Enantioselective Copper-Catalyzed Synthesis of Trifluoromethyl-Cyclopropylboronates

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ABSTRACT: A copper-catalyzed enantioselective cyclopropanation involving trifluorodiazoethane in the presence of alkenyl boronates has been developed. This transformation enables the preparation of 2-substituted-3-(trifluoromethyl)-cyclopropylboronates with high levels of stereocontrol. The products are valuable synthetic intermediates by transformation of the boronate group. This methodology can be applied to the synthesis of novel trifluoromethylated analogues of trans-2-arylcyclopropylamines, which are prevalent motifs in biologically active compounds.

Cyclopropanes are widespread carbocycles in bioactive natural and synthetic compounds. It is currently a standard fragment in drug discovery, which allows one to modulate properties such as lipophilicity, metabolic stability, pKa or binding, among others. Nowadays, it is present in numerous drugs, for example Ticagrelor, which is active against cardiovascular diseases, or Tezacaftor, which is used to treat cystic fibrosis.

Numerous methods have been described for the synthesis of substituted cyclopropanes. Among all the different possibilities, the preparation of cyclopropanes with fluorinated groups, in particular trifluoromethyl, is of special interest. This functional group is present in a vast number of therapeutic compounds. However, the enantioselective procedures for the preparation of trifluoromethylcyclopropanes are scarce in the literature. All the existing protocols, which are summarized in Scheme 1a, led to cyclopropanes with an unsubstituted carbon on the three-membered ring. For this reason, there is still a need to develop efficient enantioselective methodologies to prepare all-carbon-substituted trifluoromethylcyclopropanes.

On the other hand, the synthesis of versatile cyclopropanes, such as cyclopropylboronates, has also attracted the interest of the synthetic community. A boronate group can be easily transformed into a wide range of different functional groups. This allows the generation of compound libraries from a common structure. In this area, several strategies have been recently developed to prepare optically active cyclopropylboronates, including cyclopropanation of alkyl boronates with diazo compounds, borylative cyclization of allylic carbonates, phosphonates, or epoxides, hydroboration of cyclopro-
2 h (Table 1, entry 1). This point was crucial from a practical point of view, as cyclopropane 2a was not easily separable from the starting material by column chromatography. Further increases in the amount of the diazo compound (4 equiv) combined with a longer reaction time (6 h) raised the conversion to 90% (Table 1, entries 2–4). The relative configuration of cyclopropane 2a was determined by $^1$H NMR experiments (see the Supporting Information).

Gratifyingly, good results of diastereoenantiocontrol were obtained under these catalytic conditions (92:8 dr, 95:5 er). We examined different organic solvents such as THF or toluene (see SI). Toluene significantly reduced reactivity and diastereoselectivity, and THF led to no conversion of the olefin. Subsequently we investigated different co-merically available BOX ligands. Whereas the iPrBOX (L2) ligand decreased the conversion and stereocntrol of the reaction, PhBOX (L3) slightly improved the diastereoselectivity (entries 5–6). At this stage, concentration of trifluorodiazoethane was increased from ca. 0.5 to 1 M, con-ducting to complete conversion (entry 7). Furthermore, the amount of diazo compound could be reduced to 2 equiva-lents (entry 8).

Under the optimized conditions, using 5 mol % of [Cu(NCMe)$_4$]PF$_6$ and fBuBOX as the catalyst and 2 equiv of trifluorodiazoethane added during 6 h, 69% of cyclopropylboronate 2a was isolated, with high level of stereo-control (94:6 dr, 95:5 er). With the optimized conditions in hand, the scope of the cyclopropanation was examined (Scheme 2). The procedure was successful with a variety of (E)-alkenyl boronates, considering electron-withdrawing and electron-donating groups (alkyl, halogens, trifluoromethyl, ether and ester substituents) at different positions in the aromatic substituent of the olefin. Moderate to good yields were obtained for the entire series (40%–77%) and high stereoselectivity was also achieved, in terms of diastereoselectivity (up to 95:5) and enantioselectivity (up to 97:3). Notably, both parameters increase as the electron density of the aromatic ring decreases. A similar result was obtained with an electron-rich heterocycle such as thiophene (2l), with moderate enantioselectivity (90:10 er). Furthermore, an aliphatic-substituted cyclopropane (2m) was also accessible with moderate yield and levels of enantioinduction. In several substrates, an increase of the equivalents of trifluorodiazoethane was necessary to achieve complete conversion, whereas the reaction was suppressed in the presence of functional groups such as nitrile or nitro. The absolute configuration of the stereogenic centers of the cyclopropane were determined by single-crystal X-ray diffraction (XRD) analysis of 2-bromo and 2-methoxy derivatives 2i and 2l (Scheme 2).$^{15}$

As mentioned above, cyclopropylboronates are versatile intermediates in organic synthesis by the transformation of the C–B bond. To highlight the synthetic utility of the new compounds, we performed several transformations of the pinacol boronate group, following reported methodologies (Scheme 3). Boronic acid 3 was smoothly obtained by treatment with methylboronic acid.$^{20}$ Standard conditions of Suzuki–Miyaura cross-coupling led to 3-trifluoromethyl-1,2-diarylsubstituted cyclopropane 4 in good yield. Furthermore, oxidation of the boronate group could be achieved under basic conditions to get alcohol 5.$^{10}$ Finally, amination of the cyclopropylboronate was accomplished by using BCl$_3$ and BnN$_3$ to get the benzylamine derivative in good yield (6).$^{21}$ The latter transformations gave access to substituted trans-2-trifluoromethylcyclopropan-1-amine and trans-2-trifluoromethylcyclopropanol, rarely described in the literature in an enantioselective manner.$^{12}$

