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Pd-catalysed synthesis of carborane sulfides from carborane thiols

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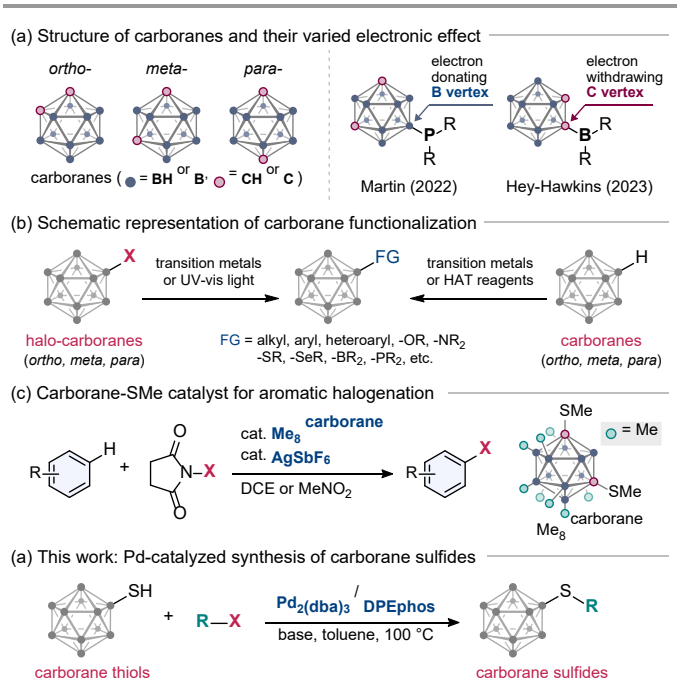
Carboranes are an interesting class of aromatic molecules with icosahedral geometry, high stability, and unique electronic effects. We herein report a Pd-catalysed coupling reaction of carborane thiols with aryl halides. This protocol was applicable to the controlled synthesis of di(carboranyl) sulfides, and their catalytic performance for aromatic halogenation was examined.

Icosahedral carborane ($C_2B_{10}H_{12}$) derivatives are an important subset of polyhedral boron cluster molecules bearing unique three-dimensional aromaticity.[1,2] There are three possible isomeric forms considering the position of two carbon vertices within the cage, and these are colloquially referred to as *ortho*-, *meta*-, and *para*-carboranes (Scheme 1a, left). Because of the difference in electronegativity of the carbon and boron atoms, the carborane framework would exert diverse electronic effects when bound to functional groups. In particular, substituents experience either a strong electron-withdrawing effect on the carbon vertices or strong electron-donating effect on the boron (more precisely, B9 and B10) vertices (Scheme 1a, right).[3] Such an inherent dichotomy[4] of the carborane cluster has been beneficial for modulating the function of connected heteroatoms. Additionally, the close relationship between 2D and 3D aromatic scaffolds was extensively studied by Sola and Teixidor.[5] The development of practical synthetic methods for functionalised carborane derivatives have attracted significant interest owing to its wide application in catalysis,[6] ligand design,[4,7] bond activation,[8] etc. (Scheme 1b).

Transition-metal catalysed cross-coupling reactions have emerged as a powerful synthetic tool for the functionalised carboranes and related boron cluster compounds.[9] As the pioneering work for carborane-heteroatom bond forming reactions, Bregadze and Beletskaya reported Pd-catalysed amination and etherification of iodo-carboranes.[10] Afterward, a substantial contribution to this field has been made by research groups of Hawthorne, Hey-Hawkins, Spokoyny, Xie, and others.[11] In addition, direct functionalization of carborane derivatives through B–H or C–H bond activation has been in limelight over the last decade.[12] More recently, light-promoted radical reactions have been adopted for the synthesis of functionalised boron cluster compounds.[13] A cutting-edge work on the carboranyl radical formation via hydrogen atom transfer (HAT) process was established by Yan et al.[14]



Scheme 1 Synthesis and application of functionalised carborane derivatives.

