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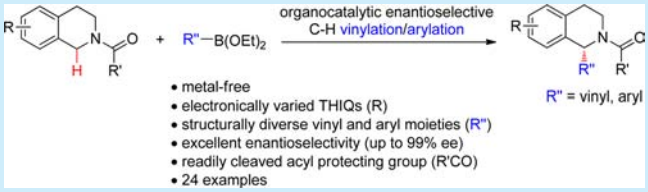
Organocatalytic Asymmetric C−H Vinylation and Arylation of *N*-Acyl Tetrahydroisoquinolines

Xigong Liu, Shutao Sun, Zhilin Meng, Hongxiang Lou, and Lei Liu*

Key Lab of Chemical Biology of Ministry of Education, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, China

Supporting Information

ABSTRACT: The first organocatalytic enantioselective oxidative C−H functionalization of *N*-acyl tetrahydroisoquinolines with vinyl and aryl boronates promoted by a chiral Brønsted acid is described. This metal-free process tolerates a wide range of electronically varied *N*-acyl tetrahydroisoquinolines and structurally diverse boronates with good to excellent enantioselectivities.



C1-Arylethyl and -aryl substituted tetrahydroisoquinolines (THIQs) are commonly encountered in a wide assortment of biologically active natural products and synthetic pharmaceuticals (Figure 1).[1] The enantioselective addition of carbon

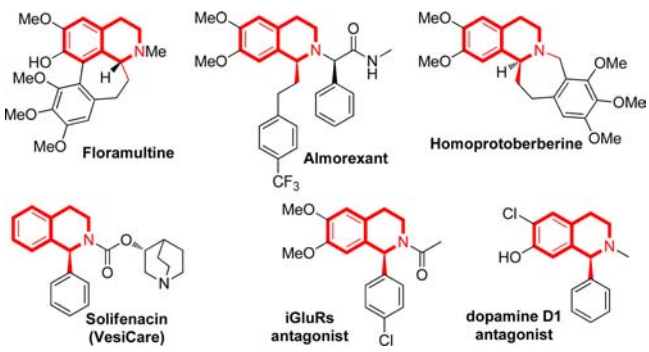


Figure 1. Representative C1-arylethyl and -aryl THIQs.

nucleophiles to THIQ-based imines and iminiums has been identified as an efficient strategy to prepare such enantiopure scaffolds.[2−5] However, the overwhelming majority of existing methods rely heavily on the employment of metals. For example, Seto et al. disclosed their pioneering studies on the highly enantioselective vinylation and arylation of dihydroisoquinoline *N*-oxide.[4] However, stoichiometric organozinc reagents and chiral catalysts were required for the high enantiocontrol. Moreover, unproductive steps were required for the preparation of *N*-oxide precursors.

Recently, the direct enantioselective C−H functionalization of THIQs emerged as an attractive alternative without prior installation of functional groups.[6] Several elegant catalytic asymmetric methods have been developed for the reaction of *N*-aryl THIQs, though the majority of them relied on the employment of metal catalysts.[7,8] However, the direct C−H alkynylation and arylation were not well explored, with limited substrate scope and unsatisfactory enantioselectivity.[3e,8g] Moreover, employing the aryl moiety as the activating and protecting group for THIQs proves to be a problem because the aryl group is not easily cleaved.[9] Using an easily removable acyl group as the protecting group instead of the aryl one would provide an attractive solution for this problem.[10] However, the asymmetric oxidative C−H functionalization of *N*-acyl THIQs remains relatively unexplored probably due to the compromised reactivity of the substrate and stability of the acyliminium electrophile. Sodeoka described the first catalytic enantioselective example involving the cross-dehydrogenative coupling (CDC) of *N*-Boc THIQs with malonates promoted by a chiral palladium complex with up to 86% ee.[11] However, this method is only effective for dimethoxy substituted electron-rich THIQs. Recently, we reported a catalytic asymmetric CDC of electronically varied *N*-Cbz THIQs with a wide range of terminal alkynes.[8h,i] However, metals including CuBr and stoichiometric $Yb(OTf)_3$ were required for the reaction.

Biphenol-catalyzed asymmetric boronate additions represent practical and efficient alternatives to metal-catalyzed reactions.[12] Schaus and co-workers developed an organocatalytic system mediated by tartaric acid derived diols, allowing the enantioselective alkenylation and arylation of chromene acetals, and the asymmetric vinylation of *N*-acyl quinoliniums.[13] Herein, we describe the first organocatalytic enantioselective C−H functionalization of *N*-acyl THIQs with a variety of vinyl and aryl boronates.

