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Abstract

Nowadays, human beings are facing several global health challenges that are threatening human survivals. The global health challenges are so complicated that none of a single study or organization can tackle it by their own. For instance, medicines could play an important role in this process, yet it is also necessary to take account of diagnostics, vaccines, intellectual property, health policies, etc. Under current regime of highly fragmented disciplines, it is crucial to find a new discipline or mechanism to integrate relative studies in order to effectively resolve the issues.

This study aims to propose an integrated multi-directional approach to relieve the burden of malaria as an example to establish a new mechanism in the area of diseases of poverty, eventually contribute to the development of a new type of studies – Advanced Integrated Studies in Human Survivability. Malaria was chosen as a –representative example for its unique characteristics as a disease of poverty, as well as its severity of the disease burden. It is a parasitic disease which is widely spread in developing countries in tropical and subtropical regions. In 2015 alone, there were 212 million new cases and 429,000 deaths, most of which were children under 5 years old in Africa (estimated 303,000 deaths).

Successful research and development (R&D) models have proved that intellectual property (IP) sharing and IP creation are two important factors to explore. Based on this background, one dimension of the approach in this study focuses on the IP sharing. With regard to medicines, IP generally has been criticized as a barrier when it concerns diseases of poverty due to highly disproportionate distribution of medical technologies and needs. The studies on access to the existing medicines and medical technologies have been attracted a considerable attention from various stakeholders. Recently, public-private partnership mechanism was developed by international organizations to ease the burden of diseases of poverty through IP sharing. Under the regime of the public-private partnerships, the potential use of IP sharing in the diseases of poverty was successfully demonstrated by emphasizing the positive role of IP. A thorough investigation on stakeholders within a representative public-private partnership was carried out to identify the important group of stakeholders, and a broader scope of stakeholder mapping was conducted based on the information obtained. To further improve IP sharing, an interactive and integrated IP sharing mechanism concerning a variety of research outcomes in the field of malaria drug development was proposed to address the issues identified in the current model. This research intends to assist scientists to build on the success of the previous work to further develop the promising candidates into products, as well as to learn from the negative results to strategically conduct future research.

The other dimension of the approach is creating new IP – development of innovative synthetic methods to simultaneously access to the multiple drug candidates as the direct contributions to the upstream R&D activities in the fight against malaria. Careful review on existing antimalarial drugs poses an important and urgent issue – drug resistance. In order to address drug resistance issues, two different types of natural product derivatives with prospect anti-malarial activities were designed.

The first synthetic method was to achieve improvement of lead compounds – quinolones. Accumulation of knowledge on drug mechanism revealed the potential use of quinolone derivatives as the next generation

antimalarial drugs. The research boom on screening a large amount of such derivatives resulted in several positive results and further consolidated this possibility. Based on this background, a new asymmetric synthetic method has been developed to obtain newly designed quinolone derivatives through the same type of versatile chiral intermediates which are also anticipated have antimalarial activity to a certain degree. The author found that the new benzothiadiazine catalyst significantly improved the enantioselectivity of the enantioselective epoxidation of α,β-unsaturated amides, and the subsequent transformations of the resulting chiral intermediates provided the desired functionalized dihydroquinolin-2-ones bearing various aryl groups at the C4 position.

The second synthetic method was built on the recent breakthrough on innovative antimicrobial peptides which target a wide range of pathogens. Their application to the antimalarial drugs is limited, yet it has a huge potential to widen the horizon of research dimension. To contribute to this research strategy, establishment of the challenging direct α-selective *N*-glycosylation was planned to add additional functionalities to the antimicrobial peptides. The method involves a smart integrated catalytic system with halogen bond donor, diarylthiourea, nucleophilic solvent, and additive. This is the first report which has succeeded in the direct α-selective *N*-glycosylation reaction with easily accessible substrates.

In conclusion, this research is to achieve one goal – combatting malaria from different perspectives – by focusing on IP sharing and IP creation. It is to demonstrate that an integrated approach is necessary to combat diseases of poverty by focusing on malaria as an example.

Introduction

i. Integrated studies in human survivability

Nowadays, human beings are facing several challenges that are threatening human survivals, such as energy shortage, environmental pollution, human health problems, growing population, etc. All these challenges are linked to each other and tackling one of them often resulted in alleviation or sometimes deterioration of others at certain level, since our society is united and functioning as a whole. For example, energy shortage can be settled with the help of nuclear energy. However, the nuclear energy presents serious safety issues to environment and human health without proper management. Human beings are forced to seek for an alternative solution as long as the safety of nuclear energy is not guaranteed. The connections among survival problems require complex and sophisticated approaches to address one specific problem without bringing negative influences to others. Hence, integrated studies are necessary to tackle social problems and ensure human survivals. Advanced Integrated Studies in Human Survivability are a group of harmonized design study to effectively resolve human survival issues and minimize possible collateral damages at the same time.

Under the scope of Advanced Integrated studies in Human Survivability, this study focuses on the gap between disease burden and scientific research and proposes an integrated approach to tackle it.

ii. The disease burden and scientific research

According to the latest data (2015) from World Health Organization (WHO)[1], the disease burden worldwide is as below:

① 52% of all deaths in low-income countries were caused by the communicable diseases, maternal causes, and conditions arising during pregnancy and childbirth, and nutritional deficiencies. On the contrary, less than 7% of deaths in high-income countries were due to such causes.

② Non-communicable diseases (NCDs) are responsible for 37% death in low-income countries and 88% in high-income countries. All but 1 of the 10 leading causes of deaths in high-income countries were NCDs. In terms of absolute number of deaths, however, 78% of global NCD deaths occurred in low- and middle-income countries.

From this data, it is easily to tell that low-income countries and high-income countries are suffering from different types of disease burdens. In low-income countries, communicable diseases are still a big issue while in high-income counties non-communicable diseases are the major threat. Yet, for all the countries in the world, scientific research is the key to the innovation which could in turn relieve the disease burdens. Research is vital in developing a medical technology, a medicine, a vaccine, as well as other types of medical products. Fortunately, the research on global health is steadily growing in the last few decades. Unfortunately, there is still a huge gap between disease burden and scientific research.

The landmark 1990 report from the Commission on Health Research for Development had shown that

less than 10% of global research spending was targeted at diseases that are responsible for more than 90% of the global burden of ill-health. This was owing to the low investment (5% of all funds) in the diseases in developing countries since the most research was arising from developed countries that have paid less attention to these diseases. The report recommended that more financial support for research should be obtained through international partnerships to lower the gap between research focus and disease burden.[2] In the following 20 years, there has been a growth of research worldwide. Major causes of illness and deaths have become a basis for setting research priorities,[3] and investment in research and development (R&D) activities were increased to turn these research priorities into research studies. In high-income countries, the investment in R&D is static in relation to gross domestic product (GDP), while in low-income countries investment in R&D has been growing 5% per year faster than GDP which is likely ascribed to the emerging economy in China and other eastern Asian countries (**Figure I).**

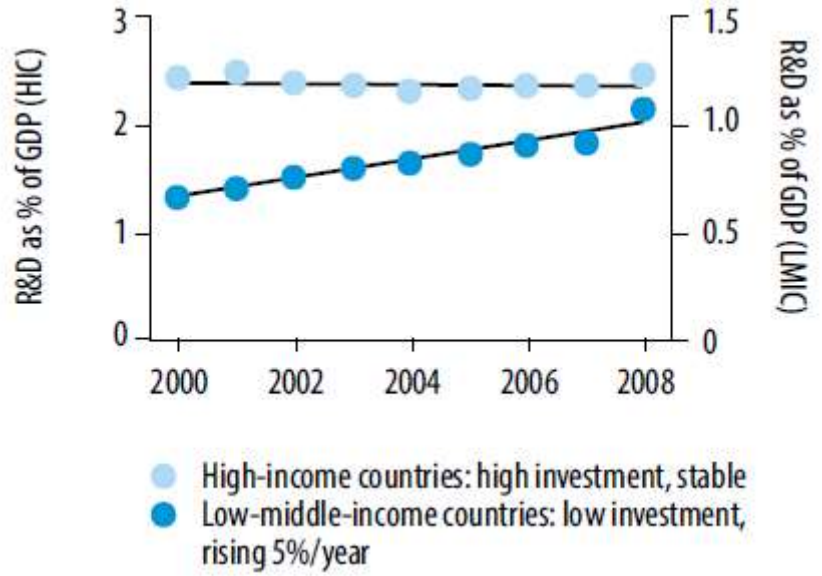


Figure I. Investment in R&D activities.
Source: WHO, *The World Health Report 2013*

Furthermore, the gap in research and disease burden has slowed down with international approaches to increase the funding for R&Ds in neglected diseases which mainly affect low- and middle-income countries.[4] In despite of all these improvements, there is still a significant gap in scientific research and diseases of poverty.

iii. Diseases of poverty and intellectual property

The disproportionate distribution of global R&D activities and diseases of poverty is due to the fact that intellectual property is playing a significant role in promoting innovations in pharmaceutical industry. The intellectual property system was developed to incentivize inventors mainly through a monetary reward.

Therefore, the innovation is hardly to occur when the market is not big enough, as the case of diseases of poverty.

According to the World Intellectual Property Organization (WIPO), intellectual property refers to creations of the mind. In general, intellectual property is protected in law, for example, patent law, copyright law and trademark law, which incentivizes people to earn recognition or financial reward from what they create or invent and eventually promote innovations. It gives the invention proper protection as a form of reward. At the same time, the information on the invention will be open to the public so that public can learn from the invention and develop further based on the information. In other words, intellectual property has two fundamental properties: providing incentives to the inventors/creators and disclosing information to the public. Due to the legal protection of intellectual property, it often causes access issues when it comes to public interests. Intellectual property associated with other factors (trade, government policy, etc.) is often criticized as a barrier to the access to the technologies or products that can serve public interests.

Nowadays, every industry relies on intellectual property at different levels to recoup their investment on the inventions, particularly in the developed world that has a more mature intellectual property system. Among them, the pharmaceutical industry's extreme and disproportionate reliance on intellectual property, especially on patents is confirmed and studied in previous work.[5] As is widely known, there are two reasons behind this. First of all, the development of a medicine usually requires a huge amount of money. Generally one billion US dollars are invested on a new medicine on average (now exceeds 2.5 billion US dollars)[6], which includes the money that has been spent to the failed R&D activities in the drug development process. In order to retrieve the investment costs, intellectual property is crucial since it can give appropriate legal protection for a certain period of time. Moreover, small molecules that are developed into medicines are very easy to be reverse engineered and copied by other parties with a relatively low cost. Due to the above unique properties of pharmaceutical industry, it is highly dependent on intellectual property. Consequently, the extreme dependence on current intellectual property system has raised a series of problems.

Patent monopoly is widely acknowledged issue in pharmaceutical industry. Some experts argue that their extreme focus on business is depriving patients' right to access to the medicines and medical technologies. In addition to that, one of the most important issues is that intellectual property cannot incentivize innovations in medical products for diseases of poverty, such as neglected tropical diseases[7], malaria and tuberculosis. These diseases affect the poor who are unable to, or have limited sources to obtain effective and affordable medical products, such as medicines, vaccines, etc. Furthermore, these diseases can largely reduce patient's standard of living by causing severe illness, sometimes even cause death. Widely spread diseases of poverty – neglected tropical diseases, malaria, tuberculosis – together have affected more than one billion people in the world, mainly populations living in poverty.

