| RGC Ref.: N_CUHK451/13<br>NSFC Ref. : 21361162001 |
|---|
| *(please insert ref. above)* |

# 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

Palladium-catalyzed Asymmetric Allylic Alkylations and Its Application in Total Synthesis of Cryptotrione and Bolivianine

**鈀催化的不對稱烯丙基取代反應及其在Cryptotrione和Bolivianine全合成中的應用**

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

| | Hong Kong Team | Mainland Team |
|---|---|---|
| Name of Principal Investigator *(with title)* | Professor Henry N. C Wong | Professor Xue-Long Hou |
| Post | Research Professor of Chemistry | Research Fellow |
| Unit / Department / Institution | NA/Chemsitry/The Chinese University of HongKong | Shanghai Institute of Organic Chemistry / The Chinese Academy of Sciences |
| Contact Information | hncwong@cuhk.edu.hk | xlhou@sioc.ac.cn |
| Co-investigator(s) *(with title and institution)* | Professor Xiao-Shui Peng<br><br>Research Associate Professor | Professor Chang-Hua Ding<br>Associate Research Fellow<br>and<br>Professor Bing-Feng Sun<br>Associate Research Fellow |

### 3. Project Duration

| | Original | Revised | Date of RGC/ Institution Approval *( must be quoted*) |
|---|---|---|---|
| Project Start date | 01/01/2014 | NA | NA |
| Project Completion date | 31/12/2017 | NA | NA |
| Duration *(in month)* | 48 | NA | NA |
| Deadline for Submission of Completion Report | 31/12/2018 | NA | NA |

## Part B: The Completion Report

## 5. Project Objectives

### 5.1 Objectives as per original application

1. To develop an efficient protocol of new Pd-catalyzed asymmetric cyclopropanation and allylic alkylations using ferrocene-based *P*,*N*- and SIOCPhox ligand series.
2. To apply the newly developed Pd-catalyzed asymmetric cyclopropanation and allylic alkylations with hard carbanion to the total synthesis of cryptotrione and bolivianine.
3. To synthesize potentially active compounds that could provide important insights into their structure-activity relationships via Pd-catalyzed asymmetric cyclopropanation and allylic alkylations using ferrocene-based *P*,*N*- and SIOCPhox ligand series.

4. To apply the newly developed protocol to the synthesis of more elaborate structures leading to the total synthesis of structurally complex and biologically significant natural products or drug lead compounds.
5. To strengthen the research collaboration between Hong Kong and the Chinese Mainland.