Initially, the oxidative C−H functionalization of *N*-Boc THIQ **1** with styrenyl boronate **2a** was selected as the model reaction for optimization (Table 1). While biphenol **L1** did not promote the reaction, tartaric acid (**L2**) catalyzed the coupling giving **3a** in 20% ee (Table 1, entries 1 and 2). Then, several tartaric acid derived amides were examined, and the steric effect on the amide proved to be crucial to the enantioselectivity, with the *N*,*N*-diisobutyl **L6** being the best catalyst (Table 1, entries 3−6). The enantioselectivity was found to be highly dependent on the solvent choice, and CF_3CH_2OH afforded the best

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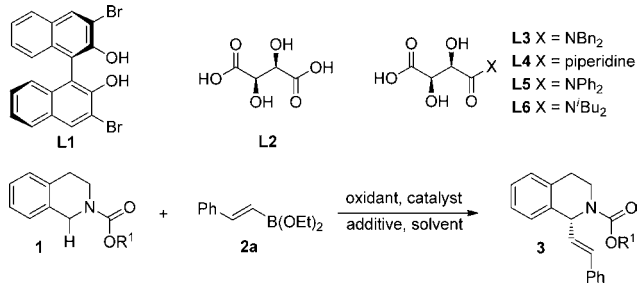
Table 1. Reaction Condition Optimization[a]



entry	L	solvent	additive	yield (%)[b]	ee (%)[c]
1	**L1**	CH_2Cl_2	–	<5	n.d.
2	**L2**	CH_2Cl_2	–	28	20
3	**L3**	CH_2Cl_2	–	30	45
4	**L4**	CH_2Cl_2	–	26	41
5	**L5**	CH_2Cl_2	–	28	43
6	**L6**	CH_2Cl_2	–	35	49
7	**L6**	$PhCF_3$	–	45	63
8	**L6**	CF_3CH_2OH	–	61	73
9	**L6**	CF_3CH_2OH	CCl_3CH_2OH	67	89
10[d]	**L6**	CF_3CH_2OH	CCl_3CH_2OH	66	95
11[d,e]	**L6**	CF_3CH_2OH	CCl_3CH_2OH	70	57
12[d,f]	**L6**	CF_3CH_2OH	CCl_3CH_2OH	68	76

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), DDQ (0.1 mmol), catalyst (0.015 mmol), additive (1.0 mmol) in solvent (2.0 mL) at 0 °C for 48 h, unless otherwise specified. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Reaction at −20 °C. [e]R^1 = Me. [f]R^1 = Bn. n.d. = not determined.

enantiocontrol (Table 1, entries 6−8). Introducing CCl_3CH_2OH (10 equiv) as an additive was beneficial for the reaction efficiency, and 95% ee was observed when the reaction was performed at −20 °C (Table 1, entries 9 and 10). Optimization of the carbamate protecting group identified the Boc moiety to be optimal (entries 11 and 12).

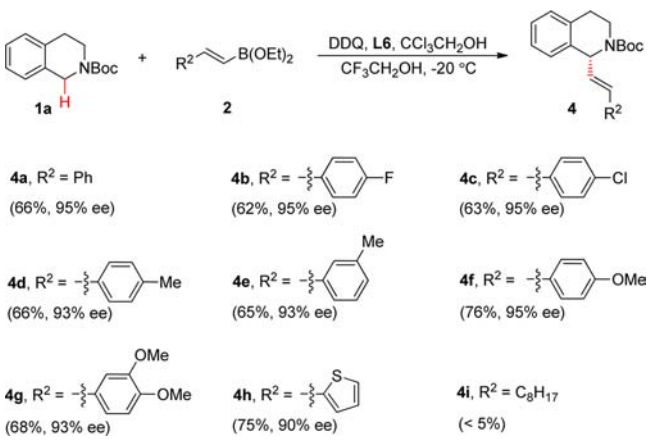
With the optimized conditions in hand, the boronate scope was investigated (Scheme 1). A broad range of styrenyl boronates bearing both electron-withdrawing and -donating functional groups with different substitution patterns participated in the organocatalytic enantioselective oxidative C−H functionalization of **1a** smoothly, affording desired products **4a**−**4g** with excellent enantioselectivities (93−95% ee). Heteroaryl vinyl boronate (**2h**) was well tolerated in 90% ee. Alkyl boronate (**2i**) was not a suitable component.

The scope of *N*-Boc THIQs was next explored (Scheme 2). *N*-Heterocycles with electron-donating substituents were well tolerated (**6a**−**6c**). Substrates bearing electron-withdrawing moieties were then systematically studied given that these substrates were not tolerated with Sodeoka's method.[11] To our delight, a variety of electron-deficient substrates were also well tolerated in modest yields and excellent ee (**6d**−**6l**). The compatibility of chloro- and bromo-substituents (**6d**−**6l**) with the method would be useful for facile product diversification.