As a consequent, there have been no major breakthroughs in the field of diseases poverty. Historically, it is well known that the public sector researchers have performed the upstream, basic research while the industry further developed the outcome into products with or without the help of public sector.[8] In the field

of diseases of poverty, the public sector has been the major stakeholder and it alone cannot meet all needs.

iv. A new model: public-private partnership

As illustrated above, pharmaceutical companies that mostly reside in developed countries have been paying little attention to diseases of poverty since it is hard to guarantee a return on the large investment in R&D which is necessary for the development of medical products despite of high disease burden. High technology barrier and low success rate of drug discovery process is worsening the situation. To improve the situation and relieve the disease burden, the public-private partnership was proposed by non-governmental organizations and international organizations. The public-private partnership refers to uniting the strength of the public sector and private sector to promote R&D activities and isolate R&D cost from the final price so that the product is affordable for poor people. It is broadly adopted by a few international organizations and non-governmental organizations throughout the world.

Most of the public-private partnerships focus on the downstream R&D activities to target low-hanging fruit. Among the few public-private partnerships who are targeting upstream R&D activities, WIPO Re:Search is known as the biggest public-private partnership which is specialized in this area. WIPO Re:Search consortium was established by the World Intellectual Property Organization (WIPO) in collaboration with Bio Ventures for global Health. The consortium gathered leading pharmaceutical companies and research organizations in the world to share their intellectual properties, more specifically compounds, expertise, and know-hows to develop medical products for neglected tropical diseases, malaria, and tuberculosis. Over the last five years, more than 100 members have joined the WIPO Re:Search consortium, and numerous collaborations have been facilitated to develop new medical products by focusing on the positive role of intellectual properties,[9] and explicit links are being made among the different organizations involved in discovery, development and deployment of new technologies.

v. Solutions to the diseases of poverty

The efforts from public -private partnerships in diseases of poverty have been significantly contributed to narrowing down the gap between disease burden and scientific research through sharing IP and research collaborations. This approach indicates that sharing intellectual property within the stakeholders through partnerships and creating innovative intellectual property to produce innovative solutions are the two important factors to be taken into consideration in the diseases of poverty under current intellectual property regime. In this study, malaria was chosen as an example, and an integrated approach concerning effective intellectual property sharing and innovative intellectual property creation was designed. More specifically, the role of public sector as the most important stakeholder in public-private partnerships was revealed to support strategic planning in basic research, and a new mechanism was proposed in order to effectively accelerate intellectual property sharing among this group of stakeholders in the field of malaria. At the same time, cutting-edge synthetic methods were developed as a model example to create new

intellectual property which aims to mitigate the disease burden as well.

Chapter 1. Strengthening intellectual property sharing

1.1 General information on malaria

Malaria is a parasitic disease which is widely spread in developing countries in tropical and subtropical regions (**Figure 1-1**). In 2015 alone, there were 212 million new cases and 429,000 deaths, most of which were children under 5 years old in Africa (estimated 303,000 deaths). Despite of all the efforts that have been made in the last 10 years, malaria ranks fourth among the major infectious diseases in causing death after pneumococcal acute respiratory infections, HIV and tuberculosis, and millions of people still lack access to the tools and medical products they need to prevent and treat the disease across Africa. Funding shortfalls and fragile health systems restrict access to life-saving interventions and jeopardize the attainment of global targets.[10] According to the WHO World malaria report, fewer than half of the 91 malaria-affected countries and territories are on track to achieve the 2020 milestone of a 40% reduction in case incidence and mortality.[11]

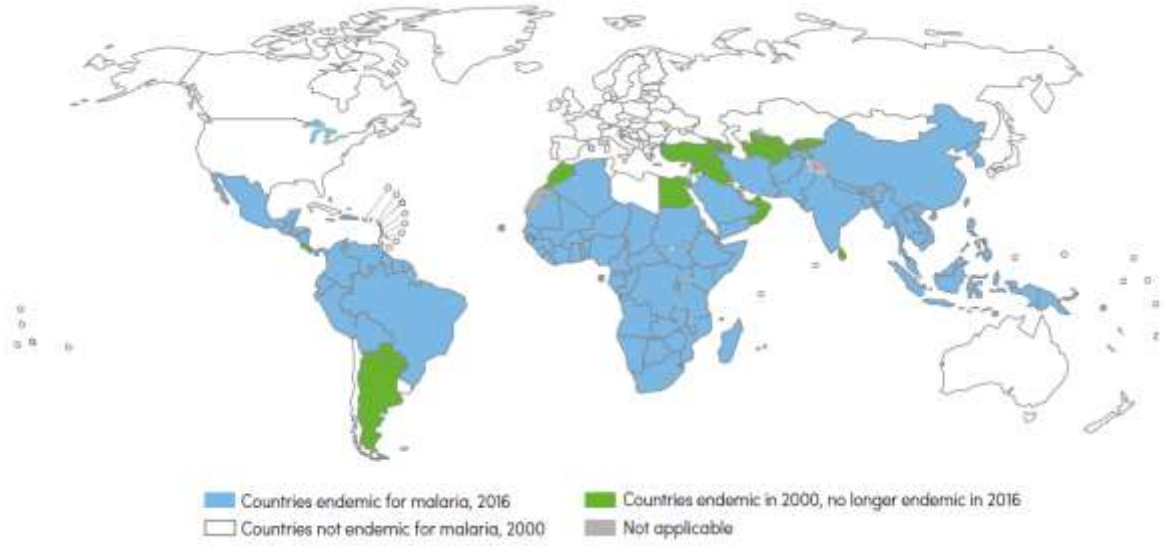


Figure 1-1. Countries endemic for malaria in 2000 and 2016. Countries with 3 consecutive years of zero indigenous cases are considered to have eliminated malaria. No country in the WHO European region reported indigenous cases in 2015 but Tajikistan has not yet had 3 consecutive years of zero indigenous cases, its last case being reported in July 2014. Source: WHO World Malaria Report 2016

To ease the disease burden, generally two different approaches are combined. First of all, prevention is necessary to control the disease pandemic. In the case of malaria, it can be achieved through vector control to stop mosquitoes from biting human beings, or providing vaccination or drugs that suppress infections. Among them, vector control is the most commonly used method and has demonstrated its powerful effectiveness in reducing malaria incidence. During 2001 – 2015, it is estimated that the vector control measurements account for 50% of the decline in parasite prevalence among children aged 2-10 years in

sub-Saharan Africa. The second important approach is treatment, mainly concerning drugs. Current available antimalarial drugs have been largely contributed to combatting malaria for the last few decades. However, they also have raised various issues such as drug resistance, toxicity, and high cost. Among them, drug resistance is a serious challenge to the treatment of malaria in some areas. In Cambodia, high failure rates after treatment with an Artemisinin-based Combination Therapy (ACT) have been detected (**Figure 1-2**) In order to resolve this problem and eventually eliminate malaria from the earth, it is important to develop new drugs which are affordable to people in developing countries. Regardless of huge demand in developing world, no new synthetic antimalarial drug has been discovered during the last four decades.[12]

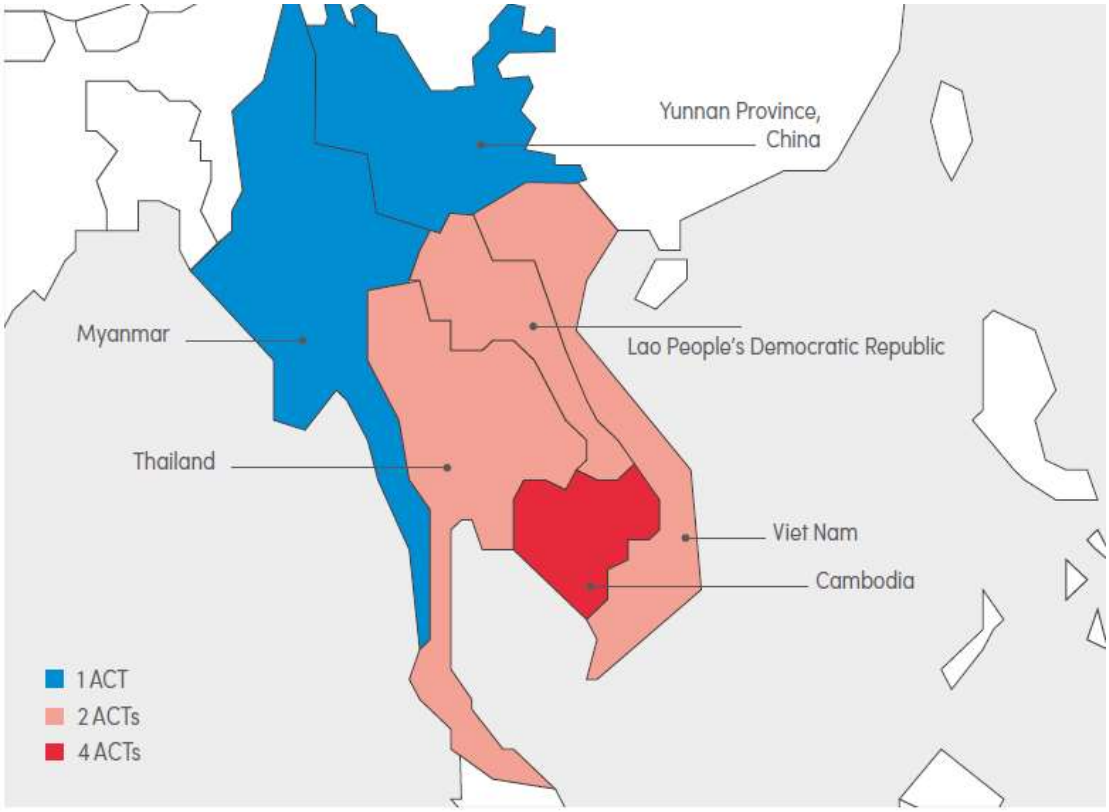


Figure 1-2. Distribution of malarial multidrug resistance, 2016.
Source: WHO World Malaria Report 2016

This study focuses only on development of new drugs for malaria, especially the early stage of research and development (R&D) activities (preclinical stage). The prevention measurements are out of the scope. It aims to contribute to accelerating drug discovery process as well as reducing the cost of R&D by proposing a new scheme of sharing intellectual property in the early stage of R&D activities in malaria.

1.2 Drug development for malaria

In general, preclinical activity is relatively high risk, and most of the compounds investigated in this stage end up with failure. It consists of three major stages, which are: defining hits, hit-to-lead-phase, lead optimization phase.

During this process, thousands of compounds were screened to identify one candidate which has a moderate chance to enter the clinical phase. There is an ongoing debate on how to improve the success rate in the basic upstream activities before starting clinical trials to reduce the cost and bring more innovative drugs to the patients.[13] In 2010, to answer the call in anti-malarial drug discovery campaign, 256,263 distinct chemical entities were screened and validated *P. Falciparum* blood-stage active hits for oral drug discovery were disclosed by a group of scientists in Medicines for Malaria Ventures. The screening resulted 3209 primary hits (hit rate of 1.25%), and further refining investigation confirmed 1985 active compounds. The overall hit rate of screening is 0.77%.Through a series of selecting process, 61 compounds in 33 clusters were prioritized among the 3209 primary hits. The overall rate is 0.2%, while the selecting rate from primary hits is 1.9% (**Figure 1-3**). This indicates it still has room for improvement.[14] To ease this issue, it is necessary to identify key stakeholders in this stage and improve the efficiency.

