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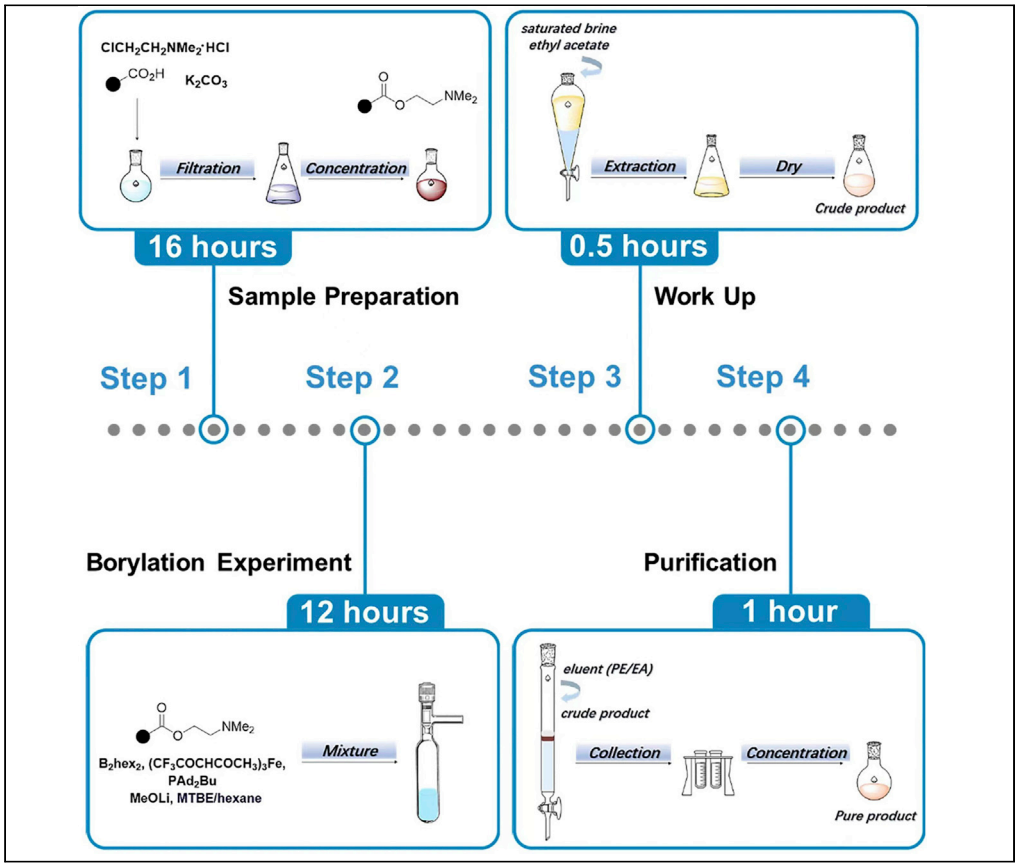

We present a protocol for the eco-friendly synthesis of aryl and alkyl boronic esters from aryl and alkyl carboxylic acids. We describe steps for aryl and alkyl carboxylates preparation. We further detail procedures for the synthesis of borylated products using aryl and alkyl carboxylates through iron-catalyzed decarbonylation at 100°C–130°C, followed by purification of the crude products by flash column chromatography.

Publisher's note: Undertaking any experimental protocol requires adherence to local institutional guidelines for laboratory safety and ethics.

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Highlights

Decarbonylative borylation via iron catalysis

Efficient synthesis of aryl and alkyl boronic esters

Decarbonylation of aryl and alkyl carboxylic acids under mild conditions

The protocol is suitable for alkyl carboxylic acids

Bai et al., STAR Protocols 3, 101909
December 16, 2022
https://doi.org/10.1016/j.xpro.2022.101909

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A one-pot protocol for iron-catalyzed decarbonylative borylation of aryl and alkyl carboxylic acids

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https://doi.org/10.1016/j.xpro.2022.101909

SUMMARY

We present a protocol for the eco-friendly synthesis of aryl and alkyl boronic esters from aryl and alkyl carboxylic acids. We describe steps for aryl and alkyl carboxylates preparation. We further detail procedures for the synthesis of borylated products using aryl and alkyl carboxylates through iron-catalyzed decarbonylation at 100°C–130°C, followed by purification of the crude products by flash column chromatography.

