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Temperature-controlled sequential Suzuki–Miyaura reactions for preparing unsymmetrical terphenyls

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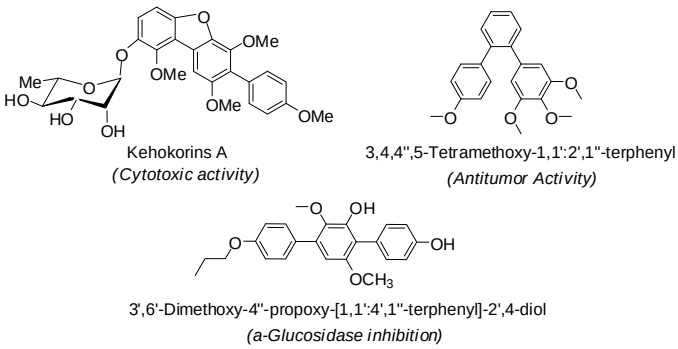
A one-pot protocol of double Suzuki–Miyaura reactions has been developed for the synthesis of unsymmetrical terphenyls. In the absence of a ligand, potassium bromophenyltrifluoroborate reacts with arylboronic acid and then sequentially with hetero/aryl bromide by controlling the reaction temperature, providing unsymmetrical *p-, m*-terphenyls compounds in moderate to good overall yields. This protocol provides a convenient and practical approach to unsymmetrical terphenyls under ligand-free and aerobic conditions.

Introduction

Unsymmetrical terphenyls and their analogues distributed widely in mushrooms exhibit significant biological activities, including potent immunosuppressant, neuroprotective, and antimicrobial activities (Scheme 1).[1-6] Additionally, unsymmetrical terphenyls are important structural motifs for construction of various liquid crystals and fluorescent compounds.[7] Over the years, numerous synthetic strategies, including transition-metal catalyzed cross-coupling reactions[8-14] and cyclization reactions,[15-18] have been developed to access these valuable molecules. However, harsh reaction conditions, circuitous steps and low yields are still problems. The palladium-catalyzed Suzuki–Miyaura (SM) cross-coupling reaction has been recognized as a powerful tool for construction of carbon-carbon bonds, because of the broad functional group tolerance and the low toxicity associated with boron compounds.[19, 20] The traditional SM reaction procedures for preparing unsymmetrical terphenyls require multi-step reactions in the presence of a ligand: (i) preparing a biphenyl intermediate by the SM reaction, (ii) halogenation of the biphenyl intermediate, and (iii) proceeding the finally SM reaction to provide unsymmetrical terphenyls.[21, 22] Recently, one-pot double SM reactions for the synthesis of unsymmetrical terphenyls have received great attention.[23-25] A variety of dielectrophilic reagents, such as dibromobenzene,[26, 27] 1-bromo-4-chlorobenzene,[28, 29] and arene diazonium tetrafluoroborate salts,[30] have been used as building blocks to couple with arylboron compounds for construction of unsymmetrical tri(hetero)aryl derivatives (Scheme 2a). In 2015, Watson's group[31] reported that bromophenyl *N*-methyliminodiacetic acid boronates underwent one-pot sequential SM cross-coupling smoothly by nucleophile speciation control, and various unsymmetrical tri(hetero)aryl derivatives were prepared in good yields (Scheme 2b).



Scheme 1 Structures of bioactive unsymmetrical terphenyls

Selective control of organoboron reactivity is a great challenge in synthetic organic chemistry. Our group has been focusing on the development of efficient SM reaction systems with different arylboron compounds.[32-39] Herein, we report a temperature-controlled sequential SM coupling strategy for the synthesis of unsymmetrical terphenyls using potassium bromophenyltrifluoroborates as building blocks (Scheme 2c).

Results and discussion.

Our previous investigation found that potassium aryltrifluoroborates usually took a longer time for a complete cross-coupling than arylboronic acids at room temperature.[37, 40] This result led us to explore whether a chemo-selective cross-coupling of arylboronic acids over potassium aryltrifluoroborates is possible. Therefore, we studied the