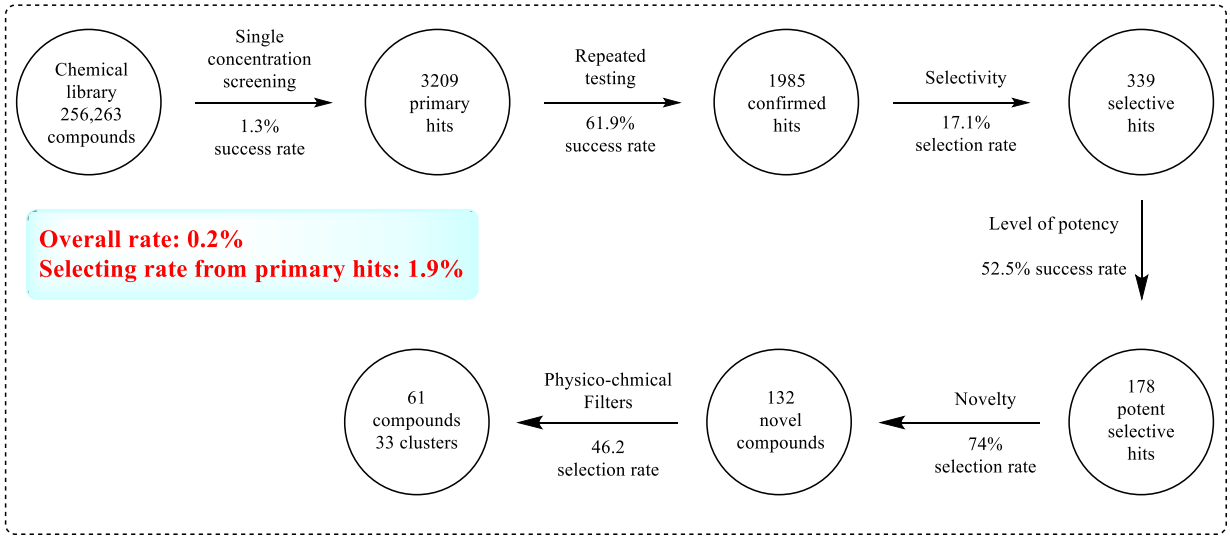


Figure 1-3. Generation and prioritization of hits from chemical library.

According to the study conducted in 2011 on malaria medicine and vaccine R&D, the stakeholder in this stage is the public sector under the traditional drug development model (Table 1.1).[15] 82% of investment in malaria R&D came from the public or philanthropic sectors. In the early stage discovery, this percentage is increased to 99.8%. As illustrated before, this is because the market failures when it comes to antimalarials, and the industry pays less attention to it. As illustrated above, the role of public sector is clear in traditional drug development model. Public sector is one of the main actors for innovation and economic development both in developing countries and developed countries. Although their structures, functions and performance are diverse across countries, they all have one common characteristic – connecting government, private

sectors, universities, and international organizations. Public sectors rarely operate in isolation and they have strong connections with other stakeholders. As the consequence, the diversity in research is also observed. Some of the research is in collaboration with government to address social issues; some perform "blue sky" research; some focus on more short-term market oriented projects.[16] In developed countries, public sectors have become a key driver in economic growth by engaging more business-like operational models. It has been moving towards openness, increased responsiveness, and increase in clarity over research roles. In developing countries, public sectors perform bridging activities among different players in most industries.

	Early Stage Discovery	Late Stage Discovery	Clinical Trials
Who pays?	Non-industry (99.8% of investments)	Non-industry (64–80% of investments)	Non-industry (78–89% of clinical trials)
Who performs?	Non-industry (88% of sample articles)	Non-industry (87% of sample articles)	Non-industry (85–88% of clinical trials)
Why do they perform?	Contributing to malaria eradication (72% of survey respondents), enjoyment (67%) and networking with other malaria researchers (52%)	Enjoyment (79% of survey respondents) and contributing to malaria eradication (71%)*	(Included in late stage discovery)
Is there collaboration?	Yes (83% of sample articles)	Yes (99% of sample articles)	(Included in late stage discovery)
Are results open access?	No (28% of sample articles)	Yes (65% of sample articles)	(Included in late stage discovery)
Are results in the public domain (i.e. not patented)?	No (33% of survey respondents)	Potentially* (64% of survey respondents)	(Included in late stage discovery)
Who owns patents?	(Typically too early for patents)	Both, with non-industry owning 54–56% of patents	(Included in late stage discovery)
Are physical results available for external researchers?	No (36% of survey respondents)	Potentially not* (36% of survey respondents)	(Included in late stage discovery)

* Small sample size

Table 1.1. Malaria medicine and vaccine R&D in 2011

Source: doi:10.1371/journal.pone.0117150.t002

Within the new model, the public-private partnership model, the role of the public sector is not clear. In order to promote innovation in the R&D activities, the identification of the stakeholder is the most important. A case study was performed to answer the below questions:

- Is the public sector the most important stakeholder?
- What is their role in public-private partnership?

WIPO Re:Search was studied as the case study, and the members within the consortium were studied. Three factors – research purpose, research activities, and collaboration partners – were taken into consideration to measure their impact and value in the global health system within the public-private partnership. The data was collected through the website study and consultation with managers of WIPO Re:Search. A summary of results is shown below (see supporting information for more details).

- Among the WIPO Re:Search members, there are 13 NGOs/NPOs, 106 public institutions and universities, and 9 pharmaceutical companies. Only 1 NGO, and 37 public institutions and universities are from malaria endemic areas.
- The activities of the NGOs/NPOs focus on expanding the network.
- The activities of the public institutions and universities focus on conducting research and looking for

collaboration partners.

- NGOs/NPOs, public institutions and universities are actively engaged with other stakeholders and open to collaborations.
- The private companies' activities in the field of malaria and other neglected diseases are mainly for the corporate social responsibility purpose and taking part in policy discussions through United Nations agency.

Although the scientific research capacity of the public institutions is hard to compare with private sector, its relatively broad network, especially in developing countries, indicates it a the most important stakeholder in terms of research activities and network expanding in public-private partnership. This theory was further supported by the fact that all the collaborations involve public sector (public research institutions or universities). Hence, the role of public sector in public-private partnership is conducting research and adding additional network to the partnership.

Yet, two issues were identified within public sector. First of all, public sector that is playing a significant role in certain countries from malaria endemic areas is not included in the partnership. Based on the below criteria which describes current members of WIPO Re:Search consortium, 25 institutions were identified.
Criteria: 1) The organization plays leading role in malaria research in the country or region. 2) The organization has a broad network and capacity to connect other stakeholders. 3) The organization is open to collaborations.

	Country	Name
1[a]	Papua New Guinea	Papua New Guinea Institute of Medical Research
2	Solomon Islands	Atoifi Health Research Group
3	Laos	Centre d'Infectiologie Christophe Mérieux du Laos
4	Laos	Institut Pasteur in Lao PDR
5	Philippines	National Institutes of Health, University of the Philippines Manila
6	Philippines	De La Salle Health Sciences Institute
7	Vietnam	Hanoi School of Public Health Center for Public Health and Ecosystem Research
8	Vietnam	Hanoi Medical Unversity
9[a]	Bangladesh	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)
10	Bangladesh	Institute of Epidemiology, Disease Control and Research
11	Bangladesh	Bangladesh Medical Research Council
12	Pakistan	National Institute of Health
13	Sri Lanka	Medical Research Institute
14	Somalia	Somali Medical Research Institute
15[a]	Kenya	Kenya Medical Research Institute
16	Kenya	Amref Health Africa

17	Tanzania	National Institute for Medical Resarch
18	Tanzania	IFAKARA Health Institute
19	Tanzania	Mbeya Medical Research Center
20	Mozambique	Manhiça Health Research Centre
21	South Africa	Wits RHI
22	South Africa	Anova Health Institute
23	South Africa	National Institute for Occupational Health
24	South Africa	National Health Laboratory Service
25	South Africa	The Aurum Institute

Table 1-2. Eligible institutions

a) Later it joined the WIPO Re:Search consortium based on the proposal made by this research.

In addition to that, the information sharing is not sufficient among the members. For instance, a collaboration between McGill University and Northeaster University was facilitated by WIPO Re:Search in 2014. It describes "*A Northeastern University researcher will synthesize an inhibitor previously demonstrated by a McGill researcher to inhibit malaria parasites. The McGill researcher will utilize the compound to repeat his in vivo screens."* Scientific details on the collaboration was not revealed, as well as the outcome of it. Whether it is negative or positive results, the information could be a sign for the next related collaborations in malaria research. With sufficient information, duplicative research can also be avoided timely. Some experts argue that sometimes similar experiments can bring minor modifications to the related drugs and in the end patients will have more options to choose based on their own conditions. However, in the case of basic research in malaria, the minor change is ore tend to result in similar outcomes rather than bringing diversity, and the cost performance is extremely low. Moreover, the research result in the basic research is usually unpatentable (too early) and unpublishable (more than 90% is negative). As the consequence, it is necessary to create a mechanism which can mediate the communications among different members to share outcomes, even those are not patentable or publishable.

The three issues listed above are inter-connected. In summary, it is required to produce as many promising lead compounds as possible with limited funding and resources with the help of property information sharing so that the initiative/consortium can better leverage its outcomes to achieve the common goal – development of new drugs. Increasing the funding for malaria research is the key. On the other hand, it is also crucial to conduct research in a sustainable and effective way. In order to make the full use of limited funding and resources, sufficient information sharing with as many stakeholders as possible plays a key role in accelerating the innovation. With open and adequate amount of information, duplicative work can be avoided and scientists can make further development upon the existing discoveries and know-hows. It is noteworthy that in general different levels of information sharing are required based on the research strategies.

1.3 IP sharing movement: a new mechanism to effectively share IP

There is an implicit assumption in pharmaceutical industry that putting more compounds into R&D activities would produce more successful drugs, although there is little evidence to support the theory. For malaria and other diseases of poverty, blind following of current research model is not the best solution. On the contrary, it needs to be a more open and transparent system in which scientists can learn from past experience, share know-hows, perform collaborative research, and avoid unnecessary failures.

Under current reward system, only positive results have been published to draw more attention while negative results, which are as equally important as positive ones, are not disclosed to the society. Furthermore, possible applications and limitations of positive results are usually described in a broad and vague way, and the possibility of refining and improving negative results is unknown. Since most of groups engaged in basic research are highly expertized in one research area, issues concerns other expertise remain unsolved unless they have a chance to communicate with other experts, which is usually time-consuming and challenging.

To better promote sharing IP (i.e. know-hows, results, and other related information) and also better facilitate communications among various research group and institutions, a new scheme that ensures timely and interactive IP sharing model is proposed below (**Figure 1-4**). Positive and promising results from a rough and primary screening that has been published will be collected and re-examined by cross-referencing with low value results (unpatentable or unpublishable results) that are shared by the community. Scientists that are currently performing and planning screening can also refer to the results before they go further. Those that are confirmed with no negative record will be proceeded to the next selection cycle or be shared with the scientists who are going to be or currently doing the selection, while compounds that have potential risks will be subjected to refinement. From hits to candidates, the compounds that are not chosen to the following selection step will be recorded with estimated reasons and immediately shared with research community to prevent similar research route as well as call for collaborative work on improvement if there is still room for low value results to be promoted to promising ones again. Positive results will also be shared at a maximum allowable limit to inform the community so that other scientists can learn from the experience and build on the new discovery. Within this model, the information sharing is maximized through volunteer sharing, and all the IP assets will be credited and appreciated. The ultimate goal is to create an open and transparent IP sharing system where R&D activities can be performed effectively under collaborative efforts. The new model is a new paradigm than can accelerate the drug discovery process with minimum funding.

