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Rapid Ligand-Free Base-Accelerated Copper-Catalyzed Homocoupling Reaction of Arylboronic Acids

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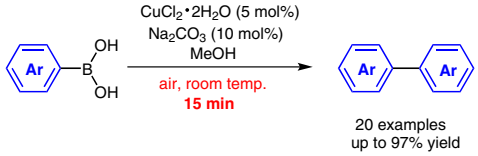

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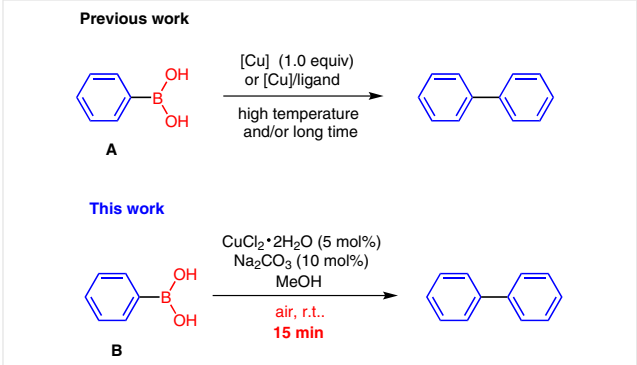
Abstract A rapid, ligand-free, base-accelerated, copper-catalyzed homocoupling reaction of (het)arylboronic acids is presented. A $CuCl_2 \cdot 2H_2O/Na_2CO_3$-based catalyst enabled the formation of bi(het)aryl compounds by a homocoupling process in moderate to excellent yields (72–97%) within 15 minutes. A mechanism for the copper-catalyzed base-accelerated reaction is proposed.

Key words homocoupling, arylboronic acids, copper catalysis, biaryls

Biaryl frameworks have a great significance in nature.[1] Natural products containing biaryl motifs have been shown to possess a wide range of biological activities. Active compounds include biphenomycin B[2] and crisamicin A,[3] which exhibit excellent antibacterial activities. Biaryls are also critical structural scaffolds in many novel functional materials,[4] ligands,[5] and drugs.[5d]

The Suzuki–Miyaura cross-coupling is a state-of-the-art method for the synthesis of nonsymmetrical biaryl compounds.[6] In the synthesis of biaryl compounds, classic Ullmann-type coupling reactions require stoichiometric amounts of copper powder and high reaction temperatures.[7] These harsh conditions limit the substrate scope of the Ullmann coupling reaction. Like aryl halides, many arylboronic acids with good air and moisture stabilities are commercially available, which has contributed to the popularity of the Suzuki–Miyaura cross-coupling reaction. Moreover, the low toxicity of organoboronic acids has encouraged their widespread use in the pharmaceutical industry.[8] Because of these practical characteristics, homocoupling reactions involving arylboronic acids have recently attracted much attention for the preparation of symmetrical biaryl compounds.

There have been many recent reports of palladium-catalyzed homocoupling reactions of arylboronic acids under mild conditions.[9–11] Other noble metals such as Au,[10b–f] Ag,[10g] and Rh[10h] also exhibit excellent catalytic activities in the homocoupling reaction. However, the requirements of industrial applications and green chemistry have driven a search for more economical and more effective methods for the synthesis of symmetrical biaryls. The use of a copper catalyst might potentially overcome the shortcomings of noble metals. Solid-state copper catalysts exhibit good reactivities and broad substrate tolerance under mild reaction conditions.[11a–e] However, the complex structures and slow dispersal of such catalysts limit their industrial applications.[12] Moreover, the use of high catalyst loadings,[11f,h] complex ligands,[11g] or copper nanoparticles[11j] is necessary in most copper salt catalyzed homocoupling reactions. Furthermore, reaction times are often long, with only moderate yields (Scheme 1,A). Recently, Cheng and Luo reported a



Scheme 1 Copper-catalyzed synthesis of biaryls

CuCl-catalyzed homocoupling of arylboronic acids in air at room temperature. By using this method, biaryls could be prepared in three hours in the absence of additives with an average yield of less than 80%. Interestingly, bases were found to inhibit the homocoupling.[11i] Therefore, the development of efficient, nontoxic, environmentally friendly, and operationally simple syntheses of biaryl compounds remains critical.

