a] $T^+BF_4^-$ (1.0 equiv) and the diisopropyl boronic ester (2.0 equiv) in $CHCl_3$. TMS = trimethylsilyl.



Scheme 3. Control experiments.

a considerable amount of an intermediate was detected by TLC analysis, which was identified as CF_3CH_2OH adduct *N*-acyl hemiaminal **8b** (Scheme 3). Therefore, control experiments were conducted to explore the roles of CF_3CH_2OH by subjecting **8a** and **8b** to the standard conditions (Scheme 3d,e). Comparable results were obtained when CF_3CH_2OH was present. However, obvious differences were observed when the additive was absent, with **8b** affording the best yield and highest *ee* value, suggesting that **8b** should be an intermediate of the reaction.

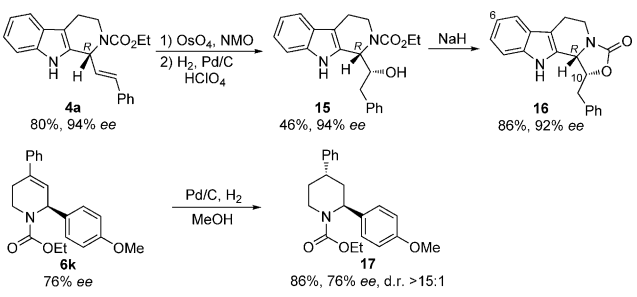
According to these preliminary studies, a plausible mechanism is proposed (Scheme 4). The C–H oxidation of carbamate **9** generating *N*-acyliminium **10** is reversible. The quick reaction of CF_3CH_2OH with **10** completes the C–H oxidation process to give *N*-acyl hemiaminal **11**. Then acidic complex **7** promotes the collapse of **11** to provide acyliminium



Scheme 4. Proposed mechanism.

12 concomitant with the generation of "ate" complex **13**. The different reactivity observed for **8a** and **8b** in the absence of CF_3CH_2OH indicates that the CF_3CH_2O moiety in **11** might act as a good leaving group to facilitate the formation of acyliminium ion **12** and ate complex **13**; the different *ee* values for **8a** and **8b** imply that the CF_3CH_2O moiety in boron ate complex **13** might be relevant to the enantiocontrol of the nucleophilic addition process, but the exact origin of the effect remains unclear.

The utility of the method in complex molecule synthesis was further demonstrated (Scheme 5). α-Arylethyl-substituted THCs are ubiquitous structural motifs in numerous indole alkaloids, such as eudistomidin B and G (**1d** and **1e**, Figure 1). Previous strategies, which relied on the Pictet–Spengler reaction, required the installation of the C10 stereocenter at the beginning of the synthesis, and therefore, the preparation of 6-bromo-substituted **16** took thirteen steps.[13] With the asymmetric C–H alkenylation of THCs in hand, the C10 stereocenter can be introduced at a late stage of the synthesis of **16** by modifying the olefin in **4a** through a three-step process consisting of diastereoselective dihydroxylation, hydrogenation, and cyclization. The concise synthetic strategy in combination with the diverse range of easily accessible



Scheme 5. Synthetic utility.

vinyl THCs would allow for efficient structure–activity relationship studies of a series of natural products. Manipulations of the unsaturation in the tetrahydropyridines allow to access optically pure 2,4-*trans*-disubstituted piperidine **17** by a simple hydrogenation.

In summary, we have developed the first organocatalytic enantioselective oxidative C–H alkenylation and arylation of *N*-carbamoyl tetrahydropyridines and THCs with a wide range of boronates. The metal-free reaction proceeds with excellent regio- and enantioselectivity and is applicable to structurally and electronically diverse tetrahydropyridines and THCs with broad synthetic utility. Mechanistic studies indicated the intermediacy of a reactive dioxaborolane and elucidated the roles of the CF_3CH_2OH additive in the C–H oxidation and nucleophilic addition processes.

Keywords: asymmetric organocatalysis · carbamates · C–H functionalization · tetrahydropyridines · tetrahydro-β-carbolines

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[12] ^{1}H NMR analysis of complex **7** showed that the methine protons in **L9**, doublets at $\delta = 4.82$ and 4.87 ppm, shifted downfield to $\delta =$ 5.25 and 5.34 ppm. ESI-MS analysis of the complex detected the carboxylate anion of **7** (m/z calcd for $C_{20}H_{27}BNO_5$: 372.20 $[M-H^+]$; found: 372.20).

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