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The Research Grants Council of Hong Kong
NSFC/RGC Joint Research Scheme
Joint Completion Report

*(Please attach a copy of the completion report submitted to the NSFC
by the Mainland researcher)*

Part A: The Project and Investigator(s)

1. Project Title

Synthesis and Enantioselective Transformation of Carborane-Fused Cyclobutenes and Alkenylcarboranes

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator <i>(with title)</i>	Professor Zuowei Xie	Professor Yong Tang
Post	Choh-Ming Li Professor of Chemistry	Professor of Chemistry
Unit / Department / Institution	Chemistry/CUHK	Shanghai Institute of Organic Chemistry, CAS
Contact Information	zxie@cuhk.edu.hk	tangy@sioc.ac.cn
Co-investigator(s) <i>(with title and institution)</i>	NA	NA

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval <i>(must be quoted)</i>
Project Start date	2015-01-01		
Project Completion date	2018-12-31		
Duration <i>(in month)</i>	36		
Deadline for Submission of Completion Report	2019-09-30		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. To prepare carborane-fused cyclobutenes and alkenylcarboranes with various kinds of substituents.
2. To design and synthesize new chiral ligands/catalysts for asymmetric transformations of carborane-fused cyclobutenes and alkenylcarboranes.
3. To develop a toolbox for the preparation of chiral carborane derivatives including chiral building blocks and carborane version of known drugs.
4. To understand the structure/activity relationships and reaction mechanisms.

5.2 Revised Objectives

NA

6. Research Outcome

Major findings and research outcome

(maximum 1 page; please make reference to Part C where necessary)

- (1) The chirality of B(4)/(5)-arylated *o*-carboranes was studied by HPLC, circular dichroism (CD) spectra and single-crystal X-ray analyses. Based on this, the first enantioselective synthesis of chiral-at-cage *o*-carboranes has been developed via Pd-catalyzed asymmetric intramolecular B–H arylation under mild reaction conditions. The absolute configuration of the products has been unambiguously assigned. Generally good to excellent yields with up to 96% ee can be achieved. The use of chiral monophosphine ligand is essential for such enantioselective B–H arylation (Pub #25).
- (2) The first asymmetric [2+2] cycloaddition of dimethyl methylidenemalonate with polysubstituted olefins has been developed using Cu(II)/SaBOX as the catalyst, giving chiral cyclobutanes in high yields with >99/1 dr and up to >99% ee. The reaction has a broad substrate scope with mono-, di-, and trisubstituted alkenes. This newly developed method has been applied to the enantioselective total synthesis of (+)-piperarborenine B, which was completed in eight steps in 17% overall yield with 99% ee (Pub #12).
- (3) Using carboxylic acid as traceless directing group, a series of efficient and regioselective transition-metal catalyzed *o*-carborane B(4)–H amination, halogenation, C(sp²)-H dehydrogenative cross-coupling, and B(4,5)–H dialkenylation, diarylation methodologies were developed. We also reported a very efficient iridium-catalyzed diborylation of cage B(3,6)–H. The resultant 3,6-(Bpin)₂-*o*-carboranes are useful synthons for the synthesis of a wide variety of B(3,6)-difunctionalized *o*-carboranes bearing cage B–X (X = O, N, C, I and Br) bonds. In addition, direct nucleophilic substitution reaction of cage B–H by Grignard reagents offered a new route to regioselective B(4)-alkylation of *o*-carboranes (Pub #2, #3, #11, #15, #17, #18, #20, #22, #26).
- (4) In addition to the *o*-carborane boron vertex functionalization, several efficient carbon vertex functionalization methods were also successfully developed using carboryne, transition-metal-mediated or photo-catalysis strategies (Pub #4, #8, #14, #19, #21, #23, #24).

Research Outcome:

This original work has resulted in 26 peer-reviewed articles published in chemistry journals including J. Am. Chem. Soc. (x 3), Angew. Chem. Int. Ed. (x 6), Nat. Commun. (x 1), Chem. Sci. (x 3), Chem. Eur. J. (x 3), Chem. Commun. (x 3), Organometallics (x 3), Dalton Trans. (x 1), Chin. J. Org. (x 1) and J. Organomet. Chem. (x 2). PI was invited to give four plenary/keynote/invited lectures at international conferences. Five postgraduate students have been trained.

Potential for further development of the research and the proposed course of action
(*maximum half a page*)

Boron cage inherent chirality could be achieved by both intra- and inter-molecular transition-metal-catalyzed asymmetric B–H bond activation of *o*-carboranes. We will explore these reactions in the future.