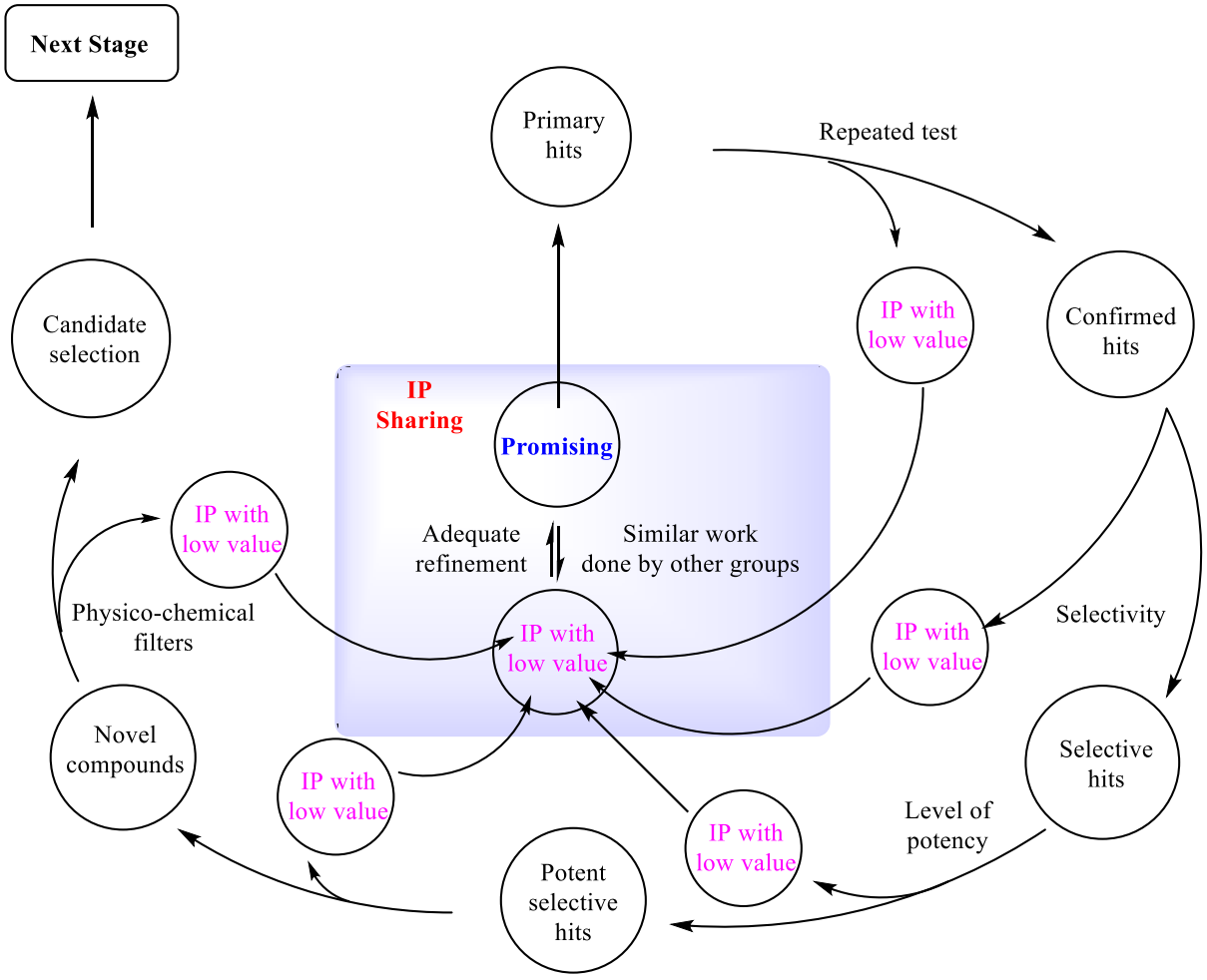


Figure 1-4. Live and interactive IP sharing model

In the case of compound libraries of pharmaceutical companies, full disclosure of information is hardly to happen since they are valuable trade secrets. However, a short description about the cluster of screened compounds and their results can be useful information as well to avoid duplicate experiments by other companies and academia.

1.5 Conclusion

The focus of this study is to identify the key stakeholders in the new drug development mechanism – public-private partnership. The public sector continues to play a leading role as an initiator and collaborator of the basic research activities due to its relatively large portion in the traditional upstream R&D activities for malaria as well as joint positions in developing countries. A further stakeholder mapping was conducted to include important public sectors in malaria endemic areas. In addition, an interactive and integrated IP sharing model that is concerning a variety of research outcomes in the field of malaria drug development is proposed. This study intends to assist scientists in these organizations to build on the success of the previous work to further develop the promising candidates into products, as well as to learn from the

negative results to strategically conduct future research.

In the current intellectual property system, only patents and copyrights (scientific literature) that represent promising results can provide financial and moral incentives to the academic research. However, in order to effectively promote innovation, all the information including “unpatentable” and “unpublishable” results can be great assets to the scientists. This study is proposing an alternative mechanism to share all the necessary information that has been neglected by the current intellectual property system.

Chapter 2: A front-line contribution with novel synthetic methods: IP creation

2.1 Background

As illustrated in the previous chapter, development of drugs is one of the most important factors to control and eradicate malaria. In order to develop a medicine, it is necessary to understand what the challenges are and what the currently available treatments are.

1. Disease characteristics

Malaria is caused by protozoan parasites of the genus *Plasmodium* that infect red blood cells which could lead to death if left untreated. The main parasite species that infect people are *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale.* Each of the four species has a distinctive appearance under the microscope, and produces a different pattern of symptoms which can be diagnosed with different tools.[17] In particular, *Plasmodium falciparum*, the most prevalent parasite among these, is extremely dangerous since it can develop aggressively and cause several life-threatening complications, and the infection with this species is responsible for one million deaths per year. *Plasmodium vivax*, one of the most infectious parasite as well as *Plasmodium falciparum*, is the most geographically widespread species, and produces less severe symptoms compared to *Plasmodium falciparum*. However, relapses can occur for up to 3 years which is generally hard to detect and prevent. *Plasmodium malariae* infections also remain in the blood for years without causing symptoms. This is problematic since an infected person with no symptoms can infect others through blood donation or mosquito bites. The last *Plasmodium ovale* is a rare one, and generally occurring in West Africa. This parasite remains dormant in the liver and can also cause relapses like *Plasmodium vivax*. In addition to these four species, *Plasmodium knowlesi,* which was previously known as a parasite of Old World monkeys, has been proven to infect humans as well.[18] Although the infection with these parasites can be generally managed and even curable if proper treatment is received timely and correctly, the overcoming of drug tolerance and the development of new drugs remain to be solved as urgent global issues.

The life cycle of *Plasmodium* starts with an infected mosquito feeding on human blood and injecting parasites, as sporozoites, into the human being's bloodstream, and the injected sporozoites subsequently travel to the liver and infect liver cells. After 5-16 days, the sporozoites grow and produce millions of haploid merozoites to a single liver cell. The merozoites exit the liver cells and enter the bloodstream. Over a period of 1-3 days, the merozoites invade red blood cells, reproduce asexually, and then the red blood cells burst to release the new merozoites. In this infection cycle, some infected blood cells develop into the sexual form of the parasite, male and female gametocytes, and circulate in the bloodstream. When a mosquito bites the infected human, the gametocytes again travel to mosquitos with blood cells. Inside the mosquito, the infected blood cells burst and release the gametocytes, which later mature into gametes. Male and female gametes fuse to form zygotes, which develop into ookinetes and later form oocysts in mosquito's midgut. For 8-15 days the oocyst grows and divides, and produces thousands of haploid sporozoites. Finally, the oocyst releases sporozoites into the mosquito's body. When the mosquito

bites another human, it injects sporozoites into the human's bloodstream, and the infection cycle starts again (**Figure 2-1**).

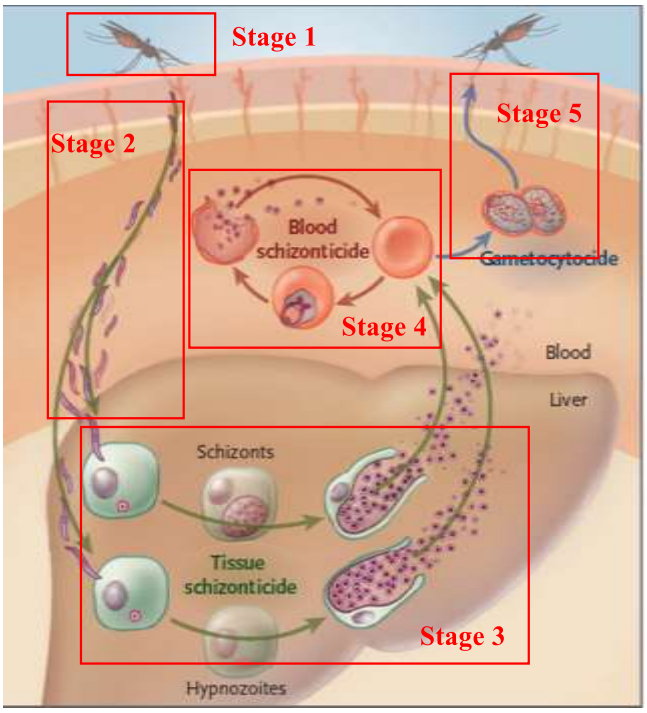


Figure 2-1. Infection cycle. (Source: *N. Engl. J. Med*, **2005**, *352*, 15.)

2. Existing drugs

Most of the existing drugs target blood stage of infection cycle. The roots of most antimalarial treatments are based on four natural products: quinine, quinazoline, lapachol and artemisinin (**Figures 2-2 ~ 2-5**).[19] All of them were isolated from traditional medicines which had shown activities against malaria parasites and later were proven their therapeutic activities by modern medicinal chemistry.

Quinine is the first widely used antimalarial drug which was isolated from *Cinchona calisaya* tree. It kills parasites by blocking the polymerization of the toxic byproducts of haemoglobin degradation, haem, into insoluble pigment granules which results in parasite cell auto-digestion.[20] Later developed quinine derivatives have the similar functionalities. In general, quinine and its derivatives target chemical reactions rather than a specific protein. Hence, the parasite is unable to gain resistance at a specific target cite, and the development of resistance is relatively slower than other drugs that target proteins. The discovery of chloroquine was a milestone in quinine-type antimalarial drugs. It was the main antimalarial drug that was used for prophylaxis and treatment for the second half of the 20th century. Further synthetic efforts have resulted in the development of many different types of quinoline derivatives, such as amodiaquine, mefloquine, halofantrine, lumefantrine, piperaquine, and pyronaridine, which have contributed to the treatment of malaria as one of the major types of antimalarial drugs (**Figure 2-2)**. However, it has been reported that these medicines have the cardiac safety issues due to their long half-life and high-dose administration. In addition, the emergence of resistant parasites requires continuous effort with more diverse and innovative quinoline derivatives.[21] Although there is clinical evidence that some molecules can

reverse chloroquine resistance,[22] new molecules with superior benefits over known quinoline derivatives are still needed.