Then, we focused our interest in amine derivative 6, as a trifluoromethylated analogue of trans-2-arylcylopropylamines. This scaffold is common to numerous biological active
compounds\textsuperscript{23} and is present in drugs such as Tranylcypromine (an antidepressant), Ticagrelor (a platelet aggregation inhibitor), or candidates under clinical trials for the treatment of cancer and neurodegenerative diseases.\textsuperscript{23,24} Because of the implication of F atoms in the properties of bioactive compounds,\textsuperscript{25} we targeted the enantioselective synthesis of a CF\textsubscript{3} analogue of a lysine-specific demethylase 1 (LSD1) inhibitor (Scheme 4). The amination of cyclopropylboronate 2a with 3-(azidomethyl)-2-methoxypyridine (7) allowed us to obtain the trifluoromethyl analogue 8 of LSD1 inhibitor in a good yield.

**Scheme 2. Substrate Scope of Copper-Catalyzed Cyclopropanation of Alkenyl Boronates\textsuperscript{4}**

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| Reaction conditions: | [Cu(NCMe)\textsubscript{4}]PF\textsubscript{6} (0.03 mmol, 5 mol \%), (S,S)-L3 (0.03 mmol, 5 mol \%), DCE (1.5 mL), inert atmosphere trifluorodiazoothane in DCE (2 equiv), 6 h slow addition. Isolated yields. | 76% at 1.25 mmol scale. |
|----------------------|---------------------------------------------------------------------------------|------------------------|
| a                    | 1 (0.61 mmol), [Cu(NCMe)\textsubscript{4}]PF\textsubscript{6} (0.03 mmol, 5 mol \%), (S,S)-L3 (0.03 mmol, 5 mol \%), DCE (1.5 mL), inert atmosphere trifluorodiazoothane in DCE (2 equiv), 6 h slow addition. Isolated yields. | 76% at 1.25 mmol scale. |
| b                    | Trifluorodiazoothane (6 equiv). |
| c                    | Trifluorodiazoothane (4 equiv). |
| d                    | Thermal ellipsoids are drawn at the 50% probability level. |
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**Scheme 3. Transformations of Cyclopropylboronate Ester**

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| Reaction conditions: | (a) MeB(OH)\textsubscript{2} (5 equiv), TFA (5\%)/DCM, 8 h, 72\%. | 62% |
|----------------------|-----------------------------------------------------------------|------|
| a                    | 1 (5 equiv), TFA (5\%)/DCM, 8 h, 72\%. | 62% |
| b                    | 4-iodoanisole (1.5 equiv), Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3} (10 mol \%), PPh\textsubscript{3} (1 equiv), Ag\textsubscript{2}O (1.5 equiv), THF, 70 °C, 24 h, 45\%. | 50% |
| c                    | 3 M NaOH 30\% H\textsubscript{2}O\textsubscript{2}, THF, 30 min, 68\%. | 50% |
| d                    | BCl\textsubscript{3} (5.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 1.5 h), then BnN\textsubscript{3} (3.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, from 0 to 25 °C, 2 h), 51\%. | 51% |
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**Scheme 4. Preparation of a Trifluoromethyl Analogue of LSD1 Inhibitor**

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| Reaction conditions: | (a) BCl\textsubscript{3} (5.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 1.5 h), then BnN\textsubscript{3} (3.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, from 0 to 25 °C, 2 h), 51\%. | 55% |
|----------------------|-----------------------------------------------------------------|------|
| a                    | BCl\textsubscript{3} (5.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 1.5 h), then BnN\textsubscript{3} (3.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, from 0 to 25 °C, 2 h), 51\%. | 55% |
| b                    | BnN\textsubscript{3} (3.0 equiv, CH\textsubscript{2}Cl\textsubscript{2}, from 0 to 25 °C, 2 h), 51\%. | 51% |
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In summary, we have developed a catalytic approach for the preparation of enantiomerically enriched 2-substituted-3-(trifluoromethyl)cyclopropylboronates by cyclopropanation of (E)-alkenyl boronates with trifluorodiazoothane. This methodology is general for a variety of substrates, using commercially available copper catalyst and ligand. Valuable synthetic intermediates can be obtained by the functionalization of the C–B bond. This route provides straightforward access to enantioenriched 2-aryl-3-(trifluoromethyl)-cyclopropylamines, a relevant scaffold in medicinal chemistry.
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02420.

Experimental procedures; characterization data; 1H, 13C, 11B and 19F NMR spectral data; HPLC; mass spectrometry data of new compounds and X-ray crystallographic data for 2i and 2l (PDF)

Accession Codes

CCDC 2079480 and 2079481 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 1 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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In the future, this research may be extended to the synthesis of other functionalized cyclopropanes, possibly with applications in drug discovery and materials science.

(23) This paper provides a detailed protocol for the synthesis of 1,2,3-trisubstituted cyclopropanes using gem-dizinc reagents, highlighting the versatility of this methodology in the construction of complex organic scaffolds.

(24) The authors have synthesized a variety of functionalized cyclopropanes, demonstrating the utility of their protocol for the synthesis of diverse and functionalized cyclopropane derivatives.

(25) Although the focus of this paper is on the synthesis of cyclopropanes, the methodologies described could be extended to the synthesis of other challenging carbon frameworks, offering new possibilities for the construction of complex organic molecules.