5.2 Revised Objectives

Date of approval from the RGC: NA

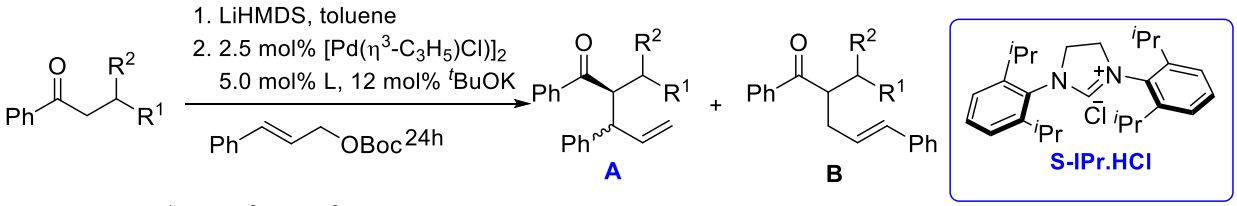
Reasons for the change: NA

## 6. Research Outcome

### Major findings and research outcome

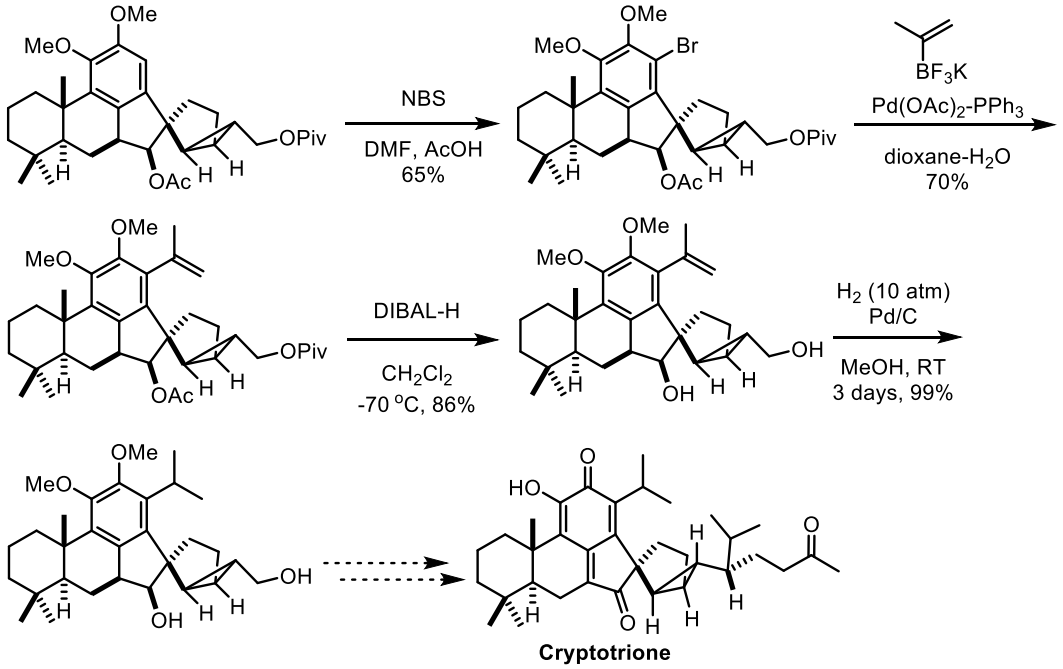
***(maximum 1 page; please make reference to Part C where necessary)***

A novel, simple and effective Pd/NHC-catalysed protocol has been developed to produce acyclic a-allylated ketones bearing three contiguous stereocentres with excellent regio and diastereoselectivities, starting with readily available ketones and allyl reagents. This reaction features facile yet highly efficient Pd catalysis, the use of commercially available NHC ligands and wide substrate scope. It was found that substituents on the NHC and b-substituents on ketones have a critical impact on the stereochemistry of the reaction. The synthetic applications of the methodology have also been examined preliminarily. The products from current protocol are likely to be useful in the synthesis of more complex molecules.




**a:** $R^1$ = H; $R^2$ = H; $R^3$ = Ph: 95% yield, A/B = 95/5; *syn/anti* = 20/80
**b**: $R^1$ = $R^2$ = Me; $R^3$ = Ph: 98% yield, A/B = 99/1; *syn/anti* = 92/8

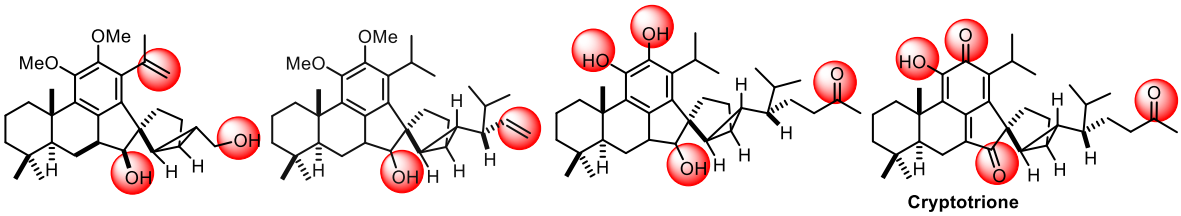
With our preliminary results of producing fused bicyclo[3.1.0]hexane motif, we applied the strategies for the total synthesis of cryptotrione, one of the most bioactive members of cryptotrione family. Up to date, the critical constructing the core bicyclo[3.1.0]skeleton of cryptotrione was achieved through the conversion of the 1,5-enyne precursors into a substituted bicyclo[3.1.0]hexane unit. Upon accomplishment of our proposed formation of *trans*-polycyclic core followed by isopropylation, the key *trans*-polycyclic diol precursor with all the carbon ring systems was achieved. Obviously, the subsequent installation of the side chain followed by generation of the relevant quinone methide unit with suitable oxidative reagents from this diol adduct would eventually afford our synthetic target cryptotrione.




