

RGC Ref.: M-HKUST607/12

(please insert ref. above)

**The Research Grants Council of Hong Kong
SRFDP & RGC ERG Joint Research Scheme
Completion Report**

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

Part A: The Project and Investigator(s)

1. Project Title

Development of New Environmentally Friendly Green Catalytic Processes for Chiral Drug Discovery

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

	Hong Kong Team	Mainland Team
Name of Principal Investigator <i>(with title)</i>	Jianwei Sun	Jing Zhao
Post	Assistant Professor	Professor
Unit / Department / Institution	Department of Chemistry HKUST	School of Life Sciences, Nanjing University
Contact Information	+852 2358 7351 sunjw@ust.hk	+86-25-89681978 jingzhao@nju.edu.cn
Co-investigator(s) <i>(with title and Institution)</i>		
PhD student(s) (with period of involvement)	Wanxiang Zhao, from <u>1 Mar 2013</u> to <u>31 Dec 2013</u> Zhaobin Wang, from <u>1 Mar 2013</u> to <u>31 Aug 2014</u> Hui Qian, from <u>1 Mar 2013</u> to <u>31 Aug 2015</u> Yong Wang, from <u>1 Sep 2014</u> to <u>29 Feb 2016</u> Institution: Hong Kong UST	

Note: The Hong Kong project team must involve at least one research postgraduate student pursuing a Doctor of Philosophy degree at the UGC-funded university (PhD student) at any time throughout the project period.

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval (<i>must be quoted</i>)
Project Start date	1 Mar 2013		
Project Completion date	29 Feb 2016		
Duration (<i>in month</i>)	36		
Deadline for Submission of Completion Report	28 Feb 2017		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. *To develop chiral organic acid-catalyzed rapid construction of alkaloid-type polycyclic compounds with anticancer activity.*
2. *To expand the structural diversity of the multicomponent reaction with a matrix of diverse starting materials.*
3. *To evaluate the biological activities of the 1,2,3,4-tetrahydroisoquinoline (THIQ) products and identify drug candidates through additional structure-activity relationship studies.*

5.2 Revised Objectives

NA

6. Research Outcome

Through this project, we have achieved a range of new reactions catalyzed by organic catalysts. The major findings and research outcome are listed here.

- (1) We have developed a novel catalytic asymmetric intermolecular process for the efficient formation of *acyclic all-carbon quaternary* stereocenters from racemic tertiary alcohols.

- (2) We have developed a new organocatalytic transfer hydrogenation strategy for the efficient asymmetric synthesis of 1,1-diarylethanes, an important family of compounds with broad medicinal and agricultural applications.
- (3) We have developed the first catalytic enantioselective desymmetrization of azetidines. Despite the low propensity of azetidine ring-opening and significant challenge in stereocontrol, the smooth intermolecular desymmetrization of a wide range of 3-substituted azetidines has been achieved with both excellent efficiency and remarkable enantioselectivity, enabled by optimal combination of catalysts, protective groups, nucleophiles, and reaction conditions.
- (4) We have developed a new general and mild catalytic asymmetric 1,6-conjugate addition process of *para*-quinone methides. The process represents not only a new member of the small family of asymmetric reactions of *p*-QMs, but also the first of such processes with general scope enabling efficient and mild formation of all-carbon quaternary stereocenters.
- (5) We have developed the first catalytic asymmetric intermolecular alcohol addition to *o*-QMs.
- (6) We have established the first Brønsted acid catalyzed enantioselective addition of thiols to the in situ generated *o*-QMs.
- (7) We have developed a new catalytic asymmetric approach for the synthesis of chiral 1,4-dioxanes, an important scaffold of broad utility but lacking general and efficient access. It is also the first demonstration of organocatalytic oxetane desymmetrization by an alcohol nucleophile.
- (8) We have developed an efficient organocatalytic enantioselective intermolecular addition of naphthols to in-situ generated *para*-quinone methides.
- (9) Asymmetric opening of oxetanes is a challenging topic. In this project, we achieved the first asymmetric chloride opening of oxetanes, providing expedient access to highly functionalized three-carbon chiral building blocks with excellent efficiency and stereocontrol.
- (10) The Piancatelli rearrangement is a large family of powerful transformations that provide rapid access to valuable cyclopentenone building blocks. However, the catalytic enantioselective example of this family has remained unknown. In this project, we have achieved the first example of this family.

