Enantioselective copper-catalyzed synthesis of trifluoromethyl-cyclopropylboronates

Julia Altarejos, David Sucunza, Juan J. Vaquero, Javier Carreras*

Universidad de Alcalá, Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química Andrés Manuel del Río (IQAR), Alcalá de Henares 28805, Spain; Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid 28034, Spain; E-mail: javier.carreras@uah.es

up to 95:5 dr, 97:3 er
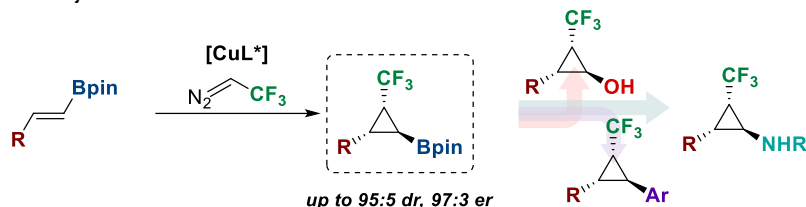
ABSTRACT: A copper-catalyzed enantioselective cyclopropanation involving trifluorodiazoethane in the presence of alkenyl boronates has been developed. This transformation enables the preparation of 2-substituted-3-(trifluoromethyl)cyclopropylboronates with high levels of stereocontrol. The products are valuable synthetic intermedi-ates by transformation of the boronate group. This methodology can be applied to the synthesis of novel trifluoromethyl-ated analogues of trans-2-arylcyclopropylamines, which are prevalent motifs in biologically active compounds.

Cyclopropanes are widespread carbocycles in bioactive natural and synthetic compounds.[1] It is currently a standard fragment in drug discovery, which allows to modulate properties such as lipophilicity, metabolic stability, pK_a or binding, among others.[2] Nowadays, it is present in numerous drugs, for example *Ticagrelor*,[3] active against cardiovascular diseases, or *Tezacaftor*,[4] to treat cystic fibrosis.

Numerous methods have been described for the synthesis of substituted cyclopropanes.[5] Among all the different possibilities, the preparation of cyclopropanes with fluorinated groups, in particular trifluoromethyl, is of special interest.[6] This functional group is present in a vast number of therapeutic compounds.[7] However, the enantioselective procedures for the preparation of trifluoromethylcyclopropanes are scarce in the literature.[8] 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.[9] A boronate group can be easily transformed into a wide range of different functional groups.[10] 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 alkenyl boronates with diazo compounds,[11] borylative cyclization of allylic carbonates, phosphonates,[12] or epoxides,[13] hydroboration of cyclopropenes,[14] zinco-cyclopropanation of allylic alcohols[15] and C-H borylation.[16]

In this context, we focused our attention on the enantioselective preparation of cyclopropanes that include simultaneously a trifluoromethyl group and a pinacol boronate as substituents. These versatile compounds would give access to a wide range of trifluoromethyl-cyclopropane derivatives. In the literature, there are only three examples of this type of compounds, all of them obtained as racemates from monosubstituted vinyl boron derivatives (Scheme 1b).[17]

Herein, we report the enantioselective cyclopropanation of *trans*-alkenyl boronates with trifluorodiazoethane catalyzed by a copper(I)-bisoxazoline complex to obtain versatile 2-substituted-3-(trifluoromethyl)cyclopropylboronates. It is worth mentioning that the reactivity between alkenyl boroxines and trifluorodiazoethane has been recently reported to prepare α-trifluoromethyl allylboronic acids,[18] by formation of highly electrophilic BINOL boronate derivatives in a metal-free procedure.

Scheme 1. Previous synthesis of trifluoromethylcyclopropanes and trifluoromethyl-cyclopropylboronates.