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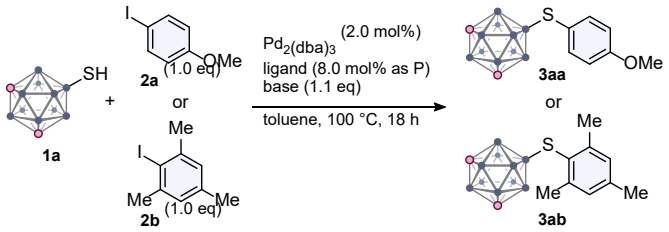
Last year, our group has introduced carborane-based sulfide catalysts for the halogenation of aromatic compounds using *N*-halosuccinimides (NXS) (Scheme 1c).[6b] The electronic property of *meta*-carborane scaffold was the most suitable for the catalysis, and further chemical functionalization of the cluster vertices was crucial for enhancing the catalytic activity. Encouraged by this result, we have envisioned developing an effective and general synthetic method for carborane sulfide derivatives. Herein, we report a Pd-catalysed coupling reaction of carborane thiols and aryl halides (Scheme 1d). Both B-substituted and C-substituted thiols are readily accessible from the parent carboranes,[15] whereas their use in catalytic reaction has been elusive.[16] The established reaction system was also applicable to the controlled synthesis of di(carboranyl) sulfides, and their catalytic performance for the aromatic halogenation was evaluated.[17,18]

As an initial attempt, we tested the coupling reaction of *meta*-carborane-9-thiol (**1a**) with 4-iodoanisole (**2a**) adopting $Pd_2(dba)_3$ as catalyst and KO^{t}Bu as base, and the corresponding sulfide **3aa** was obtained in 12% yield (Table 1, entry 1).

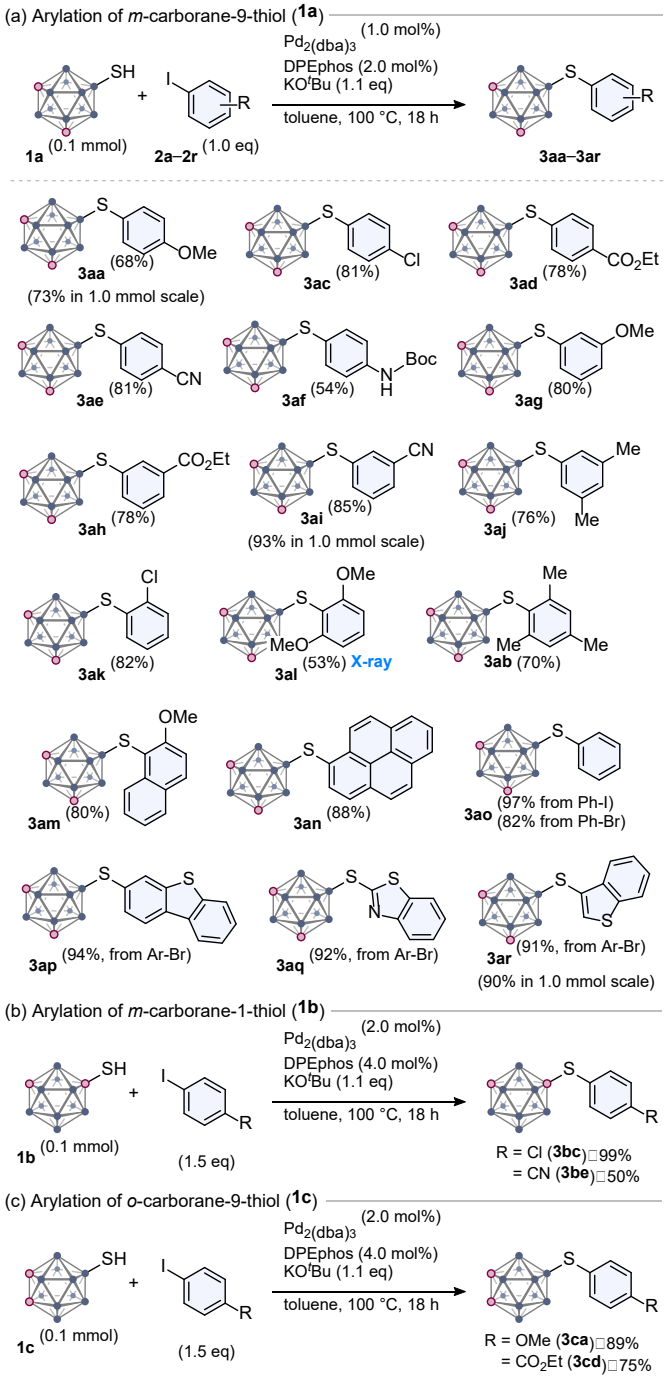
Table 1 Optimization study



entry	aryl halide	ligand	base	yield [a]
1	**2a**	--	KO^{t}Bu	12%
2	**2a**	PPh_3	KO^{t}Bu	97%
3	**2a**	DPPE	KO^{t}Bu	85%
4	**2a**	DPPBz	KO^{t}Bu	quant (80%)
5	**2a**	DPEphos	KO^{t}Bu	84%
6	**2a**	DPPBz	DBU	71%
7	**2a**	DPPBz	NEt_3	28%
8	**2a**	DPPBz	K_2CO_3	11%
9	**2a**	DPPBz	K_3PO_4	27%
10 [b]	**2b**	PPh_3	KO^{t}Bu	trace
11 [b]	**2b**	DPPE	KO^{t}Bu	trace
12 [b]	**2b**	DPPBz	KO^{t}Bu	trace
13 [b]	**2b**	DPEphos	KO^{t}Bu	73% (70%)

Reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), toluene (1.0 mL). [a] Estimated by NMR analysis using CH_2Br_2 as an internal standard. Isolated yield in parentheses. [b] 1.0 mol% of $Pd_2(dba)_3$ and 4.0 mol% of ligand (as P) were used.

The productivity was significantly improved by the addition of phosphine ligands (entries 2–5). The coupling product was obtained in 71% yield by using DBU (1,8-diazabicyclo[5.4.0]-7-undecene) as the base (entry 6), whereas NEt_3, K_2CO_3, and K_3PO_4 were not suitable for this transformation (entries 7–9). In order to identify the most effective phosphine ligand, we further examined the reaction of **1a** with 2-iodomesitylene (**2b**). Here the amount of Pd catalyst and ligand was reduced to 2.0 mol% each. The target product **3ab** was not obtained using PPh_3, DPPE, and DPPBz (entries 10–12). In sharp contrast, **3ab** was isolated in considerably high 70% yield using DPEphos (entry 13), and this reaction system was adopted for the following study (see the Supplementary Information for additional data).

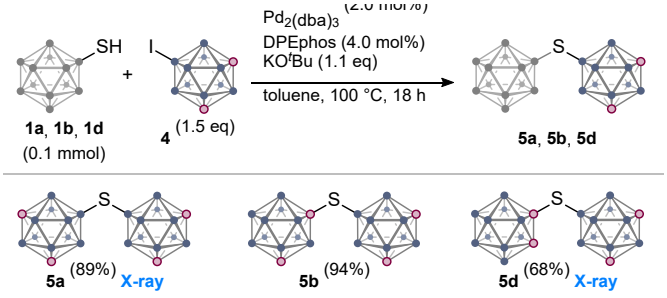


Scheme 2 Scope of the Pd-catalysed arylation of *meta*-carborane-9-thiol (**1a**), *meta*-carborane-9-thiol (**1b**), and *ortho*-carborane-1-thiol (**1c**). Yield is of isolated materials.

Next, we examined the scope of the Pd-catalysed arylation with respect to aryl halides (Scheme 2a). A series of iodoarenes bearing functional groups such as alkoxy (**2a**, **2g**), chloro (**2c**), ester (**2d**, **2h**), cyano (**2e**, **2i**), Boc-amine (**2f**), and methy (**2j**) substituents at the para or meta positions were readily tolerated under the standard conditions to give the corresponding sulfide in moderate to high yields. This method

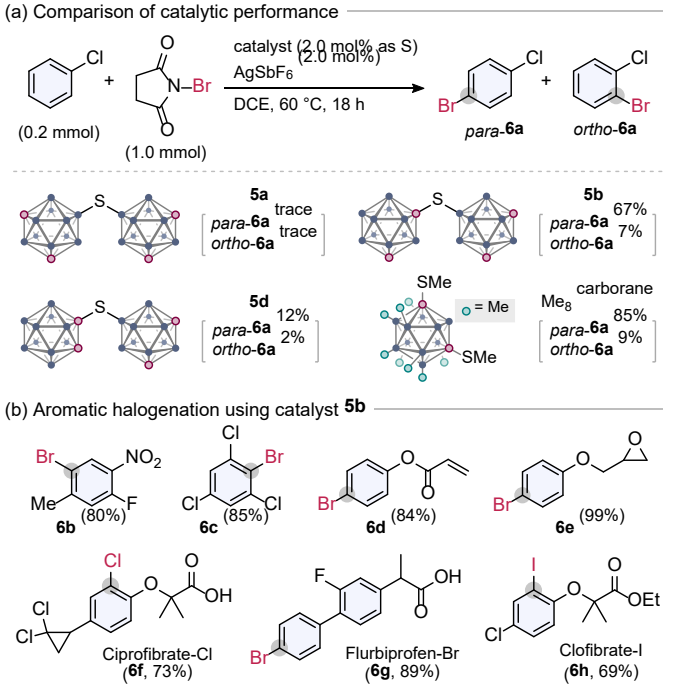
was also applicable to the arylation with sterically demanding ortho-substituted arenes (**2b**, **2k**, **2l**) and 1-iodo-2-methoxynaphthalene (**2m**). The structure of **3al** was unambiguously determined by an X-ray crystallography (CCDC 2369107). The reaction with 2-iodopyrene afforded the corresponding sulfide **3an** in 88% yield. To our delight, bromoarenes also could be used as the arylating reagents in the present protocol: phenyl sulfide **3ao** was obtained in high yield either with adopting iodobenzene (97% yield) or bromobenzene (82% yield). Several heteroaryl bromides were successfully coupled with the carborane thiol **1a** to afford the corresponding products **3ap**–**3ar**. The reaction of **2a**, **2i**, and **2r** could be conducted in 1.0 mmol scale. The established catalytic system was also effective for the arylation of *meta*-carborane-1-thiol (**1b**) and *ortho*-carborane-9-thiol (**1c**). As shown in Scheme 2b and 2c, these thiols were smoothly arylated with para-substituted iodoarenes, giving the corresponding sulfides **3bc**, **3be**, **3ca**, and **3cd** in 50–99% yield.