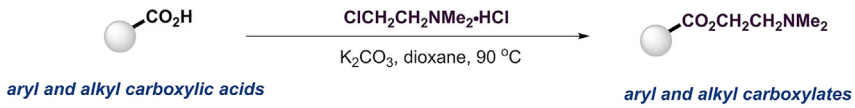
For complete details on the use and execution of this protocol, please refer to Wen et al. (2022).[1]

BEFORE YOU BEGIN

Carboxylic acids have received increasing attention due to their wide applications in transition metal-catalyzed transformations. Organoboron compounds are of great significance in organic synthesis as essential synthetic intermediates. In recent years, examples of synthesizing organoboron compounds from carboxylic acids have been documented.

In 2018, Szostak and co-workers revealed palladium-catalyzed decarbonylative borylation of carboxylic acids.[2] Piv_2O was used to activate aryl carboxylic acids for decarbonylation of sterically-hindered acyl derivative generated *in situ* at 160°C. This strategy is suitable for the late-stage derivatization of pharmaceuticals and natural products. Shortly afterward, the Su group reported the decarboxylative borylation of aryl carboxylic acids with bis(catecholato)diboron (B_2cat_2) in the presence of $Ni(COD)_2$ and (dicyclohexylphosphino)methane (dcypm) under base-free conditions.[3] A variety of (hetero)aryl carboxylic acids with different functional groups and electronic properties can be smoothly converted into the corresponding aryl boronic esters. It was found that the choice of B_2cat_2 is crucial to the success of the decarboxylative reaction, which can activate the carboxylic acid to form the aroyloxyboron species for the subsequent oxidative addition to the Ni catalyst.

Despite remarkable progress in transition metal-catalyzed decarboxylative borylation,[2,3] these reactions could only be achieved at extreme temperatures (usually >150°C). In addition, the newly generated aryl boronic esters in these borylations processes could further undergo the Suzuki-Miyaura reaction with unconsumed substrates to produce the undesired biaryl products.[4] Moreover, previous studies have disclosed that iron catalysts are difficult to promote the Suzuki reaction. Therefore, iron-catalyzed borylation reactions are highly desirable due to their advantages of cheapness, low toxicity, and environmental friendliness. However, methods for the synthesis of organoboron compounds through iron-catalyzed cross-coupling reactions have scarcely been disclosed. Our



Scheme 1. General scheme of the preparation of aryl and alkyl carboxylates

recent work found that high-valent iron species could be reduced to *in situ* generate the highly reactive iron species with the diborane reagents and alkali metal alkoxides systems, such as B_2pin_2/*t*-BuOLi, thus allowing the borylation and silylation of unreactive bonds.[5–10]

Inspired by these advances, it is worth developing a general, effective, and eco-friendly method for the synthesis of organoboron compounds from carboxylic acids with iron catalysts, diborane reagents, and alkali metal alkoxide systems. Therefore, the current protocol describes the specific steps for the synthesis of organoboron compounds through iron-catalyzed decarbonylative borylation of aryl and alkyl carboxylic acids. The protocol is suitable for the gram-scale synthesis and late-stage functionalization of biomolecules. For the same experiment performed in batch, please see Wen's article.[1]

Preparation of the reagents and equipment

A complete list of reagents and equipment can be found in the "key resources table" and "materials and equipment".

Preparation of the reagent

Timing: 16 h

In this step, the reagents derived from aryl and alkyl carboxylic acids for the borylation reaction are prepared (Scheme 1).

1. Preparation of aryl and alkyl carboxylates (Table 1).
   a. Weigh aryl or alkyl carboxylic acids (0.2 mmol), K_2CO_3 (166 mg, 1.2 mmol), and 2-dimethylaminoethyl chloride hydrochloride (34.5 mg, 0.24 mmol) in one 10 mL round bottom flask.
   b. Add to the round bottom flask 2 mL dry dioxane with a syringe.
   c. Heat the mixture in an oil bath at 90°C for 16 h.
   d. After cooling down to 25°C, filter the mixture through a pad of Celite, wash with dry dichloromethane (3 × 2 mL), and concentrate it in vacuo.

Note: The resulting aryl and alkyl carboxylates can be used as substrates without any further purification. Using benzoic acid and 4-Phenylbutanoic acid as substrates, the corresponding carboxylates were obtained in 99% and 96% yields (determined by ^{1}H NMR spectra), respectively. The alkyl and aryl carboxylates are stable and can be stored under N_2 atmosphere at 25°C.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Benzoic acid (aryl carboxylic acid)	Alfa	Alfa#036230
4-Phenylbutanoic acid (alkyl carboxylic acid)	Alfa	Alfa#A18115
K_2CO_3	Adamas	Cat#67526D
2-Dimethylaminoethyl chloride hydrochloride	Alfa	Alfa#A15134

(*Continued on next page*)