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

In this proposal, cryptotrione is the potential active terpenes from the bark of *Cryptomeria japonica*. Therefore, the development of a general, efficient, and conceptually new strategy for the enantioselective total synthesis of cryptotrione in this proposal is particularly important and challenging. These synthetic works in our proposal will broaden the range of quinone methide terpene beyond those immediately related to cryptotrione. Since the core structure of our synthesized compounds is also similar to that of cryptotrione, and all cyclopropyl moiety and their analogs could be investigated and evaluated as biochemical tools for the study of their possible biological action, as well as serve as possible leads in the development of their relevant drug discovery. The completion of the synthesis and biological evaluation of these compounds, as well as their relevant derivatives derived after ***further***

***transformations on ketone/phenol group, hydroxyl groups***, *et al*, as shown below, would provide insight in the design of the analogs of cryptotrione. These derivatives would allow us to have a better understanding of their biological action and biogenetic synthetic approach. A continuing extension of these studies to additional cryptotrione family will be also directed at further investigation of total synthesis of other family members in biomimetic pathways.




## 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)*

In this funded project, the developed synthetic protocol and synthetic studies of cryptotrione family herein will broaden range and synthesis of bioactive derivatives beyond those related to cryptotrione. The relevant SAR studies of synthetic intermediates and their analogs could be investigated and evaluated for their relevant discovery of lead candidates, as well as for the study of their possible biological action and biogenetically synthetic protocol in nature, and could be applied for academic research and industry. With the development, the strategies herein can help to maintain the legacy of natural products in drug discovery and understanding of relevant biological actions. Generally, this proposed research will demonstrate the power and potential of our developed protocol to render scarce biologically active natural products readily available for chemical and biological investigations. Moreover, structural analysis of new compounds produced in this proposal will be carried out and this will lead to a greater understanding of the fundamental chemistry involved. This project would also yield invaluable information about a range of novel synthetic reactions and also a novel route for the synthesis of bioactive compounds.