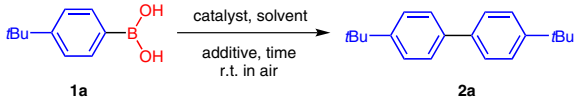
As part of our ongoing research on green synthesis and C–C coupling methods,[13] we report a ligand-free $CuCl_2{\cdot}2H_2O$-catalyzed homocoupling reaction of (het)arylboronic acids at room temperature to give the corresponding bi(het)aryls in 81–97% yield in only 15 minutes (Scheme 1,B)]. The reaction employs a catalytic amount of Na_2CO_3 as an additive to accelerate the coupling reaction.

Initially, we investigated the synthesis of 4,4′-di-*tert*-butylbiphenyl (**2a**) by the copper-catalyzed homocoupling of (4-*tert*-butylphenyl)boronic acid (**1a**; 53.4 mg, 0.3 mmol) (Table 1). Molecular sieves (4 Å; 2 grains, ~100 mg) were added to remove water. The optimization focused on the screening of copper sources. Methanol was chosen as the solvent because of its ability to dissolve various copper sources (5 mol%), which were used at room temperature. NMR spectroscopy revealed that $CuCl_2{\cdot}2H_2O$, CuBr, and CuCl showed high activities, giving **2a** in yields of 95, 87, and 92% (Table 1, entries 2, 6, and 7). The other copper salts gave moderate to low yields. Note that similar yields were obtained with $CuCl_2{\cdot}2H_2O$ (entry 2) and CuCl (entry 7), suggesting that the use of either copper source would have a minimal effect on the yield. In contrast to CuCl and CuBr, CuI (entry 8) gave only trace amounts of product **2a**. No product was formed in the presence of 4 Å MS and in the absence of a copper complex. Conversely, when a copper catalyst was added in the absence of 4 Å MS, coupling product **2a** was obtained in 87% yield after 24 hours (entries 9 and 10).

Surprisingly, we found that hydrated copper sources were more efficient than anhydrous ones, even when molecular sieves were used. We therefore investigated the role of the 4 Å MS. On the basis of the components of molecular sieves, Al_2O_3, SiO_2, and Na_2CO_3 were used as additives in the reaction. Only Na_2CO_3 facilitated the homocoupling reaction, which was complete in 15 minutes with 87% yield (Table 1, entry 13). When the loading of Na_2CO_3 was reduced from 100 mol% to 10 mol%, we were surprised to find that the yield increased to 97% after only 15 minutes. When water or ethanol was used as solvent (entries 15 and 16) or when the catalyst loading was reduced (entry 17), the reaction did not reach completion after 15 minutes, and longer reaction times were required.

Next, the substrate scope of the arylboronic acid was investigated under the optimized reaction conditions [arylboronic acid (1.0 equiv), $CuCl_2{\cdot}2H_2O$ (5 mol%), Na_2CO_3 (10 mol%), MeOH, r.t., in air, 15 min] (Scheme 2). In general, arylboronic acid possessing various substituents coupled to give the corresponding biaryls in high yields. Arylboronic acids (**1a–l**) with various electron-donating or electron-withdrawing substituents gave high yields (87–97%) of the corresponding homocoupling products in 15 minutes under the optimized conditions (Table 2). In most cases, the position of substituents had a significant impact on the coupling. For example, arylboronic acids **2i–l** possessing 4-fluoro, 4-chloro, 4-bromo, or 4-iodo groups, respectively, gave high yields of the corresponding biphenyl compounds **3i–l** in 15 minutes under the optimized conditions. Functionalized {4-[*tert*-butyl(dimethyl)siloxy]phenyl}boronic acid (**2m**) gave biphenyl **3m** in 72% yield. Sterically hindered 1-naphthylboronic acid (**1n**) and [5-(benzyloxy)-2-methoxy-