Continued

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Dry dioxane	Adamas	Cat#18326F
$(CF_3COCHCOCH_3)_3Fe$	Alfa	Alfa#039265
PAd_2Bu	Bidepharm	Cat#BD119193
MeOLi	Adamas	Cat#87055A
B_2hex_2	Adamas	Cat#39249B
Dry MTBE	Adamas	Cat#28130O
Dry hexane	Adamas	Cat#14153S
Other		
Silica gel for chromatography, 200–300 mm	Bidepharm	Cat#BD01115913
Chromatography column (Ø 17 mm, 305 mm)	Synthware Glass	Cat#C184173CR
5 mL syringe	J&K Scientific	Cat#972645
Schlenk tube	Synthware Glass	Cat#F580825D
Round bottom flask	Synthware Glass	Cat#F128250

MATERIALS AND EQUIPMENT

Synthesis of aryl boronic esters

Reagent	Final concentration	Amount
Benzoic acid (aryl carboxylic acid)	N/A	0.2 mmol
K_2CO_3	N/A	1.2 mmol
2-dimethylaminoethyl chloride hydrochloride	N/A	0.24 mmol
Dry Dioxane	N/A	2 mL
$(CF_3COCHCOCH_3)_3Fe$	N/A	0.03 mmol
PAd_2Bu	N/A	0.06 mmol
MeOLi	N/A	0.9 mmol
B_2hex_2	N/A	0.6 mmol
Dry MTBE	N/A	0.5 mL
Dry hexane	N/A	0.5 mL
Dry dichloromethane	N/A	6 mL
Total	N/A	3.23 mmol

Store at 25°C for no more than 3 months.

Synthesis of alkyl boronic esters

Reagent	Final concentration	Amount
4-Phenylbutanoic acid (alkyl carboxylic acid)	N/A	0.2 mmol
K_2CO_3	N/A	1.2 mmol
2-dimethylaminoethyl chloride hydrochloride	N/A	0.24 mmol
Dry Dioxane	N/A	2 mL
$(CF_3COCHCOCH_3)_3Fe$	N/A	0.03 mmol
PAd_2Bu	N/A	0.06 mmol
MeOLi	N/A	0.9 mmol
B_2hex_2	N/A	0.6 mmol
Dry MTBE	N/A	0.5 mL
Dry hexane	N/A	0.5 mL
Dry dichloromethane	N/A	6 mL
Total	N/A	3.23 mmol

Keep at 25°C for no more than 3 months.

STEP-BY-STEP METHOD DETAILS

Part 1: Procedure for the borylation of aryl and alkyl carboxylates

Timing: 12 h

Table 1. Preparation of aryl and alkyl carboxylates

Chemical	Amount
Aryl or alkyl carboxylic acids	0.2 mmol
K_2CO_3	1.2 mmol
2-dimethylaminoethyl chloride hydrochloride	0.24 mmol
Dry dioxane	2 mL
Dry dichloromethane	6 mL

In this step, the synthesis of borylated products (Schemes 2 and 3) has been accomplished.

1. Preparation of aryl boronic esters (Table 2 and Scheme 2).
   a. Equip one 25 mL of Schlenk tube with a magnetic stir bar.
   b. Add $(CF_3COCHCOCH_3)_3Fe$ (15.5 mg, 0.03 mmol), PAd_2Bu (21.5 mg, 0.06 mmol), MeOLi (34.2 mg, 0.9 mmol), B_2hex_2 (152 mg, 0.6 mmol) in the glove box.
   c. Dissolve the newly generated aryl carboxylate (0.2 mmol) in dry MTBE (0.5 mL) and dry hexane (0.5 mL) and then add it to the Schlenk tube.
   d. Seal the tube with a cap containing a PTFE-lined silicone septum and move it out from the glove box.
   e. Heat the mixture in an oil bath at 130°C for 12 h.

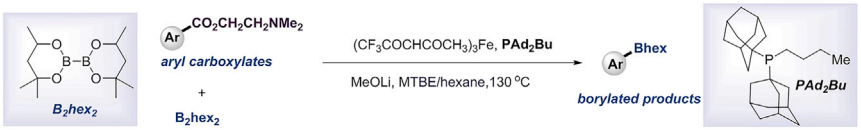
   Note: This reaction can proceed well without the use of the freshly prepared aryl and alkyl carboxylates. Aryl and alkyl carboxylates are stable and can be stored under air conditions.