# 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) *(**bold** the authors belonging to the project teams and denote the corresponding author with an asterisk*)* | 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)* | | | | | | |
| 1 | 2014 | | | | Tian, X.-Y.; Han, J.-W.; Zhao, Q.; Wong, H. N. C. | Asymmetric synthesis of 3,3,5,5-tetrasubstituted 1,2-dioxolanes: total synthesis of epiplakinic acid F<br>*Org. Biomol. Chem.*, **2014**, *12*, 3686-3700. | 2015 | Yes | No | No |
| 2 | 2014 | | | | Xiong, X.-D.; Deng, C.-L.; Peng X.-S.; Miao, Q.; Wong, H. N. C. | Heteroatom-bridged Tetraphenylenes: Synthesis, Structures, and Properties<br>*Org. Lett.,* **2014**, *16,* 3252-3255. | 2015 | Yes | No | No |
| 3 | 2014 | | | | Li, Q.; Peng, X.-S.; Wong, H. N. C. | Brønsted acid-catalyzed synthesis of carbazoles from 2-substituted indoles<br>*Org. Chem. Front*., **2014**, *1*, 1197-1200. | 2015 | Yes | Yes | No |
| 4 | 2015 | | | | Peng, X.-S.; Ylagan, R. M. P.; Siu, Y. M.; Wong, H. N. C. | Synthesis and Application of [3.3.0]Furofuranone in Total Synthesis<br>*Chem. Asian J.* **2015**, *10*, 2070-2083. | 2015 | Yes | Yes | No |
| 5 | 2015 | | | | Li, Z.-Q.; Li, Q.-J.; Liu, G.-K.; Chen, W.-M.; Peng, X.-S.; Wong, H. N. C | Gold(I)-catalyzed Domino Cyclization for the Synthesis of Tricyclic Chromones<br>*Synlett*, **2015**, 1461-1464. | 2015 | Yes | Yes | No |
| 6 | 2015 | | | | Xiong, X.-D.; Deng, C.-L.; Minaev, B. F.; Baryshnikov, G. V.; Peng, X.-S.; Wong, H. N. C. | Tetrathio and Tetraseleno[8]circulenes: Synthesis, Structures, and Properties<br>*Chem. Asian J.* **2015**, *10*, 969-975. | 2015 | Yes | Yes | No |
| 7 | 2015 | | | | Han, J.-W.; Li, X.; Wong, H. N. C. | Our Expedition in Eight-Membered Ring Compounds: From Planar Dehydrocyclooctenes to Tub-Shaped Chiral Tetraphenylenes<br>*Chem. Rec.* **2015**, *15,* 107-131. | 2015 | Yes | No | No |
| 8 | 2015 | | | | Chen, J.-X.; Han, J.-W.; Wong, H. N. C. | Synthesis and Chiroptical Properties of Double-Helical (M)- and (P)-*o*-Oligophenylenes<br>*Org. Lett.* **2015**, *17,* 4296-4299. | 2015 | Yes | Yes | No |
| 9 | 2016 | | | | Li, X.; Han, J.-W.; Wong, H. N. C. | Palladium-Catalyzed Double Ullmann Reaction: An Approach towards Tetraphenylenes<br>*Asian J. Org. Chem.* **2016**, *5*, 74-81 (**Cover paper**). | 2015 | Yes | Yes | No |
| 10 | 2016 | | | | Jia, Z.-H.; Liu, Q.; Peng, X.-S.; Wong, H. N. C. | Iron-catalysed cross-coupling of organolithium compounds with organic halides<br>*Nature Communications* **2016**, 7:10614 doi: 10.1038/ncomms10614. | 2015 | Yes | Yes | No |
| 11 | 2017 | | | | Li, X.; Han, J. W.; Zhang, Y. X.; Wong, H. N. C. | Palladium-Catalyzed Double Suzuki Reactions: Synthesis of Dibenzo 4,5:6,7 cyclohepta 1,2,3-de naphthalenes. *Asian Journal of Organic Chemistry* **2017**, *6*, 1876-1884. | NA | Yes | Yes | No |
| 12 | 2017 | | | | Chai, G. L.; Han, J. W.; Wong, H. N. C. | Asymmetric Darzens Reaction of Isatins with Diazoacetamides Catalyzed by Chiral BINOL-Titanium Complex. *Journal of Organic Chemistry* **2017**, *82*, 12647-12654. | NA | Yes | Yes | No |
| 13 | 2018 | | | | Liu, Q.; Wang, B.; Peng, X. S.; Wong, H. N. C. | Effects of Additives in Iron-Catalyzed Cross-Coupling Reactions Involving Grignard Reagents. *Chinese Journal of Organic Chemistry* **2018**, *38*, 40-50. | NA | Yes | Yes | No |
| 14 | 2018 | | | | Wu, J. L.; Lu, Y. S.; Tang, B. C.; Peng, X. S. | Total syntheses of shizukaols A and E. *Nature Communications* **2018**, *9*. 4040 | NA | Yes | Yes | No |
| 15 | 2018 | | | | Lu, X. L.; Lyu, M. Y.; Peng, X. S.; Wong, H. N. C. | Gold(I)-Catalyzed Tandem Cycloisomerization of 1,5-Enyne Ethers by Hydride Transfer. *Angewandte Chemie-International Edition* **2018**, *57*, 11365-11368. | NA | Yes | Yes | No |
| | | | | | | | | | | |
| 16 | 2015 | | | | Zhang, Q.-S., Wan, S.-L., Chen, D., Ding, C.-H., & Hou, X.-L. | Palladium-Catalyzed Asymmetric Intermolecular Mizoroki–Heck Reaction for Construction of a Chiral Quaternary Carbon Center<br>*Chem. Commun.* **2015**, *51*, 12235-12238. | 2015 | Yes | Yes | No |
| 17 | 2015 | | | | Bai, D.-C., Wang, W.-Y., Ding, C.-H., & Hou, X.-L. | Kinetic Resolution of Unsymmetrical Acyclic Allyl Carbonates Using Trimethylsilyl Cyanide via Pd-Catalyzed Asymmetric Allylic Alkylation<br>*Synlett* **2015**, *26*, 1510-1514. | 2015 | Yes | Yes | No |
| 18 | 2015 | | | | Li, H., Wan, S.-L., Ding, C.-H., Xu, B., & Hou, X.-L. | Kinetic resolution of 2-substituted-2,3-dihydrofurans by a palladium-catalyzed asymmetric Heck reaction.<br>*RSC Advances,* **2015**, *5*, 75411-75414. | 2015 | Yes | Yes | No |