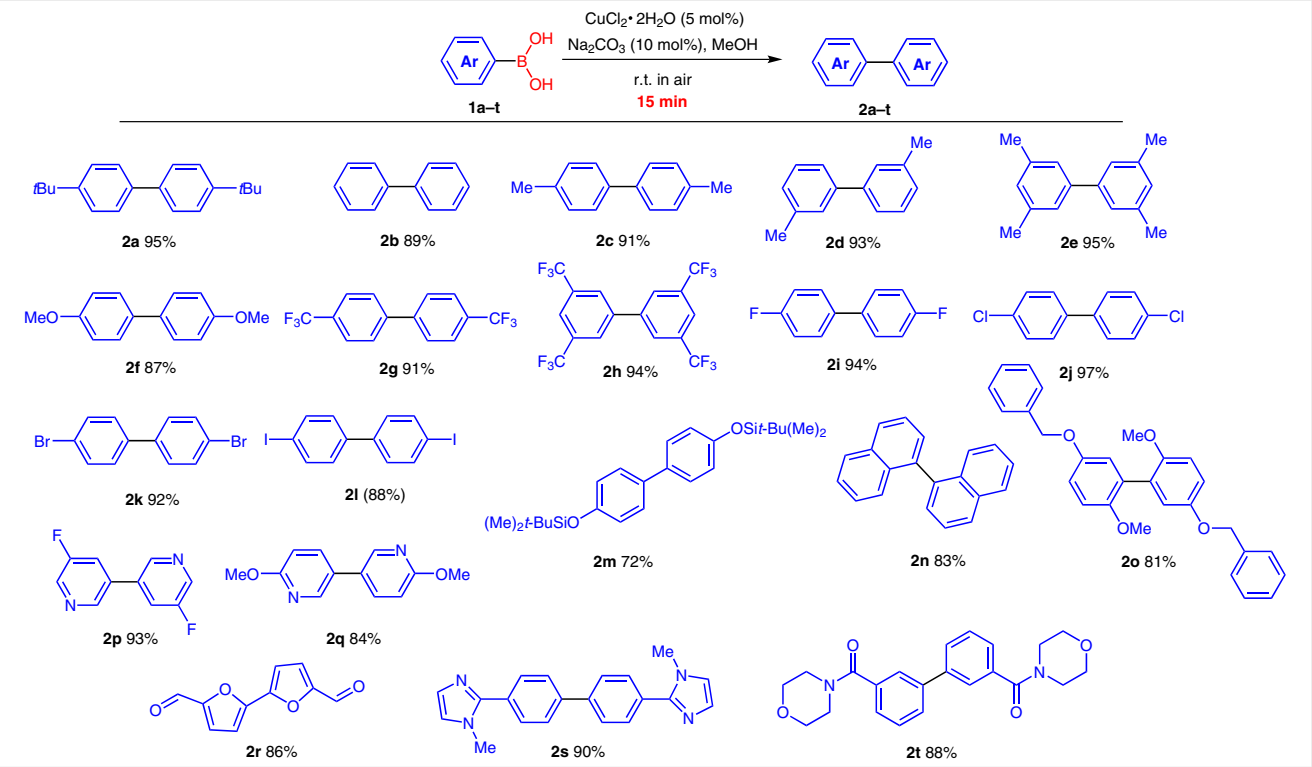
Table 1 Optimization of Copper-Catalyzed Homocoupling of 4-(*tert*-Butylphenyl)boronic Acid (**1a**)[a]



1a **2a**

Entry	Catalyst	Additive	Solvent	Time	Yield[b] (%)
1	$CuSO_4{\cdot}5H_2O$	4 Å MS	MeOH	30 min	41
2	$CuCl_2{\cdot}2H_2O$	4 Å MS	MeOH	30 min	95
3	$Cu(OAc)_2{\cdot}H_2O$	4 Å MS	MeOH	30 min	27
4	CuO	4 Å MS	MeOH	30 min	trace
5	$Cu(OH)_2$	4 Å MS	MeOH	30 min	trace
6	CuBr	4 Å MS	MeOH	30 min	87
7	CuCl	4 Å MS	MeOH	30 min	92
8	CuI	4 Å MS	MeOH	30 min	trace
9	–	4 Å MS	MeOH	24 h	0
10	$CuCl_2{\cdot}2H_2O$	–	MeOH	24 h	87
11[c]	$CuCl_2{\cdot}2H_2O$	Al_2O_3	MeOH	12 h	79
12[d]	$CuCl_2{\cdot}2H_2O$	SiO_2	MeOH	12 h	80
13[e]	$CuCl_2{\cdot}2H_2O$	Na_2CO_3	MeOH	15 min	87
14[f]	$CuCl_2{\cdot}2H_2O$	Na_2CO_3	MeOH	15 min	97
15[f]	$CuCl_2{\cdot}2H_2O$	Na_2CO_3	H_2O	1.0 h	trace
16[f]	$CuCl_2{\cdot}2H_2O$	Na_2CO_3	EtOH	1.0 h	51
17[g]	$CuCl_2{\cdot}2H_2O$	Na_2CO_3	MeOH	1.0 h	89
18[h]	$CuCl_2{\cdot}2H_2O$	Na_2CO_3	MeOH	1.5 h	85