a) Enantioselective synthesis of trifluoromethylcyclopropanes
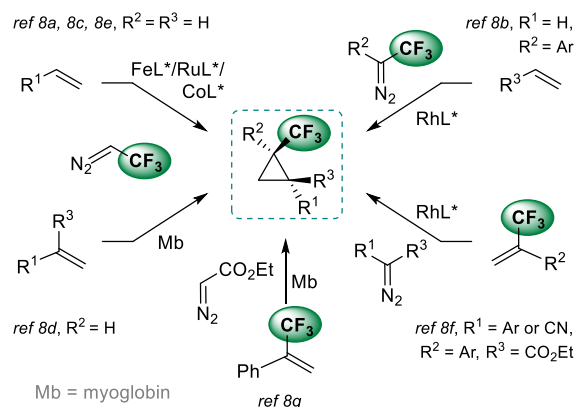
b) Synthesis of 2-(trifluoromethyl)cyclopropylboronates/borate
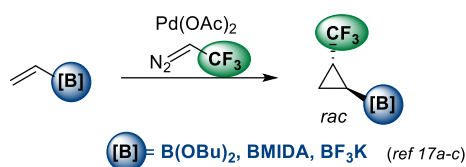
The cyclopropanation was initially studied with (*E*)-styryl pinacolboronate (**1a**) as model substrate. We commenced using Cu(I)-*t*BuBOX (5 mol%) as catalyst formed *in situ* in DCE. Initial experiments showed that alkenyl boronate was not fully consumed with 2 equiv of diazo added over the course of 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 increase of the amount of the diazo compound (4 equiv) combined with a longer reaction time (6 h) raised the conversion to 90% (entries 2-4). The relative configuration of cyclopropane **2a** was determined by ^{1}H NMR experiments (see Supporting Information).

Gratifyingly, good results of diastereo- and enantiocontrol 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 commercially available BOX ligands. Whereas the *i*PrBOX (**L2**) ligand decreased the conversion and stereocontrol 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, conducting to complete conversion (entry 7). Furthermore, the amount of diazo compound could be reduced to 2 equivalents (entry 8).

Under the optimized conditions, using 5 mol% of [Cu(NCMe)$_4$]PF$_6$ and *t*BuBOX as the catalyst and 2 equiv of trifluorodiazoethane added during 6 hours, 69% of cyclopropylboronate **2a** was isolated, with high level of stereocontrol (94:6 dr, 95:5 er).
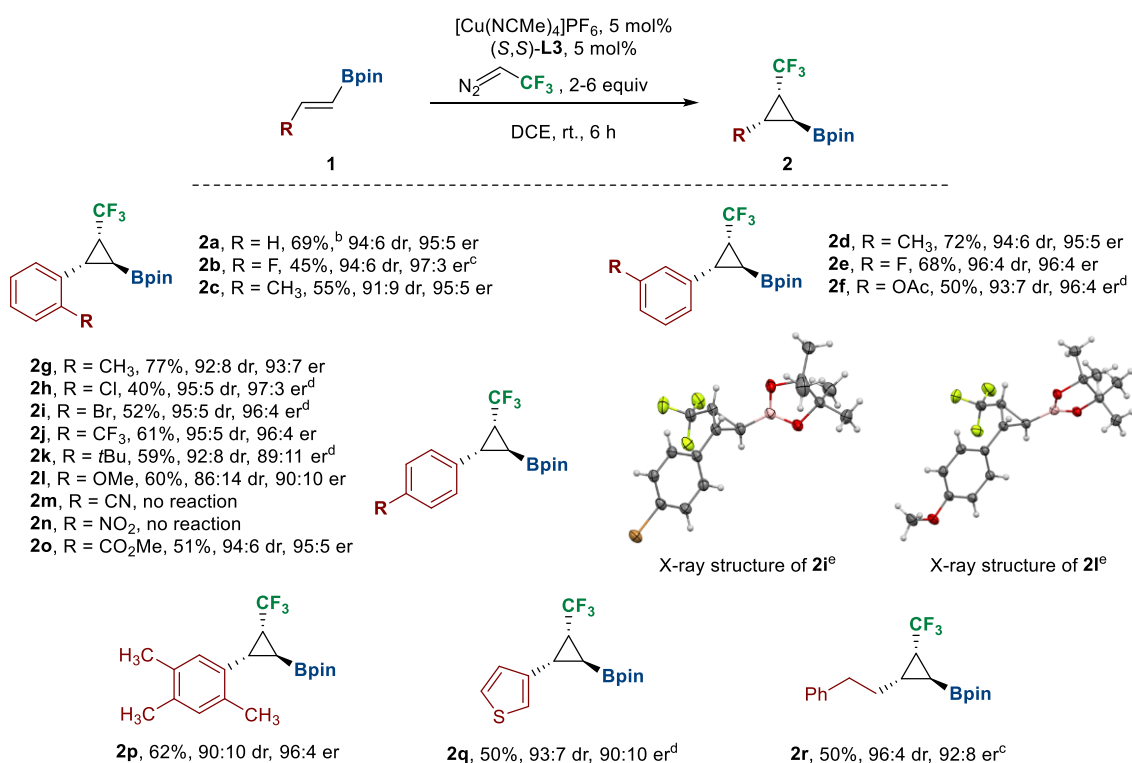
Table 1. Optimization of the Reaction Conditions.[a]
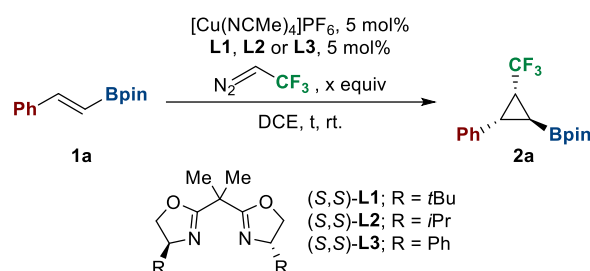
entry	ligand	diazo (equiv)	t (h)	conv (%)	dr	er
1	L1	2	2	72	92:8	-
2	L1	2	6	58	92:8	-
3	L1	4	2	89	92:8	-
4	L1	4	6	90	92:8	95:5
5	L2	4	6	72	79:21	88:12
6	L3	4	6	87	94:6	95:5
7	L3	4[b]	6	100	94:6	95:5
8	L3	2[b]	6	100 (69)[c]	94:6	95:5