As mentioned above, carborane derivatives have recently been recognised as a practical building block for tuning the electronic properties of the connected fragment, and we adopted this for developing carborane-SMe halogenation catalysts (Scheme 1c). This finding prompted us to examine the synthesis of di(carboranyl) sulfides by the Pd-catalysed coupling reaction (Scheme 3). Particularly, *meta*-carborane-9-thiol (**1a**) was treated with 9-iodo-*meta*-carborane (**4**) under the standard conditions, and the corresponding sulfide **5a** was obtained in 89% yield (Scheme 3). In a similar manner, *meta*-carborane-1-thiol (**1b**) and *ortho*-carborane-1-thiol (**1d**) were readily reacted with **4** to produce **5b** (94% yield) and **5d** (68% yield), respectively. The structures of **5a** (CCDC 2369108) and **5d** (CCDC 2369109) were confirmed by the crystallographic analysis.



Scheme 3 Pd-catalysed synthesis of di(carboranyl) sulfides. Yield is of isolated materials.

We then evaluated the catalytic activity of the obtained sulfides **5** for the halogenation of aromatic compounds (Scheme 4a). For the bromination of chlorobenzene with NBS, the target product **6a** was obtained in 74% total yield with high para selectivity (para/ortho = 90.5/9.5) when **5b** was used in combination with $AgSbF_6$ co-catalyst. This outcome was practically comparable to that of Me_8 carborane catalyst, which showed the highest activity in our previous study.[6b] Considering the ease of preparation, **5b** would be a suitable catalyst platform for the halogenation chemistry. In contrast, **5a** and **5d** could not be an effective promotor.[19] Some additional examples using **5b** as the catalyst are showcased in Scheme 4b. Electron deficient substrates were successfully halogenated to give **6b** and **6c** in high yield. Phenyl acrylate and glycidyl phenyl ether, which are prone to oligomerise in the presence of radical initiators or strong acids, cleanly converted to the desired product **6d** and **6e**. These examples would highlight the sufficiently mild reaction conditions. The developed catalytic system was also applicable to the aromatic chlorination and iodination as demonstrated by the reaction of Ciprofibrate, Flurbiprofen, and Clofibrate (**6f**–**6h**).



Scheme 4 Evaluation of the catalytic activity of carborane sulfides **5** for the aromatic halogenation.

In summary, we have developed a Pd-catalysed cross-coupling of carborane thiols with aryl halides as well as 9-iodo-*meta*-carborane. B-substituted and C-substituted thiols were successfully converted to the corresponding sulfides in synthetically useful yield. The coupling product, particularly a di(carboranyl) sulfide **5b**, exhibited high catalytic activity for the electrophilic aromatic halogenation using *N*-halosuccinimides. The sulfide **5b** is rather easily prepared than the previously optimised Me_8 carborane. The developed coupling reaction would be a handle for seeking applications of electronically tuned sulfide compounds.

Data availability

Crystallography data have been deposited at CCDC (Cambridge Crystallographic Data Centre) under the database identifier 2369107 (**3al**), 2369108 (**5a**), and 2369109 (**5b**), which can be obtained from https://www.ccdc.cam.ac.uk. Additional data supporting this article have been included as part of the Supplementary Information.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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19 A similar trend was found in our previous study (see ref 6b).