[a] Reaction conditions: **1a** (1.0 equiv), copper catalyst (5 mol%), additive [4 Å MS (2 grains, ~100 mg) or other additives], solvent (1.0 mL) (0.3 mmol scale), r.t., air.
[b] Isolated yield.
[c] Al_2O_3 (100 mol%).
[d] SiO_2 (100 mol%).
[e] Na_2CO_3 (100 mol%).
[f] Na_2CO_3 (10 mol%).
[g] $CuCl_2{\cdot}2H_2O$ (1 mol%), Na_2CO_3 (10 mol%).
[h] $CuCl_2{\cdot}2H_2O$ (5 mol%), Na_2CO_3 (10 mol%).



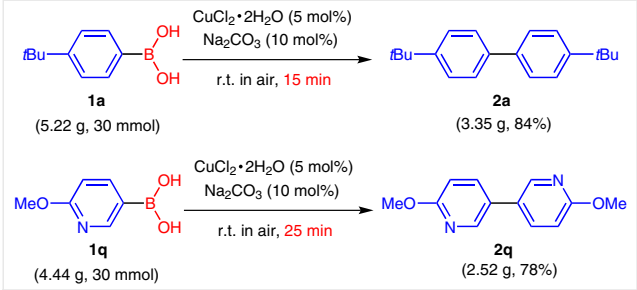
Scheme 2 Scope of arylboronic acid in the homocoupling reaction

phenyl]boronic acid (**1o**) also homocoupled under the optimal conditions to give the corresponding biaryls in 83 and 81% yield, respectively.

Heterocyclic boronic acids are considered to be challenging substrates for Suzuki homocoupling.[6a,e] To our surprise, (5-fluoropyridin-3-yl)boronic acid (**1p**), (6-methoxypyridin-3-yl)boronic acid (**1q**), and (5-formyl-2-furyl)boronic acid (**1r**) gave the corresponding biaryls **2p–r** in yields of 93, 84, and 86%, respectively, when the reaction time was extended to 25 minutes.

Heterocyclic biaryl compounds are important motifs of many pharmaceutical products. In our ongoing research on the virtual screening and synthesis of structurally simplified natural medicines,[14] we required imidazole and morpholine analogues. We therefore examined the homocoupling of boronic acids containing *N*-methylimidazole[15] and morpholine[16] moieties to give 2,2′-biphenyl-4,4′-diylbis(1-methyl-1*H*-imidazole) (**2s**) and 4,4′-[biphenyl-3,3′-diyldi(carbonyl)]dimorpholine (**2t**) in yields of 90 and 88%, respectively.

Next, we evaluated the scalability of the reaction by performing the homocoupling of 4-(*tert*-butylphenyl)boronic acid (**1a**; 5.22 g, 30 mmol). As shown in Scheme 3 (upper), the product was obtained in 84% yield (3.35 g). Given the importance of heterocycles in medicinal chemistry, we next examined the gram-scale coupling of (6-methoxypyridin-3-yl)boronic acid (**1q**; 4.44 g, 30 mmol), which gave the desired product **2q** in 78% yield (Scheme 3; lower).

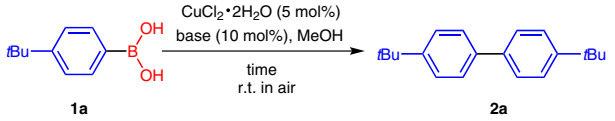


Scheme 3 Synthesis of biaryls on multigram scales

We were intrigued by the effect of Na_2CO_3, which accelerated the coupling process when present in a catalytic amount but inhibited it when present in an equivalent amount. We therefore set out to explore the effects of bases on the homocoupling reaction. To our surprise, when Na_2CO_3 was replaced with 10 mol% of an inorganic or organic base, the reaction went to completion in 15–30 minutes (Table 2). This is an unusual example of a case in which a catalytic amount of a base accelerates a chemical reaction,[17] and the mechanism of the acceleration process needs

to be investigated comprehensively. More interestingly, a basic copper source [$Cu(OH)_2$] did not assist the coupling process when present as a catalyst, even in high loadings, but it did accelerate the reaction when present as an additive (Table 1, entry 5 versus Table 2, entry 5).