Potential for further development of the research and the proposed course of action:

We have developed a range of new organocatalytic reactions in this project. Nevertheless, challenges remain to be addressed, and these are potential future efforts and directions. For example, we will need to follow up on some of the initial results we have obtained, such as more mechanistic studies and biological studies on the interesting structures. These studies will be ongoing in our laboratory.

The PI also visited the mainland team on Mar 13 and Dec 26-27, 2014 as well as May 11-12, 2015. The visits allowed scientific discussions as well as exchange on progress on the collaboration.

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)

We have developed a range of new organocatalytic asymmetric reactions, providing access to a diverse set of chiral molecules that are potentially biologically significant. Initial biological studies have demonstrated that some of the structures exhibit anticancer activity. These results not only contribute to the fundamental asymmetric catalysis, but may also lead to potential application in drug discovery.

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 belonging to the project teams and denote the corresponding author with an asterisk*</i>)	Title and Journal/ Book (with the volume, pages and other necessary publishing details specified)	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)
Year of publication	Year of Acceptance (For paper accepted but not yet published)	Under Review	Under Preparation (optional)						
2014				Wanxiang Zhao, Zhaobin Wang, Boyang Chu, Jianwei Sun*	<i>Enantioselective Formation of All-Carbon Quaternary Stereocenters from Indoles and Tertiary Alcohols Bearing A Directing Group, Angew. Chem. Int. Ed. 2015, 54, 1910–1913</i>	2014	Yes	Yes	Yes

2014				Xiuqin Dong, Jianwei Sun*	<i>Catalytic Asymmetric α-Aldol Reaction of Vinylogous N-Heterocyclic Carbene Enolates: Formation of Quaternary and Labile Tertiary Stereocenters, Org. Lett. 2014, 16, 2450–2453</i>	2017	Yes	Yes	Yes
2015				Xiuqin Dong, Wen Yang, Weimin Hu, Jianwei Sun*	<i>N-Heterocyclic Carbene Catalyzed Enantioselective α-Fluorination of Aliphatic Aldehydes and α-Chloro Aldehydes: Synthesis of α-Fluoro Esters, Amides, and Thioesters, Angew. Chem. Int. Ed. 2015, 54, 660–663</i>	2017	Yes	Yes	Yes

2015				Zhaobin Wang, Fujin Ai, Zheng Wang, Wanxiang Zhao, Guangyu Zhu,* Zhenyang Lin,* Jianwei Sun*	<i>Organocatalytic Asymmetric Synthesis of 1,1-Diarylethanes by Transfer Hydrogenation</i> <i>J. Am. Chem. Soc., 2015, 137, 383–389</i>	2017	Yes	Yes	Yes
2015				Zhaobin Wang, Fu Kit Sheong, Herman H. Y. Sung, Ian D. Williams, Zhenyang Lin,* Jianwei Sun*	<i>Catalytic Enantioselective Intermolecular Desymmetrization of Azetidines</i> <i>J. Am. Chem. Soc. 2015, 137, 5895–5898</i>	2017	Yes	Yes	Yes
2015				Zhaobin Wang, Yuk Fai Wong, Jianwei Sun*	<i>Catalytic Asymmetric 1,6-Conjugate Addition of para-Quinone Methides: Formation of All-Carbon Quaternary Stereocenters,</i> <i>Angew. Chem. Int. Ed. 2015, 54, 13711–13714</i>	2017	Yes	Yes	Yes