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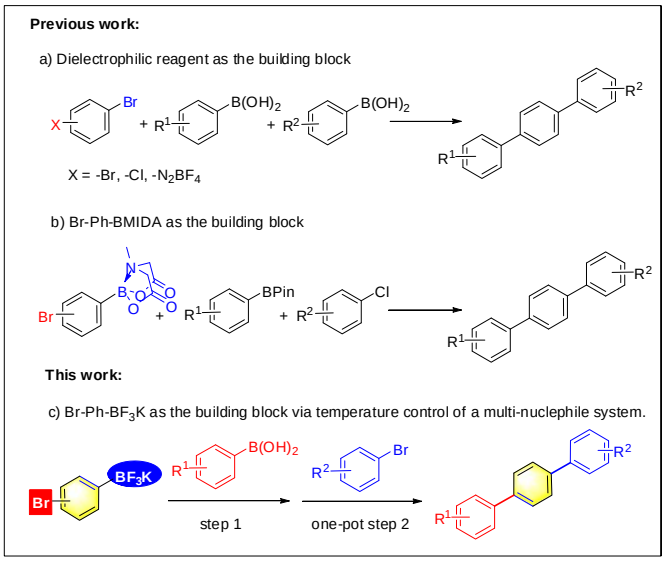
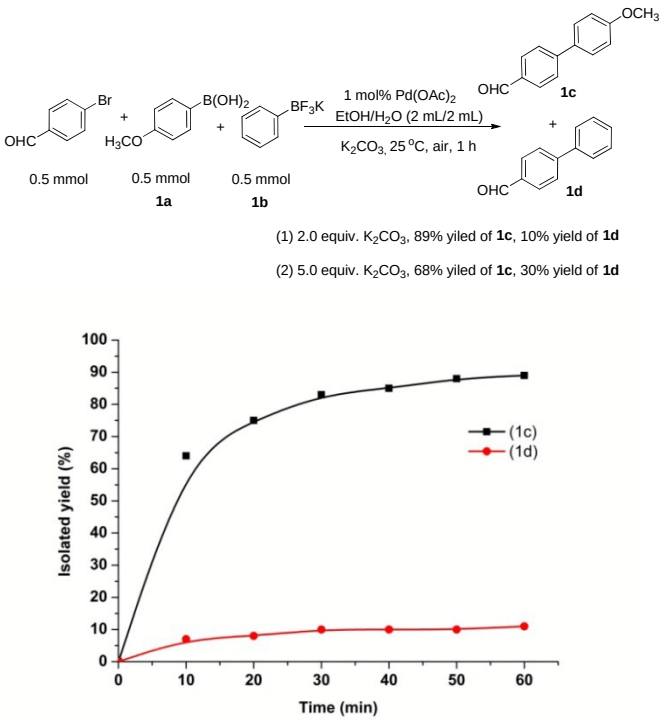


Scheme 2 Approaches to unsymmetrical terphenyls by one-pot double SM reactions

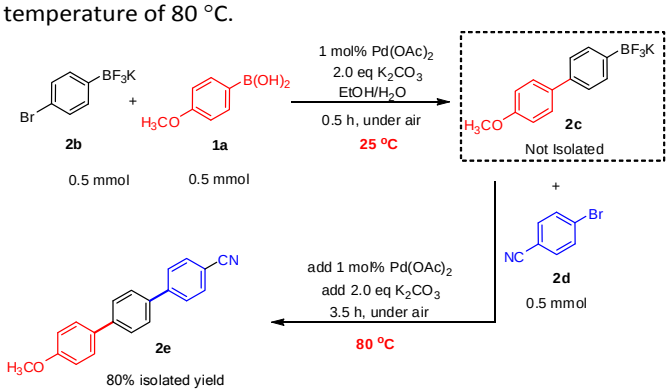
cross-coupling of 4-methoxyphenylboronic acid (**1a**) and potassium phenyltrifluoroborate (**1b**) with 4-bromobenzaldehyde in the presence of 1 mol% $Pd(OAc)_2$ and 2.0 equiv. of K_2CO_3 in 50% aqueous ethanol at room temperature (Scheme 3). It was interesting to observe a notable chemo-selectivity, and **1a** was transformed into the corresponding cross-coupled product **1c** with an 89% yield, while **1b** provided only a 10% yield of product **1d**. The high



Scheme 3 The competitive SM reactions of 4-methoxyphenylboronic acid and potassium phenyltrifluoroborate with 4-bromobenzaldehyde in the presence of different loadings of K_2CO_3

selectivity under this multi-organoboron system is proposed that 4-bromobenzaldehyde cross-couples with **1a** very fast and most of the base is consumed, which might suppress the hydrolysis of potassium organotrifluoroborates.[41] This speculation was confirmed by a control experiment using a loading of 5.0 equiv. base, the yield of **1d** increased to 30%, while the yield of **1c** was decreased to 68% (Scheme 3).