Table 2 Effect of Various Bases on the Copper-Catalyzed Homocoupling of 4-(*tert*-Butylphenyl)boronic Acid (**1a**)[a]



1a 2a

Entry	Additive	Time	Yield[b] (%)
1	—	24 h	87
2	Na_2CO_3	15 min	97
3	K_2CO_3	15 min	97
4	$K_3PO_3·7H_2O$	15 min	91
5	$Cu(OH)_2$	30 min	85
6	Et_2NH	15 min	95
7	Et_3N	15 min	95
8	pyridine	15 min	96
9	DMAP	30 min	90

[a] Reaction conditions: **1a** (1.0 equiv), $CuCl_2·2H_2O$ (5 mol%), additive (10 mol%), MeOH (1.0 mL) (0.3 mmol scale), r.t., air.
[b] Isolated yield.

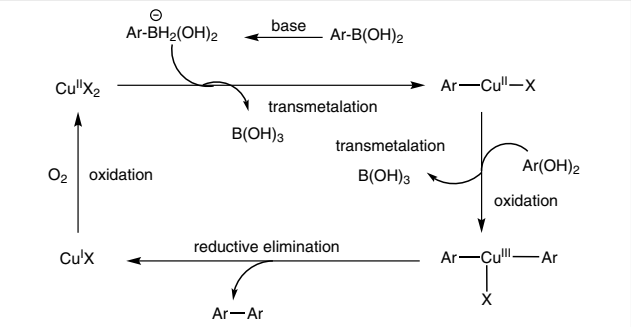
Possible mechanisms of copper(I)-catalyzed homocoupling of arylboronic acids have already been reported.[11c,d,11f–i] These studies suggested a catalytic cycle induced by redox changes in various forms of copper under aerobic conditions.[11f–i] However, the mechanism of copper(II)-catalyzed homocoupling remains unclear. Moreover, in the current case, the presence of a catalytic amount of a Lewis base in the copper(II)-catalyzed homocoupling reaction brought additional complexity to the mechanism.

To gain a little insight into the possible mechanism of the base-accelerated copper-catalyzed homocoupling of arylboronic acid, several control experiments were conducted. When $CuCl_2·2H_2O$ (5 mol%) was added to a mixture of (4-*tert*-butylphenyl)boronic acid (**1a**) and Na_2CO_3 (10 mol%) in methanol, the coupling process was complete in 15 minutes, whereas when Na_2CO_3 (10 mol%) was added to a mixture of (4-*tert*-butylphenyl)boronic acid (**1a**) and $CuCl_2·2H_2O$ (5 mol%), the coupling time was extended to about 25 minutes. When a reaction mixture of the boronic acid, copper catalyst, and base was stirred for one minute and then hydrochloric acid was added to neutralize the Na_2CO_3, the homocoupling was complete within 20 minutes. Na_2CO_3 (10 mol%) also accelerated the coupling when CuCl (5 mol%) was used as catalyst, giving complete reaction within 20 minutes, but the reaction was slower than when $CuCl_2·2H_2O$ was used. These results suggested that the base is not involved in the catalytic cycle, but does activate the arylboronic acid.

X-ray photoelectron spectroscopy (XPS) experiments were also conducted to examine changes in the valence state of copper during the homocoupling process. These showed that Cu^{II} was detected at the beginning of the reaction, whereas a mixture of Cu^{II} and Cu^{I} was present at the end. Although no Cu^{III} ion was detected by XPS, owing to its instability, we speculate that it might be involved in the catalytic cycle, because the participation of Cu^{III} in critical steps has been proposed for almost all copper-catalyzed coupling reaction mechanisms.[18]