7. The Layman's Summary

(*describe in layman's language the nature, significance and value of the research project, in no more than 200 words*)

The importance of chiral compounds and their enantioselective synthesis has been fully acknowledged to date by scientists in both pharmaceutical industry and academia. Icosahedral carboranes can be viewed as three-dimensional analogues to benzenes, whose chirality is determined by the substitution patterns on the polyhedron. Carborane cage chirality is an outstanding yet unresolved issue of great interest as the icosahedral carboranes have wide applications in medicinal and materials chemistry. In this research, we have developed efficient chiral-at-cage arylation of *o*-carboranes with high regio- and enantio-selectivities by the strategy of palladium-catalyzed asymmetric intramolecular B–H arylation and cyclization. Generally good to excellent yields with up to 96% ee can be achieved. This represents the first example of the enantioselective construction of chiral-at-cage compounds with new skeletons. On the other hand, we also developed asymmetric [2+2] cycloaddition of dimethyl methylidenemalonate with polysubstituted olefins using chiral Cu(II)/SaBOX as the catalyst, giving chiral cyclobutanes in high yields with >99/1 dr and up to >99% ee. The results obtained from this joint effort open avenues to a new class of chiral carboranes and cyclics, which may find applications in medicinal and materials chemistry.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(*Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.*)

	The Latest Status of Publications	Author(s) (<i>bold the authors</i>)	Title and Journal/ Book (<i>with the volume, pages and other necessary</i>)	Submitted to	Attached	Acknowledgement	Accessibility
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Publication No	Year of publication	Year of Acceptance (For paper accepted but not yet published)	Under Review	Under Preparation (optional)	belonging to the project teams and denote the corresponding author with an asterisk*)	publishing details specified)	RGC (indicate the year ending of the relevant progress report)	to this report (Yes or No)	aged the support of this Joint Research Scheme (Yes or No)	from the institutional repository (Yes or No)
1	2015				Da Zhao, Jiji Zhang, Zuowei Xie*	Facial Synthesis of <i>o</i> -Carborane-Substituted Alkenes and Allenes by Regioselective Ene Reaction of 1,3-Dehydro- <i>o</i> -Carborane, <i>Chem. Eur. J.</i> 2015, 21, 10334-10337	2017	Yes	Yes	No
2	2015				Hairong Lyu, Yangjian Quan, Zuowei Xie*	Palladium Catalyzed Direct Dialkenylation of Cage B-H Bonds in <i>o</i> -Carboranes Through Cross-Coupling Reaction, <i>Angew. Chem. Int. Ed.</i> 2015, 54, 10623-10626	2017	Yes	Yes	No
3	2016				Yangjian Quan, Zuowei Xie*	Palladium-Catalyzed Regioselective Diarylation of <i>o</i> -Carboranes by Direct Cage B-H Activation, <i>Angew. Chem. Int. Ed.</i> 2016, 55, 1295-1298.	2017	Yes	Yes	No
4	2016				Ruofei Cheng, Jie Zhang, Jiji Zhang, Zaozao Qiu*, Zuowei Xie*	Facile Synthesis of <i>N</i> -Carboranyl Amines through <i>o</i> -Carborane Intermediate, <i>Angew. Chem. Int. Ed.</i> 2016, 55, 1751-1754	2017	Yes	Yes	No
5	2016				Li Xiang, Zuowei Xie*	Tantalacarborane Mediated Consecutive C-C and C-N Coupling Reactions of Alkyl Isonitriles: a Facile Route to <i>N</i> -Heterocycles, <i>Organometallics</i> 2016, 35, 233-241	2017	Yes	Yes	No
6	2016				Da Zhao, Zuowei Xie*	Visible-Light-Promoted Photocatalytic B-C Coupling via Boron-Centered Carboranyl Radical: Facile Synthesis of B(3)-Arylated <i>o</i> -Carboranes, <i>Angew. Chem. Int. Ed.</i> 2016, 128, 3218-3222	2017	Yes	Yes	No
7	2016				Li Xiang, Zuowei Xie*	Reaction of $[\eta^1:\eta^5-(R_2NCH_2CH_2)_2C_2B_9H_{10}]TaMe_3$ with Isonitriles: Effects of Nitrogen Substituents on Product Formation, <i>Organometallics</i> 2016, 35, 1430-1439.	2017	Yes	Yes	No
8	2016				Tek Long Chan, Zuowei Xie*	Synthesis, structure and reactivity of an imine-stabilized carboranylphosphorus(I) compound, <i>Chem. Commun.</i> 2016, 52, 7280-7283	2017	Yes	Yes	No
9	2016				Da Zhao, Zuowei Xie*	[3-N ₂ - <i>o</i> -C ₂ B ₁₀ H ₁₁][BF ₄]: A Useful Synthone for Multiple Cage Boron Functionalization of <i>o</i> -Carborane, <i>Chem. Sci.</i> 2016, 7, 5635-5639	2017	Yes	Yes	No

