



Cite this: *RSC Adv.*, 2025, 15, 33586

Chiral binaphthol-catalyzed enantioselective conjugate addition of alkenyl trifluoroborate salts to alkenyl-substituted benzothiazoles

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Received 20th August 2025
Accepted 8th September 2025

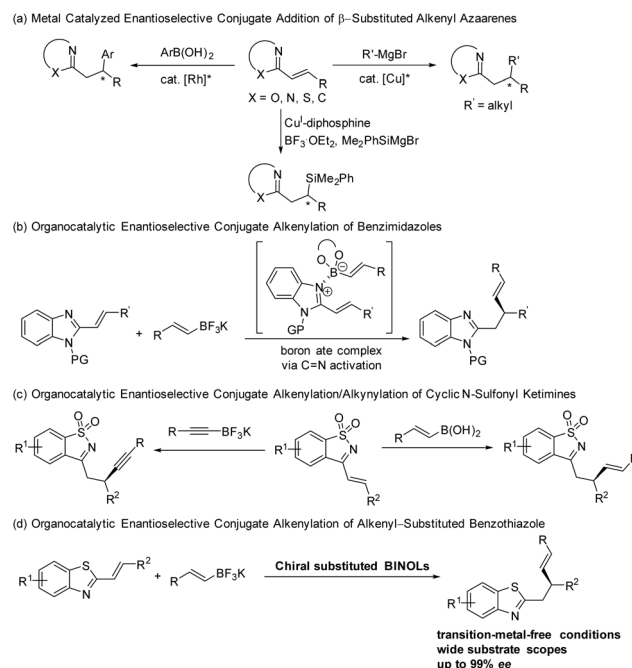
DOI: 10.1039/d5ra06155e

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The chiral binaphthol-catalyzed enantioselective conjugate addition of alkenyl trifluoroborate salts to alkenyl-substituted benzothiazoles is reported, providing the 1,4-addition products in moderate to high yields and excellent enantioselectivities (up to >99% ee). This scalable catalytic system exhibits high efficiency and broad substrate scopes. Additionally, alkenyl-substituted benzoxazole was also compatible with standard conditions.

Benzothiazoles, a class of important nitrogen- and sulfur-containing heterocycles, play an essential role in pharmaceutical ingredients and natural products, and their analogs offer a high degree of structural diversity that has proven useful in the search for new therapeutic agents.¹ The development of a synthetic method to efficiently access functionalized benzothiazoles and their derivatives has attracted much attention from organic synthetic chemists. The asymmetric conjugate addition of nucleophiles to β -substituted alkenyl azaarenes has been extensively studied.^{2–4} In 2010 and 2014, Lam described highly enantioselective Rh-catalyzed addition of arylboronic acids to β -monosubstituted alkenylheteroarenes (Scheme 1a, left).⁵ In 2016, Harutyunyan reported the Cu-catalyzed enantio- and chemo-selective alkylation of Grignard reagents to alkenyl-substituted aromatic N-heterocycles (Scheme 1a, right).⁶ In 2019, Oestreich reported the Cu-catalyzed regio- and enantioselective addition of silicon Grignard reagents to alkenes activated by azaaryl groups (Scheme 1a, bottom).⁷ Several research groups have reported organocatalyzed enantioselective conjugate addition of organic boron compounds to α,β -unsaturated carbonyl compounds,⁸ including the notable contributions from May,⁹ Chong,¹⁰ Schaus,¹¹ Sugiura,¹² Mao,¹³ and our own group.¹⁴ In 2022, Mao and Yu disclosed organocatalytic enantioselective conjugate addition of potassium alkenyltrifluoroborates to β -substituted alkenyl benzimidazoles (Scheme 1b).^{13a} Recently, our group reported the chiral binaphthol-catalyzed enantioselective conjugate addition of alkenylboronic acids, heteroarylboronic acids, and alkynyl trifluoroborates to cyclic N-sulfonyl ketimines derived from saccharin (Scheme 1c).¹⁵ The scarcity of methodologies for catalytic enantioselective nucleophilic addition to β -substituted alkenyl-

heterocycles stems from their intrinsically low reactivity,¹⁶ probably due to the relatively weak activation from the hetero-aromatic moiety. The Rh-catalyzed asymmetric additions of alkenylboron reagents to aldimines has been reported by the groups of Lam, Ellman, and Xu.¹⁷ However, the organocatalyzed enantioselective alkenylation of alkenyl-substituted benzothiazoles to afford functionalized β -alkenyl substituted chiral benzothiazoles with high optical purities remains underexplored. A general, environmentally benign, and efficient catalytic system for such 1,4-additions is still highly desirable.