By taking into consideration the effect of base on the Suzuki coupling mechanism,[19] the report of Cheng and Luo,[11i] the control experiments, the reaction phenomenon, and an analysis of the optimization results, we hypothesized a mechanism for the copper-catalyzed homocoupling that accounts for the following observations: (1) Air and the solvent have significant effects on the reaction; in other words, oxygen is involved in the catalytic cycle. (2) No formation of elemental copper or bronze-mirror phenomenon was observed during the experimental process, whereas Cu^{II} and Cu^{I} can both catalyze the reaction (Table 1, entries 1–12). (3) CuBr and $CuBr_2$ showed significant differences in yields, whereas the yields given by $CuCl_2·2H_2O$ and CuCl were close to one another; this might be attributed to the presence of Br^-, which inhibits the formation of Cu^{I} from Cu^{II}. (4) The electronegativity of cations had a significant effect on the reaction, with Cl^- giving a better yield than Br^- or I^- (Table 1, entries 2 and 6–8). (5) ^{11}B NMR spectroscopy indicated the presence of $B(OH)_3$ in the reaction residue. (6) The survival of C–I bonds in the coupling suggests that oxidative addition is not the first step of the reaction. (7) Cu^{I} and Cu^{II} ions were detected by XPS experiments. (8) More importantly, we found that a base accelerated the homocoupling in the early stages of the reaction and that the base is not involved in the catalytic cycle. In his research on the mechanism of the Suzuki coupling, Miyaura reported that bases assist organoboron compounds to form active boric anions.[20] Our observations and Miyaura's results indicated that the base accelerated the homocoupling reaction through activation of the arylboronic acid. Taking all this evidence into account, we propose a possible mechanism for the copper-catalyzed homocoupling of arylboronic acid through a $Cu^{I}/Cu^{II}/Cu^{III}$ cycle, as shown in Scheme 4.

Transmetalation of the base-activated arylboronic acid with the CuX_2 catalyst affords an $ArCu^{II}X$ species, according to the commonly accepted process in the Chan–Lam reaction.[21] Then, oxidation and further transmetalation between the $ArCu^{II}X$ species and another arylboronic acid molecule gives a trivalent copper species $ArCu^{III}ArX$, which undergoes reductive elimination to give the desired Ar–Ar product and $Cu^{I}X$. The latter is oxidized by O_2 to regenerate the $Cu^{II}X_2$ catalyst and close the catalytic cycle. Of course,



Scheme 4 Plausible mechanism for the base-accelerated, copper-catalyzed homocoupling of arylboronic acids

unlike palladium catalytic cycles in coupling reactions, copper cycles are enormously complex and no information is currently available on the active intermediate species; consequently, it is very difficult to identify the true reaction pathway.

In summary, we have developed a ligand-free copper-catalyzed homocoupling of (het)arylboronic acids to afford a wide range of bi(het)aryl compounds at room temperature in the presence of air. Importantly, we found that Na_2CO_3 or other bases can be used in catalytic amounts to accelerate the reaction. The coupling proceeds in high yields in only 15 minutes. This simple method is widely applicable to a variety of (het)arylboronic acids and exhibits good tolerance toward electron- donating or electron-withdrawing substituents. [22]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588361.

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(22) **Bi(het)aryls 2a–t; General Procedure**

A vial was charged with the appropriate (het)arylboronic acid (0.3 mmol), $CuCl_2{\cdot}2H_2O$ (2.5 mg, 5 mol%), Na_2CO_3 (10 mol%), and MeOH (1 mL), and the mixture was stirred at 25 °C in the air for 5–15 min while the reaction was monitored by TLC. The reaction was then quenched with two drops of H_2O. The mixture was then diluted with EtOAc (2 mL) and filtered through a pad of $MgSO_4$ and silica. The pad was rinsed with additional EtOAc, and the solution was concentrated in vacuum. The crude material was purified by flash chromatography (silica gel).

4,4′-Di-*tert*-butylbiphenyl (2a)

Prepared by following the general procedure with (4-*tert*-butylphenyl)boronic acid (53.4 mg, 0.3 mmol) for 15 min at r.t. Purification by flash chromatography (silica gel, PE) gave a white solid; yield: 37.9 mg (95%); mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.4 Hz, 4 H), 7.49 (d, *J* = 8.4 Hz, 4 H), 1.40 (s, 18 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.9, 138.2, 126.6, 125.6, 34.5, 31.4.