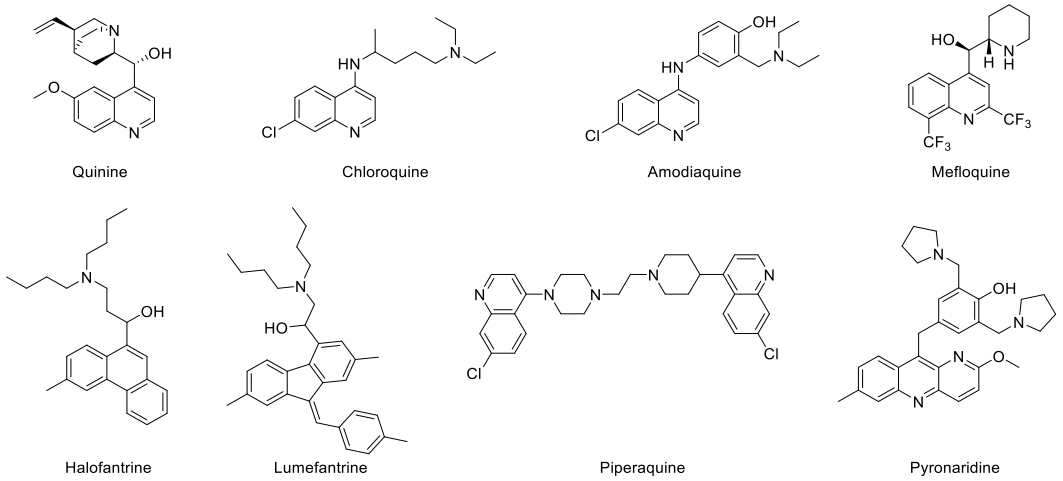


Figure 2-2. Quinine and its derivatives

The second type of antimalarial drugs is lapachol and its derivatives. Lapachol is a hydroxynaphthoquinone which was originally isolated from *Tabebuia avellanedae* and first reported in 19th century.[23] Mechanistic study revealed that lapachol and its derivatives interfere with the electron transport system of mitochondria and inhibit the cell respiratory mechanism.[24] Further research on the chemical modifications of lapachol led to the creation of lapinone and atovaquone (currently used as prophylaxis for travelers).

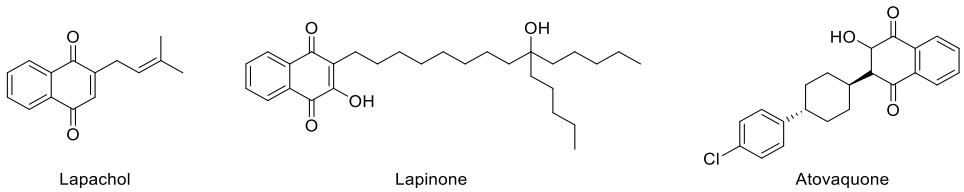


Figure 2-3. Lapachol and its derivatives

Another type of natural products that has been used for malaria treatment is quinazoline alkaloids. Febrifugine and isofebrifugine were isolated from the roots of *Dichroa febrifuga* and the plant itself was used as traditional medicine.[25] The febrifugine is no longer used due to its liver toxicity and gastrointestinal irritation. Its related derivatives, isofebrifugine and halofuginone, are promising candidates, although with minor side effects. Furthermore, halofuginone is found to be potent against chloroquine sensitive and resistant *Plasmodium falciparum*. Yet, there are still some limitations to be improved, for instance, its low activity against *Plasmodium berghei*, and the unfavorable chemical property that tends to isomerize (**Figure 2-4**).

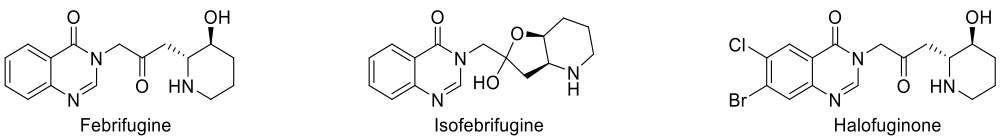


Figure 2-4. Quinazoline and its derivatives

The discovery of artemisinin was a breakthrough in the fight against malaria.[26] It is an endoperoxide-containing natural product which was discovered by a Chinese scientist - Tu Youyou - in 1972. To overcome original isolated artemisinin's limitations, several derivatives were synthesized to improve its solubility, bioavailability, and neurotoxicity.[27] Dihydroartemisinin (main active metabolite of all the derivatives), artemeter, artemotil, and artesunate were synthesized and proven to be fully active against all existing drug-resistant strains of *Plasmodium falciparum.* These compounds exhibit extraordinary efficiency on all stages of the parasite intraerythrocytic life cycle, and kill the parasites in the blood and gametocyte stages, inhibiting their growth in blood and their transmission from humans to mosquitos. Moreover, artemisinin and its derivatives are able to rapidly reduce the parasite growth and clear clinical symptoms. The down side of the artemisinins is that they generally have a short half life thus requires a multiple dose regimen in monotherapy. If they are treated with other types of antimalarial drugs that have longer half lives, the multiple dose regimes could be improved and the efficacy will be enhanced as well (**Figure 2-5**).

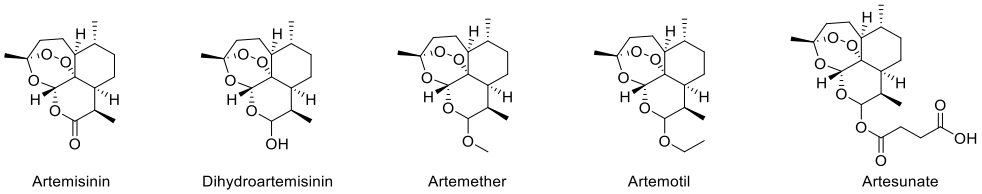


Figure 2-5. Artemisinin and its derivatives

With increasing accumulation of knowledge and information on disease properties and parasite metabolism, rationally designed molecules that target specific proteins were also developed. For instance, dihydrofolate reductase (DHFR) is an essential enzyme that catalyzes the NADPH-dependent reduction of 7,8-dihydrofolate to 5,6,7,8-tetrahydrofolate for methylation reactions. Inhibition of DHFR can result in parasite death through disruption of DNA synthesis.[28] Based on this discovery, a wide variety of antifolates were developed as antimalarial drugs. In several sub-Saharan African countries where chloroquine resistance is widely spread, antifolates drugs are used in a first-line therapy. Representative antifolates are including sulfadoxin, trimethoprim, pyrimethamine, proguanil, and so on. Proper combination of this type of drugs can result in synergistic effect. Resistance to antifolates develops relatively progressively compared to other types of drugs since these drugs only target a specific protein. Nevertheless, new antifolates are important drug candidates to be taken into consideration in the process of malaria drug development (**Figure 2-6**).[29]

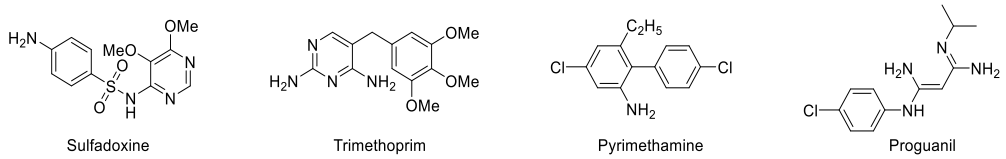


Figure 2-6. Antifolates

The last type of common antimalarial drugs are antibiotics. The drug repurposing of antibiotics and exploitation of their derivatives for malaria are limited. Some of the known examples such as tetracycline, doxycycline, clindamycin, and azithromycin are shown in **Figure 2-7**. As antibiotics generally have a different mechanism of action from known antimalarial drugs, these antibiotics might be used effectively in the areas where antimalarial drug resistance is prevailed. In combination with quinine, antibiotics like tetracycline and clindamycin have been used to treat severe malaria in all age groups, as well as in pregnant women that are hard to achieve with other types of antimalarial drugs. Additionally, some of the antibiotics exhibit synergistic effect with antimalarial drugs.[30] Yet, there is a potential risk of emerging resistant bacteria as well as resistant malaria as an unfavorable side effect.[31]

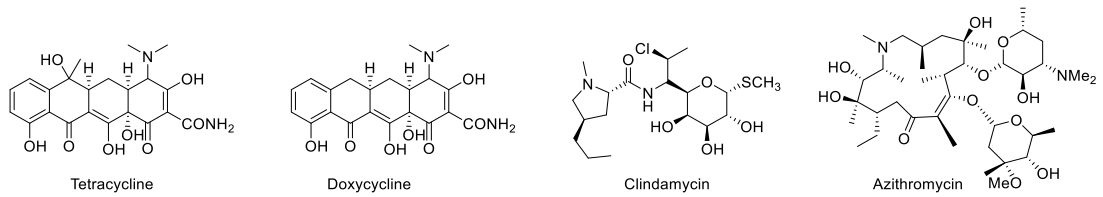


Figure 2-7. Antibiotics

3. Challenges related to existing drugs

The resistance to anti-malarial drugs such as chloroquine, sulfadoxine, pyrimethamine, and mefloquine, has emerged as a serious problem historically from 1970s.[32] The drug resistance has caused millions of deaths over the years.[33] Shortly after the discovery of artemisinin as the most potent antimalarial drug, Artemisinin-based Combination Therapy (ACT) was adopted as a first-line treatment. It was intended to slow down the development of drug resistance by combining with several distinguished classes of drugs. The frequency of mutations that might lead to resistance to drugs in *Plasmodium falciparum* is estimated at 1 in 10^{10} parasites. It is possible to lower the possibility of resistance emergence by combining two medicines with fundamentally different mechanisms of action.[34] ACTs are generally fixed dose. The first ACT is artemether-lumefantrine launched by Novartis in 2001. Amodiaquine-artesunate was developed by Drugs for Neglected Diseases Initiative (DNDi) in 2008. Other examples are, artemether-lumefantrine by Medicines for Malaria Venture, amodiaquine-artesunate by Sanofi-Aventis, DHA-piperaquine by Sigma-Tau in collaboration with Medicines for Malaria Venture, pyronaridine-artesunate by Shin Pooing in collaboration with Medicines for Malaria Venture, mefloquine-artesunate by DNDi/Farmanguinhos/Fiocruz, and lastly artemsinin-naphthoquine. Among above examples, the most widely used ACTs composed of artemisinin (or its derivative) with the other type of antimalarial drug which has longer half live, such as quinine derivative, to compensate the short half life of artemisinin (or its derivative) to make sure that patients benefit from utmost therapeutic formula. Without all these efforts, artemisinin resistance and its partner drug resistance are latent issue. Resistance on one part will increase the burden on the other partner, though ACTs will still be effective until the parasite develops full resistance against both ingredients, and vice versa. Recently, it is reported that the recommended standard ACT failed to effectively treat malaria in

the places where Artemisinin resistance has observed in the malaria parasite.[35] Thus, it is necessary to explore more derivatives of artemisinin and a wider range of partner drugs with significant advantages over existing drugs without any records on drug resistance so far.

Most of the existing drugs attack malaria parasites in the blood stage (erythrocytic stage). The parasites in the liver stage remains as a challenging issue likely due to most clinical symptoms are not generated and the mechanism is less understood. It is important to develop new drugs that target all of parasites in the five different stages to eliminate malaria completely.