Scheme 1 (a–d) Asymmetric conjugate addition to alkenyl azaarenes.

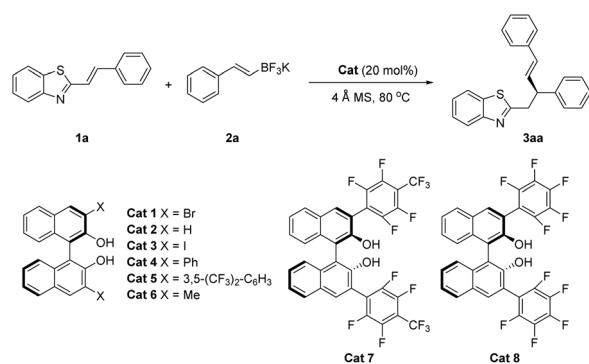
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Inspired by our previous work on chiral diol-catalyzed conjugate addition of organic boronic compounds to α,β -unsaturated imines,¹⁵ we envisioned that a related strategy could be extended to the enantioselective conjugate addition of alkenyl trifluoroborate salts to alkenyl-substituted benzothiazoles. Herein, we describe a general and highly efficient enantioselective conjugate addition of alkenyl trifluoroborate salts to benzothiazole derivatives catalyzed by chiral 3,3'-disubstituted BINOLs to access a diverse range of enantio-enriched β -alkenyl-substituted benzothiazole scaffolds with excellent stereocontrol (Scheme 1d).

First, we used alkenyl-substituted benzothiazole **1a** and *trans*-styryl-based trifluoroborate (**2a**) as model substrates to optimize the reaction conditions (Table 1). The initial experiment was conducted with 20 mol% (*R*)-3,3'-Br₂-BINOL (**Cat 1**) as the catalyst and 4 Å molecular sieves (MS) as additives in dry toluene at 80 °C, which delivered the expected 1,4-adduct **3aa** in 47% yield with 99% ee (entry 1). Next, screening various 3,3'-disubstituted (*R*)-binaphthol catalysts **Cat 2–Cat 8** with different electronic and steric properties demonstrated that the substituent on the phenyl moiety plays a crucial role in catalytic activity (entries 2–8). Commercially available **Cat 5** with electron-withdrawing and bulky groups resulted in 85% yield with >99% ee (entry 5). Subsequent investigations of solvents including benzotrifluoride (PhCF₃), *o*-xylene, *m*-xylene, chlorobenzene (PhCl), DCE, *tert*-butyl methyl ether (MTBE), THF, dioxane, and acetonitrile (MeCN) indicated that *m*-xylene was the optimal choice in terms of increased reactivity and a higher yield with excellent enantioselectivity (entry 11 vs. entries 9–17). When the temperature was increased to 100 °C with a reduced reaction time of 48 h, product **3aa** was obtained in a increased isolated yield (92% yield), while the excellent ee value was maintained (entry 18 vs. entry 11). In addition, reducing the temperature to 60 °C afforded **3aa** in a decreased isolated yield with >99% ee (entry 19 vs. entry 11). It should be noted that no reaction occurred in the absence of molecular sieves (MS) (entry 20), indicating that MS was essential to the success of the asymmetric conjugate addition. When (*E*)-styrylboronic acid was utilized in the reaction, the desired product **3aa** was obtained in 70% yield with >99% ee (entry 21). However, when the reaction was conducted with *trans*-2-phenylvinylboronic acid pinacol ester, no desired product was observed, and all substrates remained intact (entry 22). Furthermore, lowering the catalyst loading to 10 mol% with a prolonged reaction time of 72 h provided the products in 70% yield with good enantioselectivity (>99% ee) (entry 23). Thus, the optimal reaction conditions were identified as outlined in entry 18.