Next, we explored the enantioselective C−H arylation process (Scheme 3). Extensive optimization experiments revealed that the C−H arylation reaction was much more difficult than the vinylation, and reaction of *N*-Cbz THIQs **7** with aryl boronate **8** in the presence of *N,N*-diphenyl **L5** together with DDQ at 70 °C was identified as optimal. With respect to the electron-neutral *N*-Cbz THIQ, electron-rich aryl boronates were suitable components, affording aryl substituted THIQs **9a**−**9c** with 74−82% ee. No reactivity was observed for electron-neutral phenyl boronate **8d**. The electronic substituent effect on the THIQs was also examined. While no reactivity was observed for electron-rich substrates, the arylation of an electron-deficient one proceeded smoothly, giving **9f** in 61% yield with 73% ee. The Cbz group can be readily removed through the hydrogenation process without the loss of enantiomeric excess (see the Supporting Information for the absolute configuration assignment).

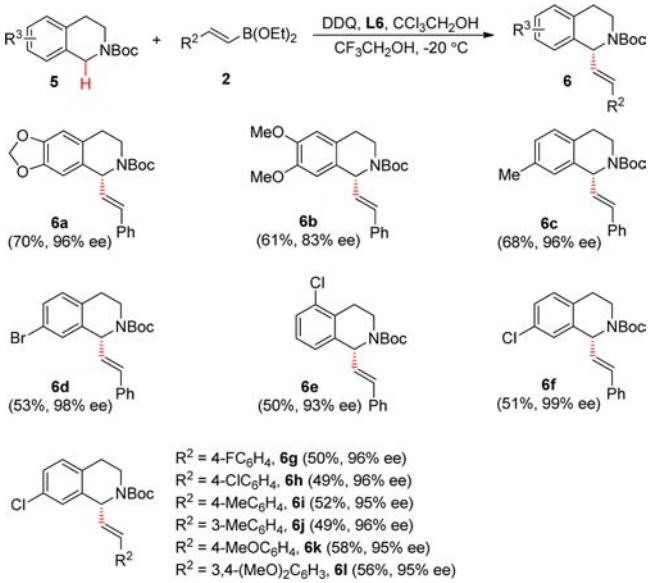
Control experiments were performed to explore the roles of CF_3CH_2OH and CCl_3CH_2OH by exposing **1a**, **11a**, and **11b** to the standard conditions, respectively (Scheme 4, eqs 1−3). Reactions in CF_3CH_2OH afforded comparable results. However, obvious differences in reactivity and selectivity were observed for **1a** and **11** in CH_2Cl_2, suggesting that **11** should be

Scheme 1. Scope of the Vinyl Boronates[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), DDQ (0.1 mmol), **L6** (0.015 mmol), and CCl_3CH_2OH (1.0 mmol) in 2.0 mL of CF_3CH_2OH at −20 °C for 48 h.

Scheme 2. Scope of *N*-Boc THIQs[a]



[a]Reaction conditions: **5** (0.1 mmol), **2** (0.2 mmol), DDQ (0.1 mmol), **L6** (0.015 mmol), and CCl_3CH_2OH (1.0 mmol) in 2.0 mL of CF_3CH_2OH at −20 °C for 48 h.