Lack of novel synthetic methods for the divergent preparation of natural product derivatives in a cost-effective way is an urgent issue. For instance, artemisinin derivatives currently are semi-synthesized from natural products and the supply of this type of drugs heavily relies on plant resources, which is problematic in terms of natural resource shortage and price fluctuations.[36]

In addition, the quality of antimalarial drugs is a huge problem. It would be difficult to guarantee the quality of antimalarial drugs due to falsified, substandard, or degraded products. The unqualified antimalarial drugs can lead to sub-optimal drug exposure and, in extreme cases, can cause deaths, disabilities, economic losses, and drug resistance.[37] To understand the situation on the quality of antimalarial drugs, WWARN developed an open-access global database that summaries all published antimalarial drug quality reports since 1946. No public reports on the quality of antimalarials are available in 60.6% (63) of the 104 malaria-endemic countries. Of 9,348 antimalarials sampled, 30.1% (2,813) failed chemical/packaging quality tests.[38] In the cases of antimalarial drugs designed based on natural products, the diminished quality of these drugs is partially derived from their structural complexity and a long and inefficient manufacturing method and poor regulatory systems by the governments in developing countries.

4. <u>This work</u>

This work aims to ease the burden of antimalarial resistance through the innovation in efficient and reproducible synthetic methods. The author planned two different synthetic strategies to contribute to the development of new antimalarial drugs. The first strategy is to explore a new chemical space for the derivatization of available drugs, which can be achieved without any knowledge of the biological target or the mechanism of action of the lead compound.[39] The second one is to design a new type of drug candidates that functions through a novel mechanism distinct from existing drugs and targets a broad range of stages of parasites.

From the synthetic chemistry point of view, the achievements by the author are as follows:

1) Designing hybrid molecules composed of quinine, lapachol, and quinazoline derived moieties as a new chemical space, and a new synthetic method to obtain these derivatives have been established.
2) Improvement on the chemical and pharmacological properties of a cutting-edge antibiotics – AMPs – was initiated through selective *N*-glycosylation.

2.2 Design of potential antimalarial hybrid molecules and a new synthetic method to achieve them

2.2.1 Background

Exploitation of derivatives of existing compounds as well as natural products has continued to be the focus of current antimalarial drug development. To combat the emerging resistant parasites more efficiently, a wide range of structurally similar derivatives of the known antimalarial drugs and natural products have been investigated, and some of them are currently undergoing clinical trials. Recent advances in understanding drug mechanism of action shed light again on quinolones that were once abandoned lead molecules. This discovery has led to a big boom in re-examination of quinolone derivatives and the result was delightful.[40] Judging from their antimalarial effects, quinolin-4(*1H*)-ones are one of the promising candidates as an alternative replacement of chloroquine.[41] For instance, WR249685, bearing an acridinone skeleton, was discovered to show selective inhibition against P. falciparum bc1 complex (IC_{50} 3 ± 2 nM) which indicates that it could be considered as a new antimalarial candidate.[42] It should be noted that *S*-isomer has greater activities than the other. ELQ300 bearing aryl ring at the C3 position has demonstrated superior efficacy (0.58 nM) and is in phase I clinical trials,[43] and Sl-2-25, having heteroarylring at the C2 position, is also in the process of preclinical evaluations.[44] (**Figure 2-8**).

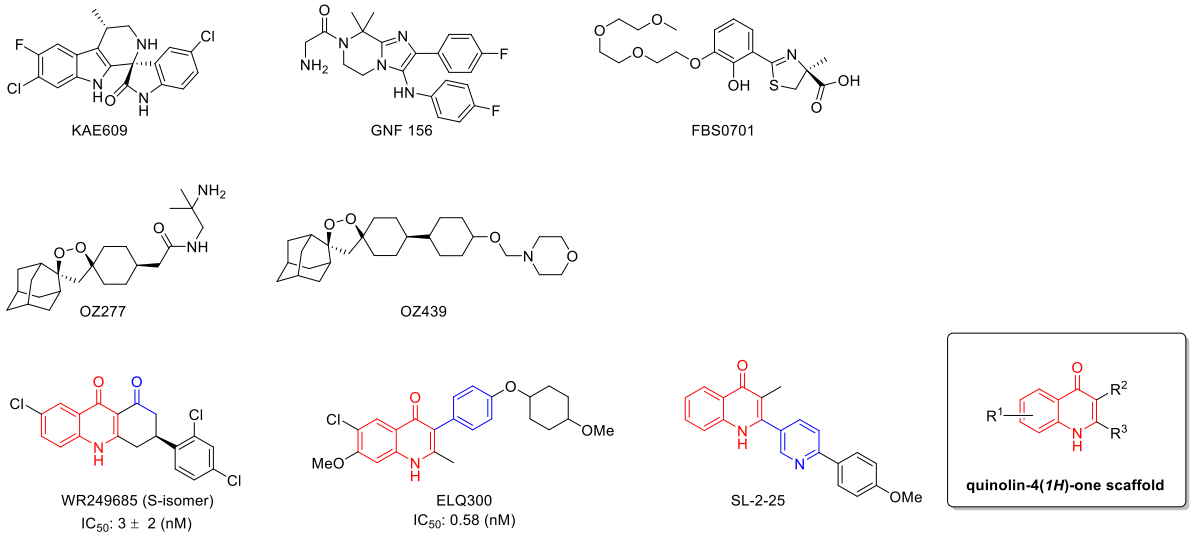


Figure 2-8. Malaria drug candidates

The author became interested in the related quinolin-2(*1H*)-ones bearing aryl ring at the C4 position for their prospect therapeutic effect against malaria as well as their abundance in the nature (**Figure 2-9**). Although certain quinolin-2(1*H*)-ones were proven to have antimicrobial, anticancer, and anti-HIV activities, their anti-malarial activities have never been explored so far.[45] In addition, 3,4-disubstitued dihydroquinolin-2(1*H*)-ones are also prevalent in pharmaceutically important natural products that have demonstrated cardiovascular, anti-inflammatory and phosphodiesterase inhibitory activities.[46]

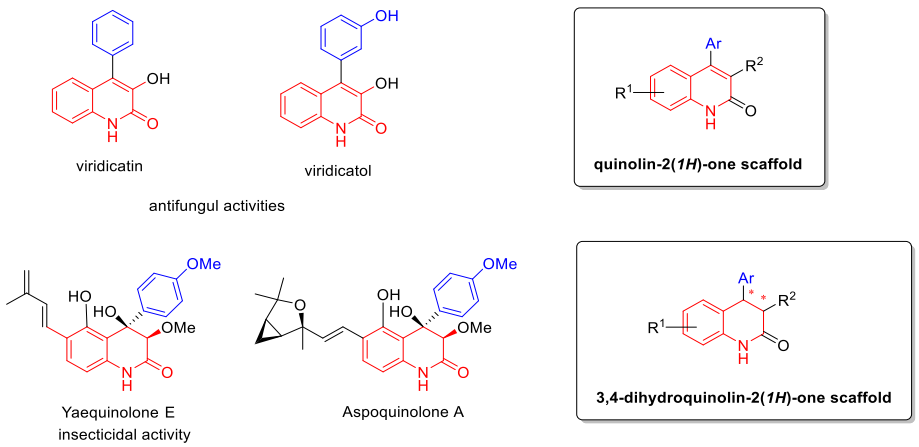


Figure 2-9. Biologically active quinolone derivatives

Although many efforts have been devoted to synthesizing functionalized quinolin-2-ones and their derivatives, only one retrosynthetic strategy has been reported for asymmetric construction of 3,4-dihydroquinolin-2(*1H*)-one scaffold (**Figure 2-10**).[47] Regarding the asymmetric synthesis of functionalized quinolone derivatives, a great progress has been made by using chiral metal and organocatalysts. Some representatives of asymmetric synthesis are depicted in **Scheme 2-1**.

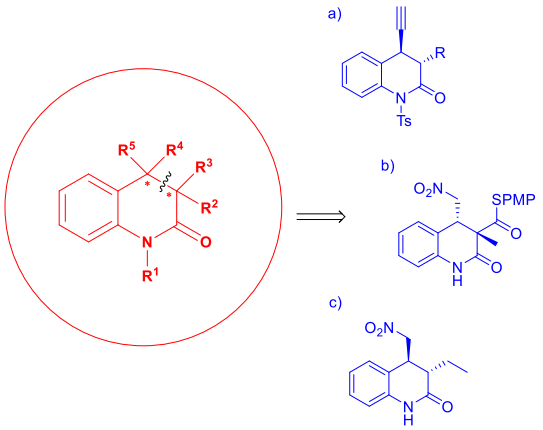
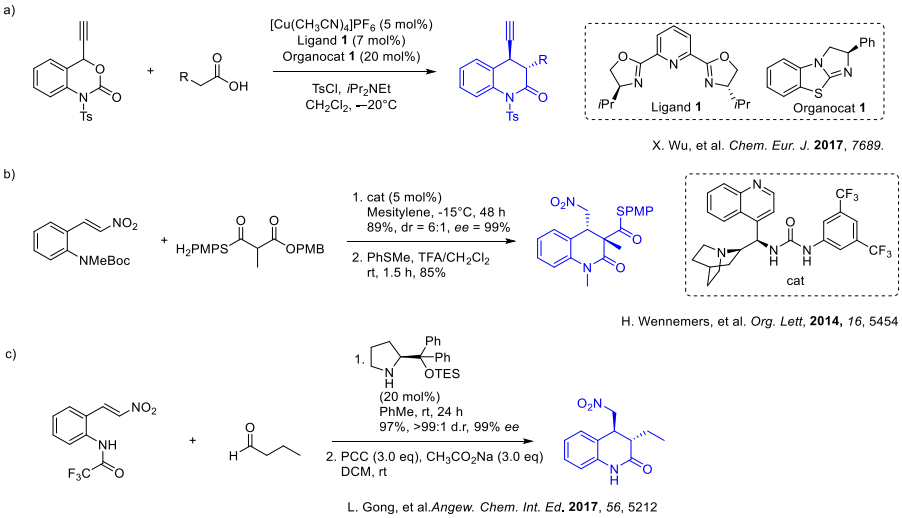


Figure 2-10. Previously synthesized achiral and chiral quinolones

Wu's group achieved the asymmetric synthesis of 3,4-disubstituted dihydroquinolin-2-ones with high diastereo- and enantioselectivity under the dual catalytic conditions (**Scheme 2-1**, a).[48] In the remaining two examples, either bifunctional urea or prolinol derivative was used for the asymmetric Michael addition of malonates or aliphatic aldehydes into nitroalkenes, providing the desired 3,3,4-trisubstituted or 3,4-disubstituted dihydroquinolin-2-ones in a highly enantioselective manner (**Scheme 2-1**, b and c).[49] Although these reactions gave the chiral target molecules stereoselectively, the substituents which could be introduced at the C3 and C4 positions are restrictively limited. In all cases, accessibility to the starting materials, ortho-substituted anilines derivatives, was also limited, following as a consequence of narrowing the substrate scope.



Scheme 2-1. Previous work on syntheses of quinolones

To echo the previous statement, it is noteworthy that there have been no successful reports on the asymmetric synthesis of 4-aryl dihydroquinolin-2-ones. Therefore, a new strategy by which a range of aryl groups could be introduced at the C4 position needs to be explored in order to allow for the screening of various quinolin-2(1*H*)-ones.