With the standard reaction conditions in hand, we then investigated the alkenyl-substituted benzothiazole substrate scope. As summarized in Scheme 2, the type of substituents on the phenyl moiety, including Me, OMe, F, Cl, Br, and CF₃ in *ortho*, *para*, or *meta* positions, had little impact on the reaction outcome, as moderate to high yields and excellent enantiomeric purities were attained for product **3ba–3ka**. The ring-fused 2-naphthyl and 1-naphthyl substituted benzothiazoles **1l** and **1m** were also well tolerated, giving the corresponding products **3la** and **3ma** in good yields (61–62%) and excellent ee values (98–

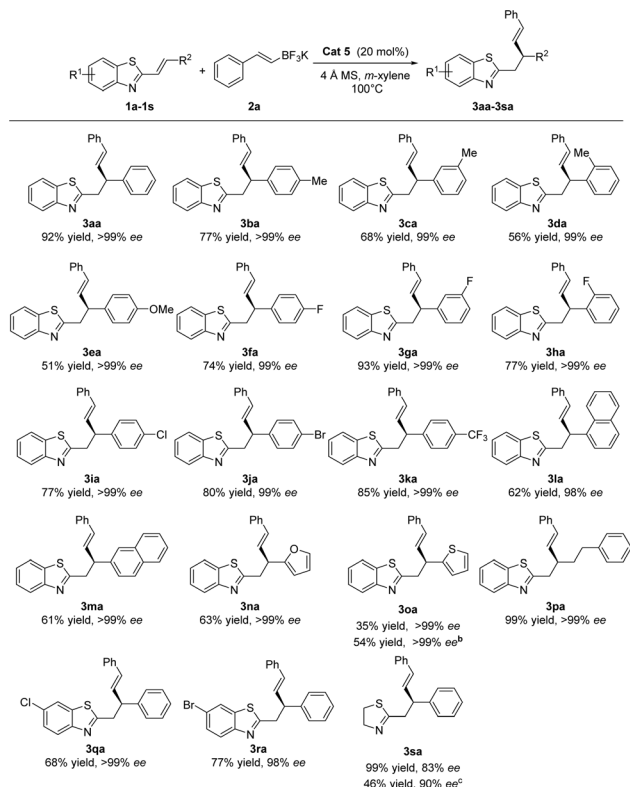
Table 1 Optimization of reaction conditions^a


Entry	Cat	Solvent	Time (h)	Yield ^b (%)	ee ^c (%)
1	Cat 1	Toluene	72	47	99
2	Cat 2	Toluene	72	Trace	—
3	Cat 3	Toluene	72	58	99
4	Cat 4	Toluene	72	Trace	—
5	Cat 5	Toluene	72	85	>99
6	Cat 6	Toluene	72	24	97
7	Cat 7	Toluene	72	36	99
8	Cat 8	Toluene	72	12	99
9	Cat 5	PhCF ₃	72	80	>99
10	Cat 5	<i>o</i> -Xylene	72	82	>99
11	Cat 5	<i>m</i> -Xylene	72	87	>99
12	Cat 5	PhCl	72	68	>99
13	Cat 5	DCE	72	14	>99
14	Cat 5	MTBE	72	83	99
15	Cat 5	THF	72	Trace	—
16	Cat 5	Dioxane	72	35	90
17	Cat 5	MeCN	72	61	82
18 ^d	Cat 5	<i>m</i> -Xylene	48	92	>99
19 ^e	Cat 5	<i>m</i> -Xylene	72	80	>99
20 ^{d,f}	Cat 5	<i>m</i> -Xylene	48	N.R.	—
21 ^{d,g}	Cat 5	<i>m</i> -Xylene	72	70	>99
22 ^{d,h}	Cat 5	<i>m</i> -Xylene	48	N.R.	—
23 ^{d,i}	Cat 5	<i>m</i> -Xylene	72	40	>99