[a]Reaction conditions: **1** (0.4 mmol), [Cu(NCMe)4]PF6 (0.02 mmol, 5 mol%), **L** (0.02 mmol, 5 mol%), DCE (1 mL), inert atmosphere, trifluorodiazoethane (0.5 M DCE, 2-4 equiv) 6 h slow addition. Conversion measured by 1H NMR. Diastereomeric ratio (dr) determined by 19F NMR analysis of the crude reaction mixture. Enantiomeric ratio (er) determined by HPLC analysis of the isolated product. [b]Trifluorodiazoethane (1.06 M DCE). [c]Isolated yield.

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 boranates, 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 whole 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 analysis of *p*-bromo and *p*-methoxy derivatives **2i** and **2l** (Scheme 2).[19]

Scheme 2. Substrate scope of copper-catalyzed cyclopropanation of alkenyl boronates.[a]

2a, R = H, 69%,[b] 94:6 dr, 95:5 er
2b, R = F, 45%, 94:6 dr, 97:3 er[c]
2c, R = CH₃, 55%, 91:9 dr, 95:5 er

2d, R = CH₃, 72%, 94:6 dr, 95:5 er
2e, R = F, 68%, 96:4 dr, 96:4 er
2f, R = OAc, 50%, 93:7 dr, 96:4 er[d]

2g, R = CH₃, 77%, 92:8 dr, 93:7 er
2h, R = Cl, 40%, 95:5 dr, 97:3 er[d]
2i, R = Br, 52%, 95:5 dr, 96:4 er[d]
2j, R = CF₃, 61%, 95:5 dr, 96:4 er
2k, R = tBu, 59%, 92:8 dr, 89:11 er[d]
2l, R = OMe, 60%, 86:14 dr, 90:10 er
2m, R = CN, no reaction
2n, R = NO₂, no reaction
2o, R = CO₂Me, 51%, 94:6 dr, 95:5 er

X-ray structure of 2i[e]   X-ray structure of 2l[e]

2p, 62%, 90:10 dr, 96:4 er   2q, 50%, 93:7 dr, 90:10 er[d]   2r, 50%, 96:4 dr, 92:8 er[c]

[a]Reaction conditions: 1 (0.61 mmol), [Cu(NCMe)₄]PF₆ (0.03 mmol, 5 mol%), (S,S)-L3 (0.03 mmol, 5 mol%), DCE (1.5 mL), inert atmosphere trifluorodiazoethane in DCE (2 equiv), 6 h slow addition. Isolated yields. [b]76% at 1.25 mmol scale. [c]Trifluorodiazoethane (6 equiv). [d]Trifluorodiazoethane (4 equiv). [e]Thermal ellipsoids are drawn at the 50% probability level.