2015				Zhaobin Wang, Jianwei Sun*	<i>Recent Advances in Catalytic Asymmetric Reactions of o-Quinone Methides, Synthesis 2015, 47, 3629-3644.</i>	2017	Yes	Yes	Yes
2015				Zengwei Lai, Zhaobin Wang, Jianwei Sun*	<i>Organocatalytic Asymmetric Nucleophilic Addition to o-Quinone Methides by Alcohols, Org. Lett. 2015, 17, 6058-6061</i>	2017	Yes	Yes	Yes
2016				Zengwei Lai, Jianwei Sun*	<i>Enantioselective Addition of Thiols to ortho-Quinone Methides Catalyzed by Chiral Phosphoric Acids, Synlett 2016, 27, 555-558</i>	2017	Yes	Yes	Yes

2016				Wen Yang, Jianwei Sun*	<i>Organocatalytic Enantioselective Synthesis of 1,4-Dioxanes and Other Oxa-Heterocycles by Oxetane Desymmetrization, Angew. Chem. Int. Ed. 2016, 55, 1868–1871</i>	2017	Yes	Yes	Yes
2016				Yuk Fai Wong, Zhaobin Wang, Wen-Xu Hong, Jianwei Sun,*	<i>A one-pot oxidation/cycloaddition cascade synthesis of 2,4-diaryl chromans via ortho-quinone methides, Tetrahedron, 2016, 72, 2748-2751</i>	2017	Yes	Yes	Yes

2016				Yuk Fai Wong, Zhaobin Wang, Jianwei Sun*	<i>Chiral phosphoric acid catalyzed asymmetric addition of naphthols to para-quinone methides</i> , <i>Org. Biomol. Chem.</i> , 2016, 14, 5751-5754	2017	Yes	Yes	Yes
2016				Wen Yang, Zhaobin Wang, and Jianwei Sun*	<i>Enantioselective Oxetane Ring Opening with Chloride: Unusual Use of Wet Molecular Sieves for the Controlled Release of HCl</i> , <i>Angew. Chem. Int. Ed.</i> 2016, 55, 6954 –6958	2017	Yes	Yes	Yes
2016				Huilin Li, Rongbiao Tong, Jianwei Sun*	<i>Catalytic Enantioselective Aza-Pinacatelli Rearrangement</i> , <i>Angew. Chem. Int. Ed.</i> 2016, 55, 15125 –15128	2017	Yes	Yes	Yes

2016				Wen Yang, Weimin Hu, Xiuqin Dong, Xin Li, Jianwei Sun*	<i>N-Heterocyclic Carbene Catalyzed α-Dihalo methylation of Enals by Single-Electron Transfer, Angew. Chem. Int. Ed. 2016, 55, 15783–15786</i>	2017	Yes	Yes	Yes
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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)
Aug, 2014 Beijing	Organocatalytic Asymmetric Ring-Opening of Strained Rings	The 29 th Annual National Meeting of Chinese Chemical Society	2014	Yes	Acknowledged in the abstract and also verbally in the presentation	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
Wanxiang Zhao	PhD	Feb. 2011	Jan. 2014
Zhaobin Wang	PhD	Sep. 2011	Aug. 2015
Hui Qian	PhD	Sep. 2011	Aug. 2015
Yong Wang	PhD	Sep. 2014	Jan. 2017

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

- (a) With this project, we also established collaborations with other prestigious universities, such as Peking University Shenzhen Graduate School and City University of Hong Kong.
- (b) Because of the initial success of this project, as a part of the research output of our group, the PI has been awarded the Thieme Chemistry Journal Award and Asia Core Program Lectureship Award.
- (c) Wanxiang Zhao, one of the members of this project, has graduated with a PhD degree and is now a professor in Hunan University, China. He is also a recipient of “Young Thousand Talent Program” from the Chinese Government. He also obtained the School Research Award from the School of Science of the Hong Kong University of Science and Technology.
- (d) Hui Qian is a recipient of the “Young Scientist Award” of the School of Science of Hong Kong University of Science and Technology. He is now a faculty member of Fudan University, China.
- (e) Zhaobin Wang graduated with a PhD degree and is currently a postdoctoral fellow at Caltech.