Based on the above results, we tried to use potassium 4-bromophenyltrifluoroborate as a building block to carry out one-pot double SM reactions with the aid of a stepwise addition of reagents for a high chemo-selectivity (Scheme 4). The selective cross-coupling reaction of muti-organoboron compounds was controlled by the reaction temperature. After careful investigation on the base, solvent, and catalyst (see ESI in detail), **1a** was coupled with **2b** under the conditions of 1 mol% $Pd(OAc)_2$ and 2.0 equiv. of K_2CO_3 at room temperature. The cross-coupled product **2c** was not necessary to be separated, and then **2d**, 1 mol% $Pd(OAc)_2$ and 2.0 equiv. of K_2CO_3 were added into the reaction mixture. An 80% yield of the terphenyl product **2e** was achieved at the reaction temperature of 80 °C.



Scheme4 One-pot double SM reactions with potassium 4-bromophenyltrifluoroborate

We next explored the scope and limitations for this one-pot cross-coupling protocol. As shown in Scheme 5, 20 unsymmetrical *p*- and *m*-terphenyl compounds with 26%-90% yield were obtained, and the results demonstrate that this reaction protocol is sensitive to electronic characteristics of the substrates. The overall yields of terphenyl compounds were largely dictated by the second step, and aryl bromides bearing an electron-withdrawing group (**3a-3c**) provided slightly better yields than those of bearing an electron-donating group (**3d-3f**). The good overall yields were obtained while using 2-bromobenzonitrile as substrate for the second cross-coupling step (**3g, 3h, 3i**). On the contrary, *ortho*-substituted arylbononic acids used for the first step afforded low product yields (**3g, 3j**). Potassium bromophenyltrifluoroborate bearing a chloro group as building block was explored, and only trace product was observed (**3k**). *m*-Terphenyls were also prepared in this protocol, and the corresponding products were obtained in 58% and 69% yields (**3l, 3m**). However, potassium 2-bromophenyltrifluoroborate has low activity in this protocol (**3n**)**.** Further study indicated that the first step was effective with arylboronic acids bearing an electronic donating group. In contrast, the second step was effective with aryl bromides bearing an electronic withdrawing group (**3q, 3r**). For example, an 84% yield of **3q** was achieved by using 4-methoxyphenylboronic acid for the first step and 4-

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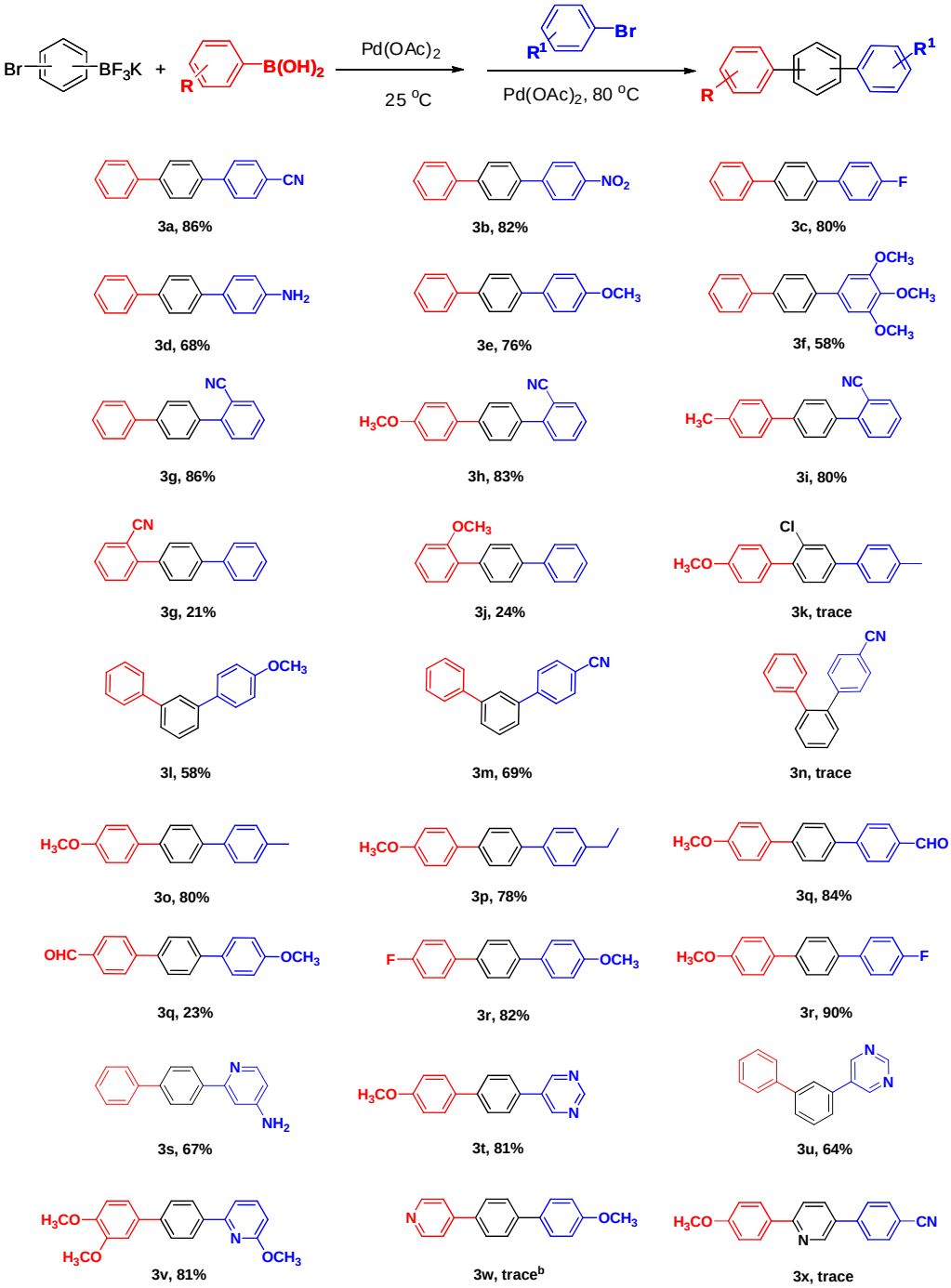
bromobenzaldehyde as the second coupling partner. However, only a 23% yield of **3q** was obtained while using 4-formylphenylboronic acid for the first step reaction and 1-bromo-4-methoxybenzene for the second step. The more difficult cases of heteroaryl bromides as substrates have been investigated, and we were pleased to find that bromo-pyridine and bromo-pyrimidine as the second step coupling partners could provide good yields of products (**3s-3v**). 4-Pyridineboronic acid pinacol ester as the first step coupling partner was ineffective (**3w**). While using potassium 6-bromopyridin-3-yltrifluoroborate as building block, only trace product was observed (**3x**).