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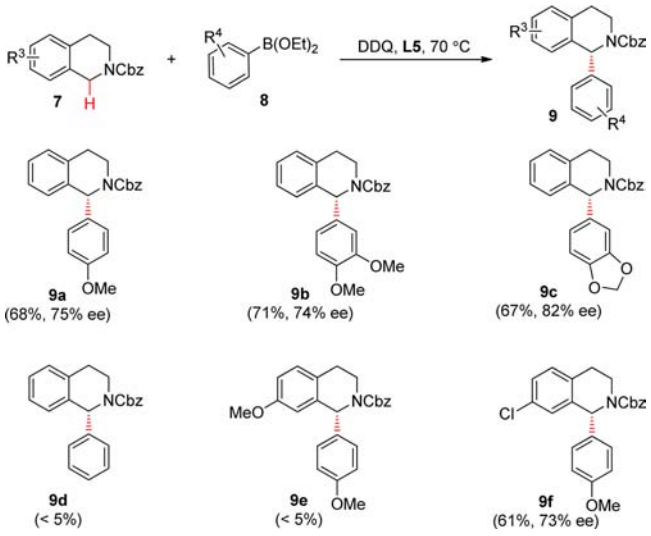
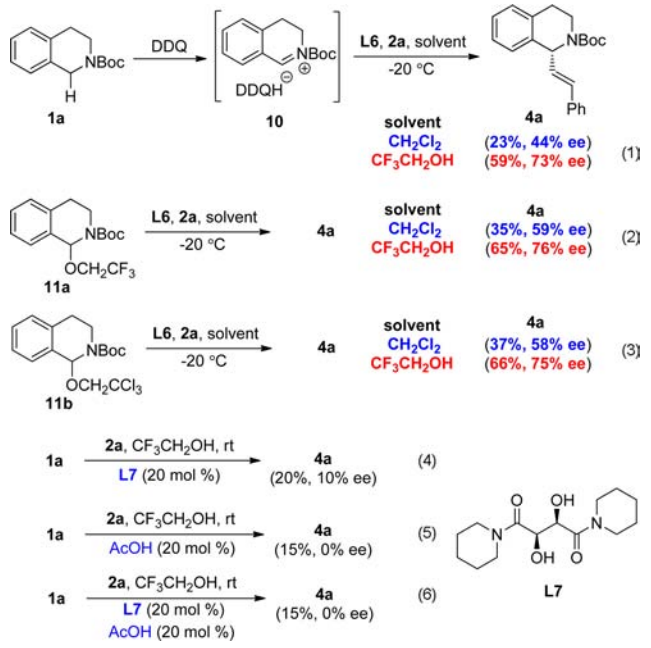
Scheme 3. C−H Arylation of *N*-Cbz THIQs[a]



[a]Reaction conditions: **7** (0.1 mmol), **8** (0.2 mmol), DDQ (0.1 mmol), and **L5** (0.015 mmol) at 70 °C for 48 h.

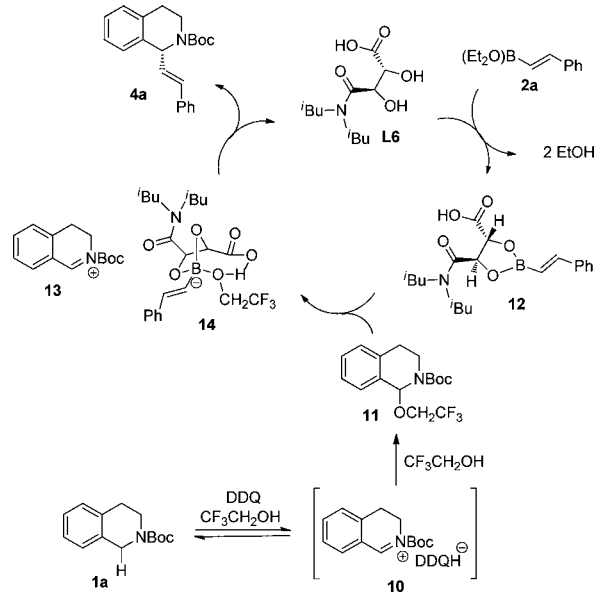
Scheme 4. Control Experiments



involved in the catalytic process. Another group of control experiments involving diamide catalyst **L7** or AcOH was next conducted (Scheme 4, eqs 4−6). For all of these reactions, substrate **1a** was completely consumed with comparable but significantly decreased yields and ee, suggesting the carboxylic acid moiety in the **L6** is crucial to the reaction efficiency and enantiocontrol.[14]

A plausible catalytic cycle is proposed in Scheme 5. Acidic CF_3CH_2OH might activate DDQ to promote the C−H oxidation of *N*-Boc THIQ **1a** generating acyliminium **10**, which is then captured by the solvent to give *N*-acyl hemiaminal **11**. According to the work from the Schaus and our groups, catalyst **L6** reacts with boronate **2a**, affording a reactive dioxaborolane complex **12**.[8h,13] The carboxylic acid moiety in **12** promotes the collapse of **11** to give acyliminium

Scheme 5. Proposed Catalytic Cycle



13 concomitant with the generation of "ate" complex **14**. The "ate" complex was activated by the CF_3CH_2O anion to promote the addition of the vinyl group to the acyliminium **13** affording **4a** together with the catalyst **L6** released for re-entry into the catalytic cycle. According to the observations in Scheme 4, the carboxylic acid moiety might be helpful in fixing the conformation of **14** in the nucleophilic addition step.[14]

In conclusion, the first organocatalytic asymmetric C−H functionalization of *N*-carbamoyl THIQs with a variety of vinyl and aryl boronates has been developed. A broad range of structurally and electronically diverse THIQs were well tolerated with this metal-free process. The *N*-carbamoyl protecting group can be easily cleaved under mild conditions, affording corresponding enantiopure secondary amines in high efficiency.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00909.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: leiliu@sdu.edu.cn.

Notes

The authors declare no competing financial interest.

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