^a Unless otherwise noted, all reactions were carried out with alkenyl-substituted benzothiazole **1a** (0.1 mmol, 1.0 equiv.), (*E*)-styryl trifluoroborate **2a** (0.2 mmol, 2.0 equiv.), catalyst (0.02 mmol, 20 mol%), 4 Å MS (100 mg), and 1.0 mL of dry solvent under N₂ at 80 °C. ^b Isolated yield. ^c The ee values were determined by chiral HPLC analysis. ^d At 100 °C. ^e At 60 °C. ^f Without 4 Å MS. ^g (*E*)-Styrylboronic acid (0.2 mmol, 2.0 equiv.) instead of (*E*)-styryl trifluoroborate **2a**. ^h *Trans*-2-phenylvinylboronic acid pinacol ester (0.2 mmol, 2.0 equiv.) instead of (*E*)-styryl trifluoroborate **2a**. ⁱ With **Cat 5** (10 mol%, 0.01 mmol). N.R. = no reaction.

99%). In addition, the heteroaromatic substituted benzothiazoles **1n** and **1o** were also applicable to deliver products **3na** and **3oa** in a moderate yields with >99% ee. Altering R¹ from aryls to alkyls was also carried out, and product **3pa** was obtained in quantitative yields with >99% ee. Furthermore, the protocol was also tolerant of monosubstitution at the benzothiazole moiety, providing the expected products **3qa** and **3ra** in good yields with excellent ee values. When the alkenylation of alkenylthiazoline **1s** was investigated, the corresponding adduct **3sa** was isolated in 99% yield with 83% ee under standard reaction conditions. Notably, product **3sa** was isolated in 46% yield with 90% ee at

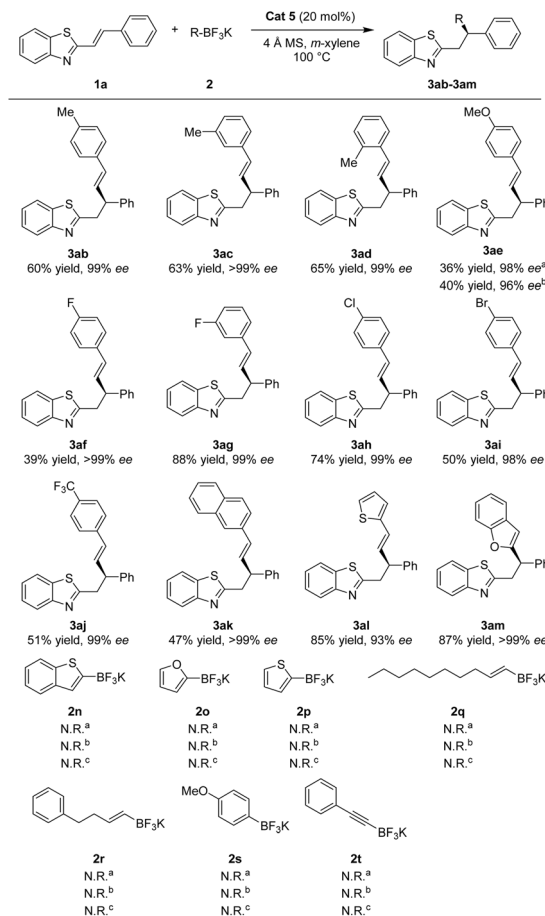




Scheme 2 Substrate scope of alkenyl-substituted benzothiazoles. ^a Reaction conditions: alkenyl-substituted benzothiazoles **1a–1p** (0.1 mmol), (*E*)-styryl trifluoroborate **2a** (0.2 mmol), **Cat 5** (0.02 mmol, 20 mol%), and 4 Å MS (100 mg) in 1.0 mL of dry *m*-xylene were stirred at 100 °C under N₂ for 48 h. Isolated yield. The ee values were determined by chiral HPLC analysis. ^b At 120 °C for 48 h. ^c At 80 °C for 48 h.

a slightly lower temperature (80 °C). The absolute configuration structure of products **3** was determined to be (*E,S*) by a comparison between the CD (circular dichroism) of **3aa** and its ECD (electrostatic circular dichroism) analysis (for details, see the SI).