Scheme 5 [a] One-pot double SM reactions. Reaction conditions: the first step, potassium bromophenyltrifluoroborate (0.5 mmol), arylboronic acid (0.5 mmol), K_2CO_3 (1.0 mmol), $Pd(OAc)_2$ (1 mol%), EtOH/H_2O (5 mL/5 mL), 25 °C, under air, 0.5 h. The second step: adding aryl bromide (0.5 mmol), K_2CO_3 (1.0 mmol), $Pd(OAc)_2$ (1 mol%), 80 °C, 3.5 h, isolated yield. [b] Pyridine-4-boronic acid pinacol cyclic ester as coupling partner for the first step.

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Conclusion

In summary, we have developed a convenient one-pot double Suzuki–Miyaura reactions protocol for the synthesis of unsymmetrical terphenyls. Potassium bromophenyltrifluoroborates proceed chemo-selective cross-coupling with coupling partners by controlling reaction temperature in the absence of any ligand. A series of *p*-and *m*- unsymmetrical terphenyls were prepared in good yields.

Experimental

General remarks

All commercially available reagents (from Acros, Aldrich, Fluka) were used without further purification. Potassium aryltrifluoroborates were prepared from corresponding arylboronic acids following the method reported in the literature.[42] All reactions were carried out under air atmosphere. NMR spectra were recorded on a Brucker Advance II 400 spectrometer using TMS as internal standard (400 MHz for ^{1}H NMR). The isolated yields of products were obtained by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90 °C), unless otherwise noted.

General procedure for one-pot double Suzuki-Miyaura reaction.

A mixture of potassium bromophenyltrifluoroborate (0.5 mmol), arylboronic acid (0.5 mmol), K_2CO_3 (1 mmol), $Pd(OAc)_2$ (1 mol%), EtOH/H_2O (5 mL/5 mL) was stirred at 25 °C under air for 0.5 h. And then aryl bromide (0.5 mmol), K_2CO_3 (1 mmol), and $Pd(OAc)_2$ (1 mol%) were added to the reaction mixture and stirred for 3.5 h at 80 °C. The mixture was added to brine (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were concentrated in vacuo and the product was isolated by short chromatography.

Acknowledgements

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Notes and references

† Electronic supplementary information (ESI) available: Characterization of cross-coupled products. See DOI:

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