2. Preparation of alkyl boronic esters (Table 3 and Scheme 3).
   a. Equip one 25 mL of Schlenk tube with a magnetic stir bar.
   b. Add $(CF_3COCHCOCH_3)_3Fe$ (15.5 mg, 0.03 mmol), PAd_2Bu (21.5 mg, 0.06 mmol), MeOLi (34.2 mg, 0.9 mmol), B_2hex_2 (178 mg, 0.7 mmol) in the glove box.
   c. Dissolve the newly generated aryl carboxylate (0.2 mmol) in dry MTBE (0.5 mL) and dry hexane (0.5 mL) and then add it to the Schlenk tube.
   d. Seal the tube with a cap containing a PTFE-lined silicone septum and move it out from the glove box.
   e. Heat the mixture in an oil bath at 110°C for 12 h.

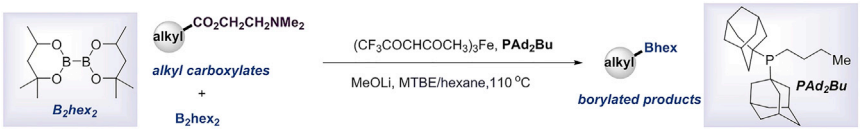
Part 2: Purification of the crude products

Timing: 2 h

3. After the reaction is completed, allow it to cool down to 25°C.
   a. Quench the mixture with saturated aqueous ammonium chloride (sat. aq. NH_4Cl, 1 mL).
   b. Dilute with 2 mL ethyl acetate and wash with 2 mL saturated brine.
   c. Shake the separatory funnel vigorously and release pressure.
   d. Allow the aqueous and organic phases to fully separate.
4. Transfer the organic phase and the aqueous phase in two 20 mL flasks.
5. Pour the aqueous phase back into the separatory funnel and then add 2 mL of ethyl acetate for extraction.



Scheme 2. Synthesis of aryl boronic esters



Scheme 3. Synthesis of alkyl boronic esters

6. Again, shake the separatory funnel vigorously, and allow the aqueous and organic phases to fully separate, then transfer the organic phase and the aqueous phase into their corresponding flasks.
7. Repeat steps 5 and 6 two times.
8. Transfer the organic layer to an Erlenmeyer flask, then add sodium sulfate. Slowly shake the flask and filter the solution in a 25 mL round bottom flask.
9. Remove the solvent by rotatory evaporation (45°C, 235 mmHg, ~15 min) to afford the dried crude product.
10. Dissolve the dried crude product in 2 mL of dichloromethane and add 50 mg of silica to it. Carefully swirl the flask and remove the solvent under vacuum (45°C, 235 mmHg, ~15 min).
11. Purify the crude product by flash column chromatography (8 cm of silica, Ø of the column = 1.7 cm) using 20:1 (by volume) mixture of PE/EA (~100 mL).
12. Monitor the fractions by TLC (These borylated products will appear as bright black spots using the phosphomolybdic acid as stain).
13. Collect the combined fractions containing pure product and concentrate under vacuum to deliver the aryl and alkyl boronic esters.

EXPECTED OUTCOMES

4,4,6-Trimethyl-2-phenyl-1,3,2-dioxaborinane **1** appears as a yellow oil obtained in 76% yield.

4,4,6-Trimethyl-2-(3-phenylpropyl)-1,3,2-dioxaborinane **2** appears as a yellow oil obtained in 63% yield.

QUANTIFICATION AND STATISTICAL ANALYSIS

4,4,6-Trimethyl-2-phenyl-1,3,2-dioxaborinane **1** (Scheme 4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 2 H), 7.42–7.36 (m, 1 H), 7.33 (dd, *J* = 7.9, 6.4 Hz, 2 H), 4.34 (m, 1 H), 1.86 (dd, *J* = 13.9, 3.0 Hz, 1 H), 1.56 (t, *J* = 5.8 Hz, 1 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 130.3, 127.4, 71.0, 65.0, 46.3, 31.3, 28.2, 23.2.

^{11}B NMR (192 MHz, $CDCl_3$) δ 24.9.

4,4,6-Trimethyl-2-(3-phenylpropyl)-1,3,2-dioxaborinane **2** (Scheme 5).