As mentioned above, cyclopropylboronates are versatile intermediates in organic synthesis by the transformation of the carbon-boron 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**. Finally, amination of the cyclopropylboronate was accomplished by using BCl₃ and BnN₃ 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.[22]

Scheme 3. Transformations of cyclopropylboronate ester.
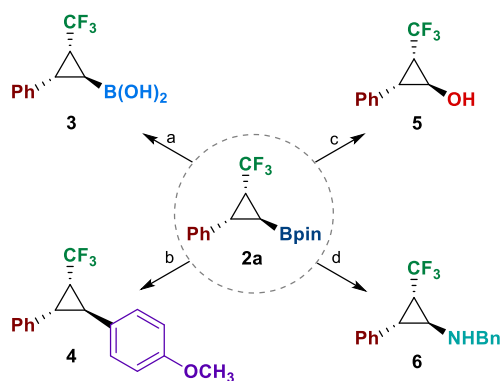
[a]Reaction conditions: (a) MeB(OH)₂ (5 equiv), TFA (5%)/DCM, 8 h, 72%. (b) 4-iodoanisole (1.5 equiv), Pd₂(dba)₃·CHCl₃ (10 mol %), PPh₃ (1 equiv), Ag₂O (1.5 equiv), THF, 70 °C, 24 h, 45 %. (c) 3M NaOH 30% H₂O₂ THF, 30 min, 68%. (d) BCl₃ (5.0 equiv, CH₂Cl₂, 25 °C, 1.5 h), then BnN₃ (3.0 equiv, CH₂Cl₂, from 0 to 25 °C, 2 h), 51%.

Then, we focused our interest in amine derivative **6**, as a trifluoromethylated analogue of *trans*-2-arylcyclopropylamines. This scaffold is common to numerous biological active compounds[23] and is present in drugs such as *Tranylcypromine* (antidepressant), *Ticagrelor* (platelet aggregation inhibitor) or candidates under clinical trials for the treatment of cancer and neurodegenerative diseases.[23,24] Due to the implication of fluorine atoms in the properties of bioactive compounds, [25] we targeted the enantioselective synthesis of a CF_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 4. Preparation of a trifluoromethyl analog of LSD1 inhibitor.
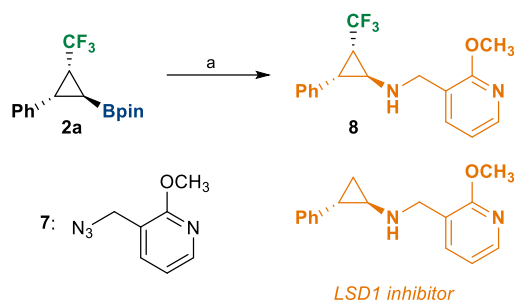
[a]Reaction conditions: (a) BCl_3 (5.0 equiv, CH_2Cl_2, 25 °C, 1.5 h), then **7** (3.0 equiv, CH_2Cl_2, from 0 to 25 °C, 4 h), 55%.

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 trifluorodiazoethane. 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 on the ACS Publications website.

Experimental procedures, characterization data, ^{1}H, ^{13}C, ^{11}B and ^{19}F 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, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Javier Carreras - Universidad de Alcalá. Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química Andrés Manuel del Río (IQAR), Campus Científico-Tecnológico, Facultad de Farmacia. 28805 Alcalá de Henares, Madrid, Spain; Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid 28034, Spain, ORCID: 0000-0002-1521-6758; E-mail: javier.carreras@uah.es

Authors

Julia Altarejos - Universidad de Alcalá. Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química Andrés Manuel del Río (IQAR), Campus Científico-Tecnológico, Facultad de Farmacia. 28805 Alcalá de Henares, Madrid, Spain; Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid 28034, Spain, ORCID: 0000-0002-2871-8597

David Sucunza - Universidad de Alcalá. Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química Andrés Manuel del Río (IQAR), Campus Científico-Tecnológico, Facultad de Farmacia. 28805 Alcalá de Henares, Madrid, Spain; Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid 28034, Spain, ORCID: 0000-0002-3307-4204

Juan J. Vaquero - Universidad de Alcalá. Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química Andrés Manuel del Río (IQAR), Campus Científico-Tecnológico, Facultad de Farmacia. 28805 Alcalá de Henares, Madrid, Spain; Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid 28034, Spain, ORCID: 0000-0002-3820-9673

Notes
The authors declare no competing financial interest.

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