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|---|---|---|---|---|---|---|---|---|---|---|
| 19 | 2016 | | | | Li, X. H.; Wan, S. L.; Chen, D.; Liu, Q. R.; Ding, C. H.; Fang, P.; Hou, X. L. | Enantioselective Construction of Quaternary Carbon Stereocenter via Palladium-Catalyzed Asymmetric Allylic Alkylation of Lactones. *Synthesis-Stuttgart* **2016**, *48*, 1568-1572. | NA | Yes | Yes | No |
| 20 | 2017 | | | | Suo, J. J.; Du, J.; Liu, Q. R.; Chen, D.; Ding, C. H.; Peng, Q.; Hou, X. L. | Highly Diastereo- and Enantioselective Palladium-Catalyzed 3+2 Cycloaddition of Vinyl Epoxides and alpha,beta-Unsaturated Ketones. *Organic Letters* **2017**, *19*, 6658-6661. | NA | Yes | Yes | No |
| 21 | 2017 | | | | Li, H.; Gao, A.; Liu, X. Y.; Ding, C. H.; Xu, B.; Hou, X. L. | Kinetic Resolution of 5-Substituted Cyclohexenols by Palladium-Catalyzed Asymmetric Redox-Relay Heck Reaction. *Synthesis-Stuttgart* **2017**, *49*, 159-166. | NA | Yes | Yes | No |
| 22 | 2017 | | | | Jiang, Z. Z.; Gao, A.; Li, H.; Chen, D.; Ding, C. H.; Xu, B.; Hou, X. L. | Enantioselective Synthesis of Chromenes via a Palladium-Catalyzed Asymmetric Redox-Relay Heck Reaction. *Chemistry-an Asian Journal* **2017**, *12*, 3119-3122. | NA | Yes | Yes | No |
| 23 | 2017 | | | | Jiang, Y. J.; Zhang, G. P.; Huang, J. Q.; Chen, D.; Ding, C. H.; Hou, X. L. | Palladium-Catalyzed Asymmetric Allylic Alkylation of Alkyl-Substituted Allyl Reagents with Acyclic Amides. *Organic Letters* **2017**, *19*, 5932-5935. | NA | Yes | Yes | No |
| 24 | 2017 | | | | Huang, J. Q.; Zhao, J. F.; Yang, Z.; Ding, C. H.; Hou, X. L.; Peng, X. S.; Wong, H. N. C. | Pd-Catalyzed Cyclopropanation Reaction of Aliphatic Ketones with Monosubstituted Allyl Reagents. *Asian Journal of Organic Chemistry* **2017**, *6*, 1769-1772. | NA | Yes | Yes | No |
| 25 | 2017 | | | | Gao, A.; Liu, X. Y.; Li, H.; Ding, C. H.; Hou, X. L. | Synthesis of beta,beta-Disubstituted Indanones via the Pd-Catalyzed Tandem Conjugate Addition/Cyclization Reaction of Arylboronic Acids with alpha,beta-Unsaturated Esters. *Journal of Organic Chemistry* **2017**, *82*, 9988-9994. | NA | Yes | Yes | No |
| 26 | 2017 | | | | Gao, A.; Liu, X. Y.; Ding, C. H.; Hou, X. L. | Diastereoselective Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to $\alpha$-Substituted Cyclic Enones. *Synlett* **2017**, *28*, 2829-2832. | NA | Yes | Yes | No |
| 27 | 2017 | | | | Bai, D. C.; Liu, X. Y.; Li, H.; Ding, C. H.; Hou, X. L. | Tandem Thorpe Reaction/Palladium Catalyzed Asymmetric Allylic Alkylation: Access to Chiral $\beta$-enaminonitriles with Excellent Enantioselectivity. *Chemistry-an Asian Journal* **2017**, *12*, 212-215. | NA | Yes | Yes | No |
| 28 | 2018 | | | | Huang, J. Q.; Liu, W.; Zheng, B. H.; Liu, X. Y.; Yang, Z.; Ding, C. H.; Li, H.; Peng, Q.; Hou, X. L. | Pd-Catalyzed Asymmetric Cyclopropanation Reaction of Acyclic Amides with Allyl and Polyenyl Carbonates. Experimental and Computational Studies for the Origin of Cyclopropane Formation. Acs Catalysis **2018**, 8, 1964-1972. | NA | 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)* |
|---|---|---|---|---|---|---|
| 10/2014/Kyoto | Planarity or Non-Planarity : Variations on a Theme of Tetraphenylene | International Symposium on the Synthesis and Application of Curved Organic pi-Molecules and Materials (CURO-pi)", | 2015 | Yes | Yes | No |
| 11/2015/Kyoto | Synthetic Studies towards Shizukaol A and Dhilirolide A | The 5th International Kyoto Symposium on Organic Nanostructures and Molecular Technology | 2015 | Yes | Yes (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 |
|---|---|---|---|
| Yin-Suo Lu | PhD | 01/05/2010 | 31/06/2015 |
| Chun-Lin Deng | PhD | 01/08/2012 | 31/07/2015 |
| Jian-Li Wu | PhD | 01/08/2012 | 31/07/2017 |
| Mao-Yun Lyu | PhD | 01/08/2013 | 31/12/2017 |

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

NA