We next investigated the substrate scope of alkenyltrifluoroborates (Scheme 3). Potassium alkenyl trifluoroborates bearing different substituents were demonstrated to be effective alkenyl viable nucleophiles. The introduction of electron-donating groups such as Me in *ortho*, *para*, or *meta* positions of the aromatic ring produced the corresponding products **3ab–3ad** in yields ranging from 60 to 65% yield and excellent ee values. The alkenyltrifluoroborate **1e** with OMe group in *para* position of the aromatic ring participated rather moderately at 100 °C or 145 °C, giving **3ae** in low yield but with high enantioselectivity. Varying halogens groups (F, Cl, and Br) on the phenyl ring of the alkenyl trifluoroborates gave adducts **3af–3ai** in 39–88% yield with enantioselectivities between 98% and >99%. It was found that a strong electron-withdrawing group (CF₃) was also tolerated to produce product **3aj** with moderate yield and good enantioselectivity. We were pleased to observe that 2-naphthalene and 2-thienyl substituted alkenyl nucleophiles provided the desired products **3ak** and **3al** in 47–85%



Scheme 3 Substrate scope of alkenyl trifluoroborates. ^a Reaction conditions: alkenyl-substituted benzothiazoles **1a** (0.1 mmol), trifluoroborates **2** (0.2 mmol), **Cat 5** (0.02 mmol, 20 mol%), 4 Å MS (100 mg), and dry *m*-xylene (1.0 mL) were stirred at 100 °C under N₂ for 48 h. Isolated yield. The ee values were determined by chiral HPLC analysis. ^b At 145 °C for 48 h. ^c With LiBr (3.0 equiv., 0.3 mmol). N.R. = no reaction.

yields with 93–99% ee. Meanwhile, benzofuran trifluoroborate salt **2m** was well tolerated, offering expected products **3am** in 87% yields with >99% ee. Unfortunately, unlike styryltrifluoroborate salts **2a–2l**, heteroaryltrifluoroborates **2n–2p**, alkyl trifluoroborate salts **2q** and **2r**, aryl trifluoroborate salt **2s**, and alkynyltrifluoroborate **2t** failed to deliver the corresponding products under the standard reaction conditions or forcing conditions at 145 °C, probably due to their poor nucleophilicity. Notably, when using 3.0 equivalent of LiBr as additives in these reactions, trifluoroborate **2n–2t** were also found to be unsuccessful nucleophiles.

On the basis of our previous work¹⁵ and other report,^{13a} a plausible mechanism is presented in Fig. 1. Initially, the difluoroborane **2a'** was formed through reversible fluoride dissociation of (*E*)-styryl trifluoroborate **2a**. Subsequent transesterification of **2a'** with **Cat 5** in the presence of 4 Å molecular sieves produces the more reactive binaphthol-derived alkenylboronate **A**. A zwitterionic boron complex **B** is then formed via the coordination of alkenylboronate **A** to the lone pair of the



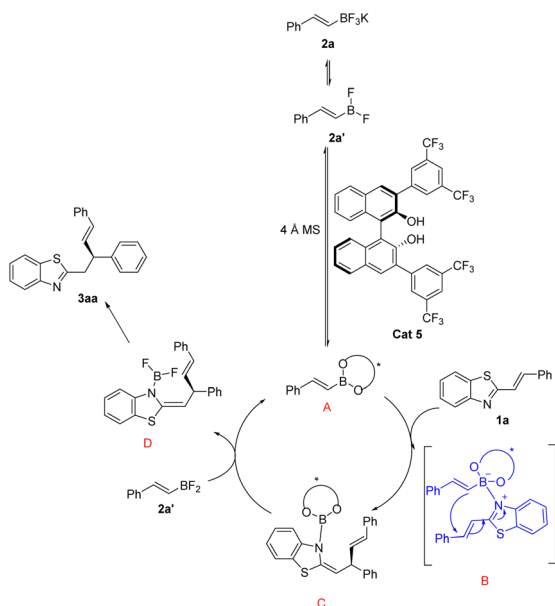


Fig. 1 Proposed reaction mechanism.

nitrogen of alkenyl-substituted benzothiazole **1a**. The formation of this complex **B** and the nature of the C_2 -symmetric BINOL create a chiral environment for the enantioselective 1,4-addition. Intramolecular C–C bond formation occurs in complex **B** to form boric amide ester **C**. Finally, the ligands exchange with alkenyldifluoroborate **2a'** followed by protonation of the generated difluoroboron amide **D** affords desired product **3aa**.