Table 2. Preparation of aryl boronic esters

Chemical	Amount
Newly generated alkyl carboxylate	0.2 mmol
B_2hex_2	0.6 mmol
$(CF_3COCHCOCH_3)_3Fe$	0.03 mmol
PAd_2Bu	0.06 mmol
MeOLi	0.9 mmol
Dry MTBE	0.5 mL
Dry hexane	0.5 mL

Table 3. Preparation of alkyl boronic esters

Chemical	Amount
Newly generated alkyl carboxylate	0.2 mmol
B_2hex_2	0.7 mmol
$(CF_3COCHCOCH_3)_3Fe$	0.03 mmol
PAd_2Bu	0.06 mmol
MeOLi	0.9 mmol
Dry MTBE	0.5 mL
Dry hexane	0.5 mL

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.4 Hz, 2 H), 7.20–7.13 (m, 3 H), 4.14 (m, 1 H), 2.58 (t, *J* = 7.8 Hz, 2 H), 1.74 (dd, *J* = 13.9, 3.0 Hz, 1 H), 1.67 (t, *J* = 7.8 Hz, 2 H), 1.42 (dd, *J* = 13.8, 11.5 Hz, 1 H), 1.25 (s, 6 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 0.71 (t, *J* = 7.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 128.6, 128.1, 125.4, 70.4, 64.5, 45.9, 38.7, 31.3, 28.1, 26.5, 24.8, 23.2.

^{11}B NMR (192 MHz, $CDCl_3$) δ 27.6.

LIMITATIONS

The protocol is limited to the primary and secondary alkyl carboxylic acids, and the tertiary substrates are not suitable for this protocol.

TROUBLESHOOTING

Problem 1

Preparation of the reagent. How to increase the yield of aryl and alkyl carboxylates in the first step?

Potential solution

These aryl and alkyl carboxylic acids can be converted to the corresponding sulfonyl fluorides or sulfonyl chlorides and then reacted with 2-dimethylaminoethyl chloride hydrochloride to yield the desired aryl and alkyl carboxylate salts.

Problem 2

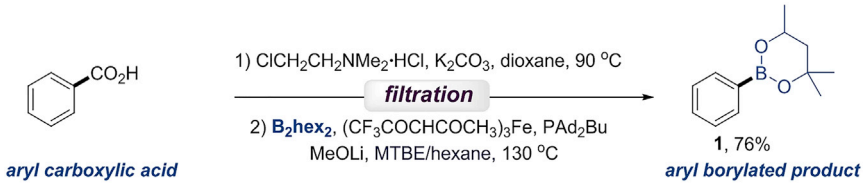
Step 1c and step 2c. How to set up the reaction using viscous aryl and alkyl carboxylates as substrates?

Potential solution

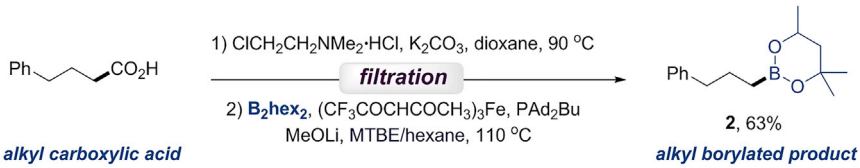
First, dissolve the viscous aryl and alkyl carboxylates with a small amount of dichloromethane (1.0 mL), then add these mixtures to a Schlenk tube, remove the solvent under vacuum, and then place the Schlenk tube into the glove box for the next procedure.

Problem 3

Step 11. What are the potential difficulties in the purification of the borylated products?



Scheme 4. General scheme of the borylation of aryl carboxylic acids



Scheme 5. General scheme of the borylation of alkyl carboxylic acids

Potential solution

The residual B_2pin_2 in the reaction may sometimes be difficult to separate from the desired product. These crude products could be purified by flash column chromatography, and then separated by thin-layer chromatography to get the high-purity products.

Problem 4

Step 13. Can the yield of the reaction be improved by increasing the amount of catalyst?

Potential solution

Increasing the amount of catalyst has little effect on the efficiency of this transformation, or even decreases the yield.

Problem 5

Step 13. What are the possible reasons for the poor reproducibility of this reaction?

Potential solution

MeOLi stored for a long time may lead to a poor yield, and the newly used MeOLi will result in a better yield.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Z.F. (fengzh@cqu.edu.cn).

Materials availability

The newly generated compounds associated with this protocol will be shared by the lead contact upon request.

This study did not generate new unique reagents.

Data and code availability

The published article (Wen et al.[1]) includes all data generated or analyzed during this study.

ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (nos. 22271031, 22201026), Natural Science Foundation of Sichuan (no. 2021YJ0413), Sichuan Key Laboratory of Medical Imaging (North Sichuan Medical College, no. 2022JB001), Chongqing Postdoctoral Science Foundation (no. cstc2020jcyj-bshX0052), China Postdoctoral Science Foundation (no. 2020M673121), and Zunyi Technology Plan Foundation (no. QKHRC[2019]-009). We are also grateful for the support from the Analytical and Testing Center of Chongqing University.

AUTHOR CONTRIBUTIONS

M.B. and Z.F. designed and wrote the protocol with inputs from all the authors. S.G., S.C., and Z.L. performed the experiment.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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