10	2016			Da Zhao, Jiji Zhang, Zhenyang Lin*, Zuowei Xie*	Unique Properties of C,C'-Linked nido-Biscarborane Tetraanion. Synthesis, Structure and Bonding of Ruthenium Monocarbollide via Unprecedented Cage Carbon Extrusion, <i>Chem. Commun.</i> 2016, 52, 9992-9995	2017	Yes	Yes	No
11	2016			Hairong Lyu, Yangjian Quan*, Zuowei Xie*	Transition Metal Catalyzed Direct Amination of Cage B(4)-H Bond in <i>o</i> -Carboranes: Synthesis of Tertiary, Secondary and Primary <i>o</i> -Carboranyl Amines, <i>J. Am. Chem. Soc.</i> 2016, 138, 12727-12730	2017	Yes	Yes	No
12	2016			Jiang-Lin Hu, Liang-Wen Feng, Lijia Wang, Zuowei Xie*, Yong Tang*, Xiaoge Li	Enantioselective Construction of Cyclobutanes: A New and Concise Approach to the Total Synthesis of (+)-Piperarboranine B, <i>J. Am. Chem. Soc.</i> 2016, 138, 13151-13154	2017	Yes	Yes	No
13	2016			Dongmei Liu, Zaozao Qiu, Zuowei Xie*	Synthesis, Structure, and Reactivity of Mixed-Sandwich Zirconacarborane Methyl Complex $\eta^5\text{-C}_5\text{Me}_5[\eta^1:\eta^5\text{-(Me}_2\text{NCH}_2\text{CH}_2\text{)}_2\text{C}_2\text{B}_9\text{H}_{10}]\text{ZrMe}$, <i>J. Organomet. Chem.</i> 2016, 822, 144-153		Yes	Yes	No
14	2017			Hangcheng Ni, Zaozao Qiu, Zuowei Xie*	Photoarylation of Iodocarboranes with Unactivated (Hetero)Arenes: Facile Synthesis of 1,2-[(Hetero)Aryl] <i>n</i> - <i>o</i> -Carboranes (<i>n</i> = 1,2) and <i>o</i> -Carborane-Fused Cyclics, <i>Angew. Chem. Int. Ed.</i> 2017, 56, 712-716		Yes	Yes	No
15	2017			Ruofei Cheng, Zaozao Qiu*, Zuowei Xie	Iridium-Catalyzed Regioselective Borylation of Carboranes via Direct B-H Activation, <i>Nat. Commun.</i> 2017, 8, 14827-14833		Yes	Yes	No
16	2017			Dongmei Liu, Zaozao Qiu, Zuowei Xie*	Reactivity of Mixed-Sandwich Zirconacarborane Alkyls with Polar Unsaturated Molecules, <i>J. Organomet. Chem.</i> 2017, 847, 97-104		Yes	Yes	No
17	2017			Yangjian Quan*, Hairong Lyu, Zuowei Xie*	Dehydrogenative Cross-Coupling of <i>o</i> -Carborane with Thiophenes via Ir-Catalyzed Regioselective Cage B-H and C(sp ²)-H Activation, <i>Chem. Commun.</i> 2017, 53, 4818-4821		Yes	Yes	No
18	2017			Cen Tang, Jiji Zhang, Zuowei Xie*	Direct Nucleophilic Substitution Reaction of Cage B-H Bonds by Grignard Reagents: A Route to Regioselective B(4)-Alkylation of <i>o</i> -Carboranes, <i>Angew. Chem. Int. Ed.</i> 2017, 56, 8642-8646		Yes	Yes	No
19	2017			Jie Zhang, Zaozao Qiu*, Zuowei Xie*	Broad Scope [4 + 2] Cycloaddition of <i>o</i> -Carboryne with Pentafulvenes Using 1-Li-2-OTf- <i>o</i> -C ₂ B ₁₀ H ₁₀ as Precursor, <i>Organometallics</i> 2017, 36, 3806-3811		Yes	Yes	No