To confirm the scalability of the current protocol, a gram-scale reaction between alkenyl-substituted benzothiazole **1a**

and (*E*)-styryl trifluoroborate **2a** was performed, providing the corresponding product **3aa** in 83% yield (1.13 g) with 99% ee (Scheme 4a). The alkenyl moiety of **3aa** could be reduced *via* Pd-catalyzed hydrogenation process, affording product **4** in 99% yield without erasing the levels of enantioselectivity (Scheme 4b). Of particular note, alkenyl-substituted benzoxazole **5a** demonstrated excellent reactivity with potassium alkenyl trifluoroborates **2f** and **2g**, affording the corresponding products **6a** and **6b** in high yields (79% and 94%, respectively) with excellent enantioselectivities (>99% and 99% ee, respectively) (Scheme 4c).

Conclusions

In summary, we have developed an efficient enantioselective 1,4-conjugate addition reaction of potassium organotrifluoroborates to alkenyl-substituted benzothiazoles catalyzed by (*R*)-3,3'-(CF_3)₂C₆H₃-BINOL under mild reaction conditions. The corresponding 1,4-adducts were afforded in moderate to high yields with excellent ee values (up to >99% ee). Alkenyl-substituted benzoxazole was compatible, and gram-scale reaction was achieved without loss of enantioselectivity. Further investigations to extend the application of the resulting products are currently under investigation in our laboratories.

Author contributions

G.-L. Chai designed and directed the project, completed product characterizations, and wrote the manuscript. W.-Y. Huang and Y.-L. Wang performed the experiments. C.-G. Li performed some analysis of products. K. Zhong performed ECD analysis. G. Zhu and J. Chang supported the project, and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

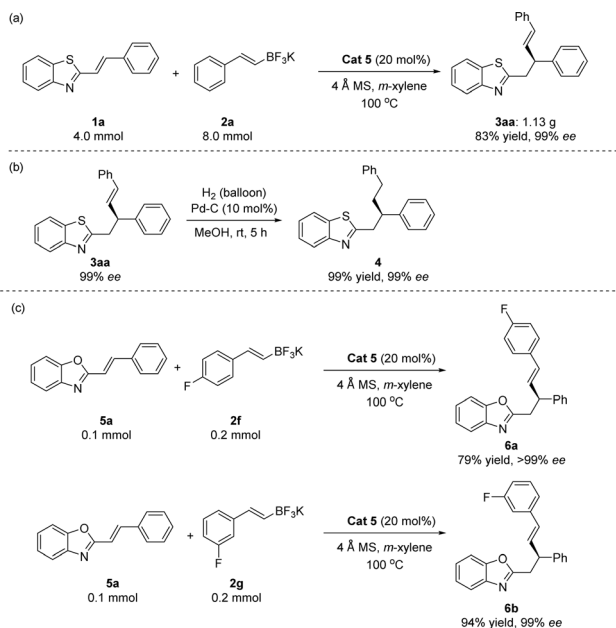
Data availability

The data supporting this article have been included as part of the SI.

Assignment of the absolute configuration of compound **3aa**, copies of 1H , $^{13}C\{^1H\}$, and $^{19}F\{^1H\}$ NMR spectra of all new compounds, chromatograms of racemic and optically active products (PDF). See DOI: <https://doi.org/10.1039/d5ra06155e>.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC) (Project No. 82130103), Key Scientific Research Projects of Colleges and Universities in Henan Province (No. 26A150021), the Natural Science Foundation of Henan Province (No. 252300421384), the Key Scientific and Technological Projects in Henan Province (No. 252102310419).



Scheme 4 Synthetic application. (a) Gram-scale reaction. (b) Further transformation of **3aa**. (c) Reaction with alkenyl-substituted benzoxazole.



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