On the other hand, a variety of chiral epoxides are known as biologically active substructures as well.[50] Several reports recently described that naturally occurring epoxy amides including Chrysamide B, Chrysamide C, and dipeptide epoxide possess potential antimalarial activities and could be one of the new classes of antimalarial drugs by further structure modifications. (**Figure 2-12)**.[51]

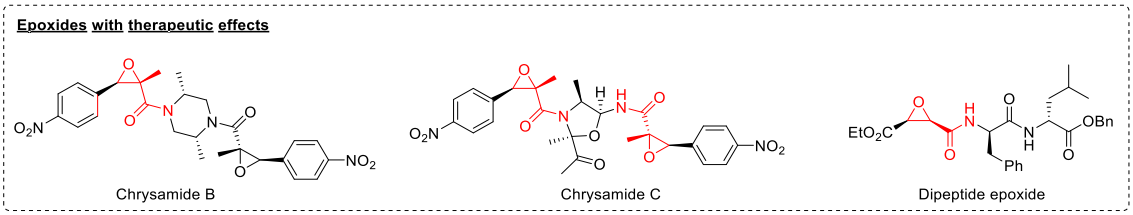
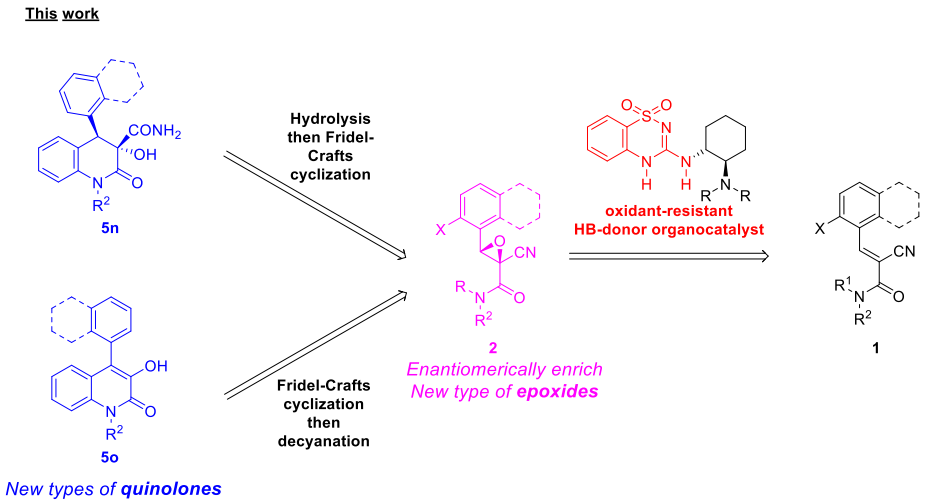


Figure 2-12. Epoxides with therapeutic effects

From the synthetic point of view, epoxides are versatile intermediates and can be ring opened with a wide range of nucleophiles with high or often complete stereo- and/or regio-selectivity, to afford two contiguous stereogenic centers.[52] Based on the background described above, the author designed a concise synthetic route which would realize a convergent access to two different types of quinolones **5n** and **5o** via epoxy amides **2** (**Scheme 2-2**). With an aim of asymmetric synthesis of these compounds, the asymmetric epoxidation of α,β-unsaturated amides **1** was adopted to synthesize chiral epoxy amides **2**. With enantiomerically enriched epoxide **2**, it is anticipated that the intramolecular Friedel−Crafts reaction of **2** would proceed to give chiral cyanohydrine derivatives of **5o**, when an appropriate Lewis acid is employed. The desired 2-quinolones **5o** can be converted by the following decyanation under the basic conditions. On the other hand, 3,4-dihydroquinolin-2(1*H*)-ones **5n** are also synthesized from the same compound **2** by the

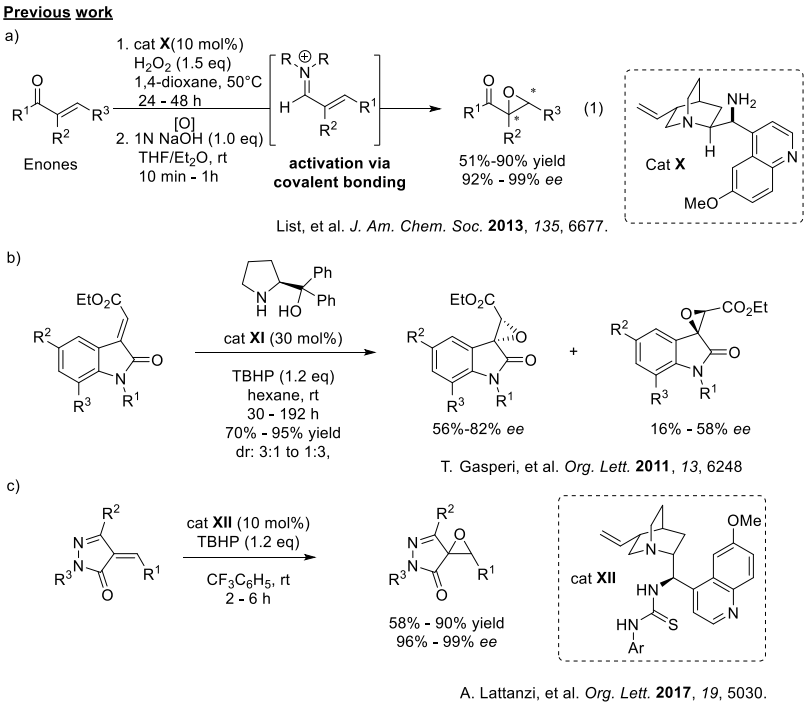
oxidative hydrolysis of a nitrile group and the subsequent Friedel−Crafts cyclization. Namely, this method provides a straight-forward synthetic tool for the transformation of α,β-unsaturated amides **1** into chiral epoxy intermediates **2**, chiral 3,4-dihydroquinolin-2(1*H*)-ones **5n**, and quinolin-2(1*H*)-ones **5o**, which can be applied to drug development for malaria. With regard to the synthetic strategy, the achievement of asymmetric epoxidation would be the key to the success. The author thus focused on the screening of chiral catalysts for the highly enantioselective epoxidation of α,β-unsaturated amides **1**.



Scheme 2-2. Synthetic strategy

Within the last few decades, considerable attention has been paid to the development of chiral epoxide synthesis. So far, enormous progress has been made in the asymmetric electrophilic epoxidation of electron-rich alkenes,[53] including Sharpless–Katsuki epoxidation. In contrast to these results, the asymmetric nucleophilic epoxidation of electron-deficient alkenes into 2-oxiranecarboxylic acids[54] and 2-oxiranecarboxamides [55] have been less explored. [56] Metal-catalyzed asymmetric nucleophilic epoxidations of α,β-unsaturated carboxylic acid surrogates have been developed for the robust method of accessing this class of oxiranes. However, these synthetic methods rely on relatively high loading of scarce lanthanide catalysts,[57] toxic manganese catalysts,[58] or iron catalysts with low to moderate yields.[59] On the other hand, we focused on the utilization of organocatalysts, which can avoid the contamination of heavy metals into the active pharmaceutical ingredient,[60] as well as to be easily handled due to their benign properties. In recent decades, organocatalyzed stereoselective epoxidations of electron-poor alkenes such as α,β-unsaturated aldehydes and ketones were also developed.[61] According to the previous reports, these substrates can generally be activated by chiral primary and secondary amines via covalent bonds, and the asymmetric epoxidation proceeds highly stereoselectively through the generated chiral iminium cation intermediates. Although the resultant chiral oxiranecarboxaldehydes can be derivatized to the corresponding amides (**Scheme 2-3**, a),[62] the direct synthesis of these amides by the asymmetric epoxidation of α,β-unsaturated amides is highly desirable in terms of redox economy.[63] However, only a few examples have been reported to date. Chiral prolinol derivative XI can be used as a catalyst, yet it affords the product in a diastereodivergent manner with low to moderate enantioselectivity (**Scheme 2-3,**

b).[64] With bifunctional amino thiourea, there has been only one report with a narrow substrate scope (**Scheme 2-3**, c).[65] Furthermore, the reaction requires high catalyst loading (Scheme 2-3b) and short reaction time (Scheme 2-3c) to be applicable due to the catalyst deactivation under the oxidative conditions. The author focused on bifunctional benzothiadiazine catalysts,[66] which have stronger hydrogen bond donating ability than that of thiourea catalysts. Although benzothiadiazine catalysts have never been applied to the oxidation reaction, we envisioned that they would promote the asymmetric epoxidation of α,β-unsaturated amides, because they have no reactive functional groups like a sulfur atom of the thiourea moiety.



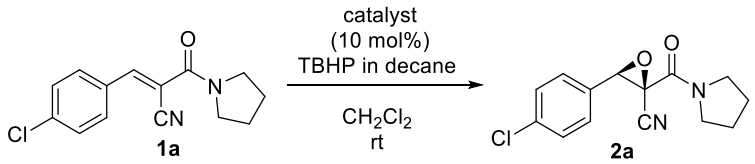
Scheme 2-3. Organocatalyzed asymmetric nucleophilic epoxidation.

2.2.2 Results

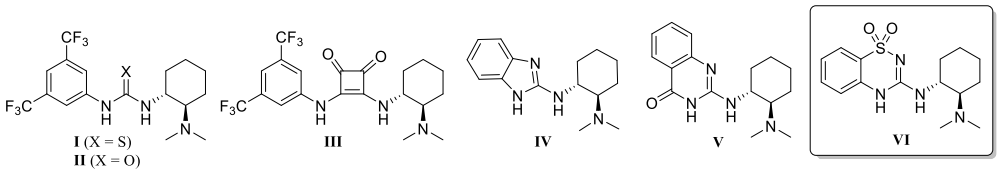
For the asymmetric epoxidation of α,β-unsaturated amides, acrylamide **1a**, obtained in good yield by the condensation of 4-chlorobenzaldehyde and α-cyanoacetamide, was used as a model substrate. Initially, the epoxidation of **1a** was carried out with 5.5 equiv of *tert*-butyl hydroperoxide (5.5 M TBHP in decane) and 10 mol% of catalysts **I-VI** in dichloromethane at room temperature (**Table 2-1**). Notably, thiourea catalyst **I** did not afford the desired product **2a**, even after a prolonged reaction time (entry 1), but urea catalyst **II** gave **2a** in moderate yield and selectivity (entry 2). These results strongly indicate that catalyst **I** was deactivated under the reaction conditions. The author then examined several hydrogen bond donor organocatalysts with different scaffolds, including squaramide (**III**),[67] benzimidazole (**IV**),[67] quinazoline (**V**),[70a] and benzothiadiazine (**VI**)[70] (entries 3–6). The author found that the best catalyst was **VI**, and the reaction was completed within 4 h to furnish **2a** in 90% yield with 70% *ee* (entry 6). In contrast, the reactions did not go to completion with the other catalysts, and the selectivities for **2a** were 40–54% *ee*

(entries 3–5). These results suggest that the hydrogen bond donating ability as well as the resistance for oxidation condition is important for substrate recognition and facilitation of the reaction.[70c]

Table 2-1. Optimization of reaction conditions.



Entry	Catalyst	Time (h)	Yield (%)[a]	Ee (%)[b]
1	I	24	0	n.d.
2	II	24	43	45
3	III	24	24	40
4	IV	24	49	54
5	V	24	27	44
6	VI	4	90	70

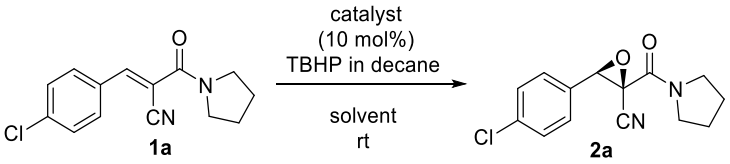


[a] Isolated yield. [b] Determined by chiral HPLC analyses. N.D = not determined. [c] 30% hydrogen peroxide was used instead of TBHP.