20	2017				Hairong Lyu, Yangjian Quan*, Zuowei Xie*	Transition Metal Catalyzed Regioselective B(4)-Halogenation and B(4,5)-Diiodination of Cage B-H Bonds in <i>o</i> -Carboranes, <i>Chem. Eur. J.</i> 2017, 23, 14866-14871		Yes	Yes	No
21	2018				Chun-Xiao Cui, Shikuo Ren, Zaozao Qiu*, Zuowei Xie*	Synthesis of Carborane-Fused Carbo- and Heterocycles via Zirconacyclopentane Intermediates, <i>Dalton Trans.</i> 2018, 47, 2453-2459		Yes	Yes	No
22	2018				Yangjian Quan, Zaozao Qiu, Zuowei Xie*	Transition Metal Catalyzed Selective Cage B-H Functionalization of <i>o</i> -Carboranes, <i>Chem. Eur. J.</i> 2018, 24, 2795-2805		Yes	Yes	No
23	2018				Rongyi Zhang, Yinggen Yuan, Zaozao Qiu*, Zuowei Xie*	Reaction of <i>o</i> -Carboryne with Furans: Facile Synthesis of Carborane-Fused Oxanorbornenes and Their Derivatives, <i>Chin. J. Chem.</i> 2018, 36, 273-279		Yes	Yes	No
24	2018				Tek Long Chan, Zuowei Xie*	Synthesis, Structure and Aromaticity of Carborane-Fused Carbo- and Heterocycles, <i>Chem. Sci.</i> 2018, 9, 2284-2289		Yes	Yes	No
25	2018				Ruofei Cheng, Bowen Li, Jie Wu, Jie Zhang, Zaozao Qiu*, Wenjun Tang, Shu-Li You, Yong Tang, Zuowei Xie*	Enantioselective Synthesis of Chiral-at-Cage <i>o</i> -Carboranes via Pd-Catalyzed Asymmetric B-H Substitution, <i>J. Am. Chem. Soc.</i> 2018, 140, 4508-4511		Yes	Yes	No
26	2018				Hairong Lyu, Yangjian Quan*, Zuowei Xie*	Rhodium Catalyzed Cascade Cyclization Featuring B-H and C-H Activation: One-Step Construction of Carborane-Fused <i>N</i> -Polyheterocycles, <i>Chem. Sci.</i> 2018, 9, 6390-6394		Yes	Yes	No

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered (Please attach a copy of each delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)

Month/Year/Place	Title	Conference Name	Submitted to RGC (indicate the year ending of the relevant progress report)	Attached to this report (Yes or No)	Acknowledged the support of this Joint Research Scheme (Yes or No)	Accessible from the institutional repository (Yes or No)
June/2015/Caen, France	Reactivity of 1,2-Dehydro- <i>o</i> -Carborane: Synthesis of Substituted <i>o</i> -Carboranes (Keynote Lecture)	11th International Conference on Heteroatom Chemistry (ICHAC-11)	2017	Yes	Yes	No

June/2016/K ingston, Canada	Transition Metal Catalyzed Selective B-H Activation and Functionalization of Carboranes (Invited Lecture)	XV Boron in the Americas Conference (BORAM XV)	2017	Yes	Yes	No
July/2017/P aris, France	Transition metal catalyzed B-H activation and functionalization of carboranes (Plenary Lecture)	International Conference On Phosphorus, Boron and Silicon 2017		Yes	Yes	No
June/2018/T aipei	Transition Metal Catalyzed Selective B-H Activation and Functionalization of Carboranes (Invited Lecture)	4 th International Conference on Organometallics and Catalysis		Yes	Yes	No

10. Student(s) trained (Please attach a copy of the title page of the thesis.)

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Hu Jiang-Lin	PhD	2011-09-01	2016-06-10
Cheng Ruofei	PhD	2013-09-01	2018-06-10
Ge Yixiu	MPhil	2014-09-01	2017-06-10
Chan Tek Long	PhD	2012-08-01	2017-05-15
Zhang Jie	PhD	2014-08-01	2018-08-01

11. Other impact (e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)

- One PhD student (Hu Jiang-Lin) has been trained under the co-supervision of both Hong Kong PI and Mainland PI.
- One Student (Cheng Ruofei) received the CAS Presidential Award from The Chinese Academy of Sciences (2018)
- We have developed a collaborative project with Prof. Zhenyang Lin of HKUST, leading to a joint publication.