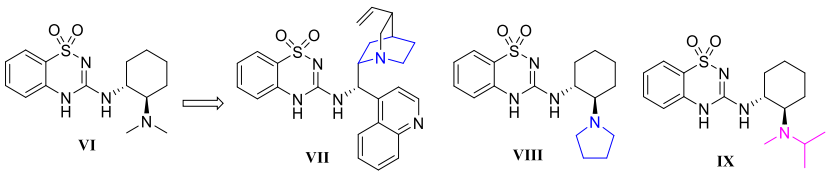
Based on these results shown in Table 2-1, the author selected catalyst **VI** as the best catalyst and further optimization was conducted regarding oxidant and solvent (**Table 2-2**, entries 1–5). As a result, it was revealed that TBHP was the oxidant of choice and either dichloromethane or MeCN could be used as solvent in terms of chemical yield and enantioselectivity. In all cases except for THF, **2a** was obtained as a single diastereomer. The relative configuration of **2a** was determined through conversion to the known literature compound. These results indicate that both the initial Michael addition of the hydroperoxide to **1a** and the subsequent epoxide formation took place quickly without a conformation change of the resulting enolate intermediate. To improve the enantioselectivity of **2a**, the author then designed and synthesized new benzothiadiazine catalysts **VII-IX** bearing different chiral scaffolds. The use of cinchonidine-derived catalyst **VII** under the same conditions enhanced the enantioselectivity to a higher 80% ee (entry 6). In contrast, cyclic tertiary amine catalyst **VIII** exhibited a slightly lower ee along with decreasing reaction rate (entries 7). Encouraged by these results, we finally examined the acyclic bulky amine catalyst **IX**,

introducing an isopropyl group, the chemical yield and enantioselectivity going up to 98% and 84% ee, respectively (entry 8).

Table 2-2. Optimization of reaction conditions.



Entry	Catalyst	solvent	Time (h)	Yield (%)[a]	Ee (%)[b]
1[c]	VI	CH_2Cl_2	21	94	20
2[d]	VI	CH_2Cl_2	24	76	24
3	VI	Toluene	2	92	57
4	VI	THF	72	60[e]	55
5	VI	MeCN	72	82	70
6	VII	MeCN	24	91	80
7	VIII	MeCN	72	95	75
8	IX	MeCN	24	98	84

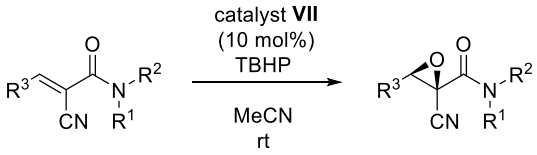


[a] Isolated yield. [b] Determined by chiral HPLC analyses. N.D = not determined. [c] 30% hydrogen peroxide was used instead of TBHP. [d] Urea hydrogen peroxide was used instead of TBHP. [e] Obtained as an inseparable diastereomer mixture.

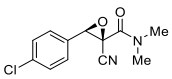
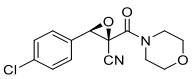
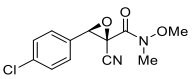
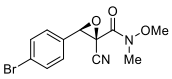
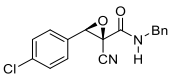
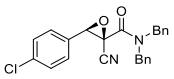
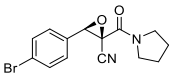
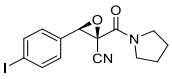
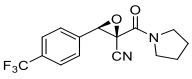
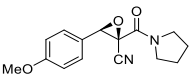
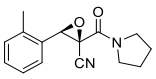
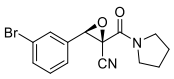
With the optimal conditions in hand, the author next investigated the substrate scope regarding the R^1 and R^2 substituents on amides **1** (**Table 2-3**). When *N*,*N*-dimethylacrylamide **1b** was used as the substrate, the corresponding epoxide **2b** was obtained in 89% yield with 74% *ee* (entry 1), but the enantioselectivities obtained with more electron-deficient amides such as morpholinylamide **2c** and Weinreb amides **2d** and **2e** were lower (42–60% *ee*; entries 2–6). The obtained Weinreb amides **2d** and **2e** could in principle be converted to a variety of ketones using Grignard and organolithium reagents (vide infra).[68] Unfortunately, the secondary and tertiary amides **1f** and **1g**, having a deprotectable benzyl group, resulted in moderate enantioselectivities, albeit in excellent yields (entries 5 and 6). The author next investigated the effect of the substituent R^3, which would be very important for the antimalarial activity (entries 7-12). The epoxidations of amides bearing both electron-withdrawing and electron-donating groups at the para positions of the aromatic rings proceeded efficiently to furnish epoxides **2h–k** in 97–98% yields with 80–84% *ee*s (entries

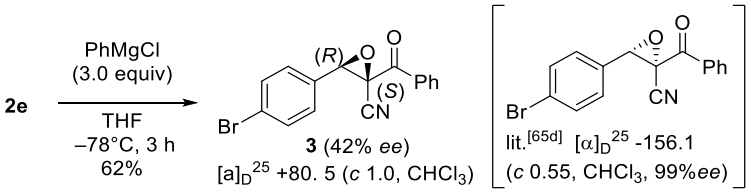
7–10), although the reaction took longer to complete when the substituent was a methoxy group (entry 10). These results suggest that the electronic properties of the amide moiety are more important for the epoxidation stereoselectivities than those of the substituent R^3. In addition, substrates **1l** and **1m** with *ortho*- and *meta*-substituted aromatic groups underwent the epoxidation smoothly to afford amides **1l** and **1m** with no detrimental effect on enantioselectivity (entries 11 and 12). As illustrated above, the author established the enantioselective synthetic method for a series of epoxyamides which are expecting to possess a promising antimalarial activity.

Table 2-3. Substrate scope.[a]



1b-p **2b-p**

1.  **2b:** 89%, 74% *ee* (36 h)	2.  **2c:** 99%, 60% *ee* (96 h)	3.  **2d:** 97%, 46% *ee* (36 h)
4.  **2e:** 96%, 42% *ee* (36 h)	5.  **2f:** 99%, 53% *ee* (36 h)	6.  **2g:** 99%, 33% *ee* (120 h)
7.  **2h:** 98%, 84% *ee* (18 h)	8.  **2i:** 98%, 84% *ee* (24 h)	9.  **2j:** 97%, 80% *ee* (18 h)
10.  **2k:** 96%, 82% *ee* (252 h)	11.  **2l:** 92%, 80% *ee* (192 h)	12.  **2m:** 97%, 82% *ee* (18 h)



Scheme 2-4. Determination of absolute configuration.

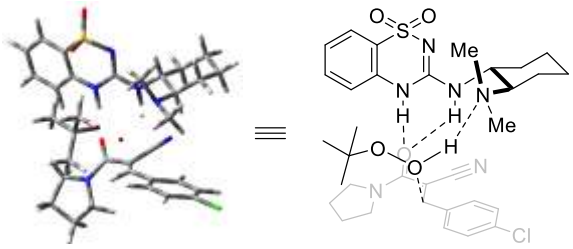
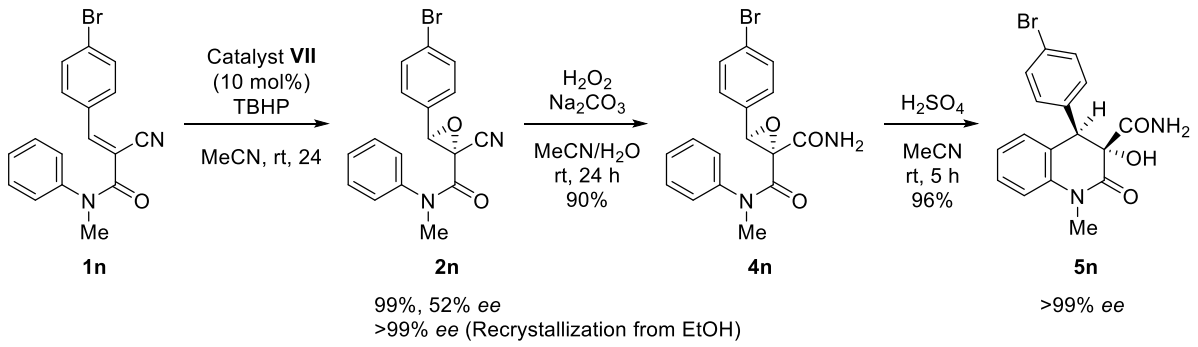


Figure 2-13. Calculated transition state using Gaussian09 at the B3LYP 6-31G* level.

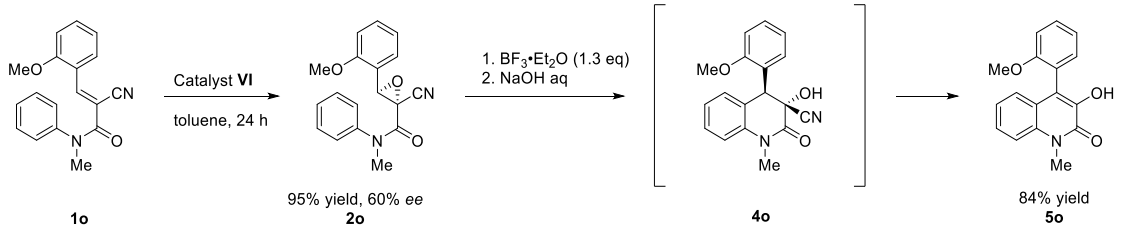
To confirm the absolute configuration of the products **2a-m**, epoxyamide **2e** was treated with phenylmagnesium bromide at low temperature (**Scheme 2-4**). Interestingly, the nucleophilic addition of the Grignard reagent took place chemoselectively at a Weinreb amide moiety of **2e** to give the corresponding ketone **3** in 62% yield, without any ring opening or addition to the CN group (**Scheme 2-4**). The absolute configuration of **3** was determined by comparing its specific optical rotation value with the literature data,[70] and the absolute configuration of **2e** was unambiguously determined to be 2*S*,3*R*. The stereochemistries of the other epoxides in Table 2 were assigned analogously to **2e**, and a plausible transition state, involving the addition of TBHP to the α,β-unsaturated amide **3a** promoted by catalyst **VI**, was calculated using Gaussian09[69] at the B3LYP 6-31G* level.[70] If the p*K*a value of TBHP is taken into consideration, a neutral ternary complex would be involved (**Figure 2-13**), although an ionic transition state via deprotonation of TBHP cannot be ruled out.

The author next turned my attention to the asymmetric synthesis of chiral 3,4-dihydroquinolin-2[*1H*]-ones by using the established method. As expected, the catalytic asymmetric epoxidation of *N*-aryl-α,β-unsaturated amide **1n** with 10 mol% of catalyst **IX** proceeded smoothly under the optimized reaction conditions, but the desired product was obtained with moderate enantioselectivity (55% ee). It should be noted that almost enantiomerically pure anilides **2n** can be obtained after a single recrystallization from EtOH. The CN group of the epoxide **2n** was chemoselectively hydrolyzed to the corresponding amide **4n** in 90% yield, which was then subjected to a sulfuric acid mediated epoxide-arene cyclization[71] without any loss of enantioselectivity to furnish chiral quinolone[72] **5n** bearing two contiguous stereocenters (**Scheme 2-5**).



Scheme 2-5. Application of epoxide **1n** to the synthesis of chiral 2-quinolone **5n**.

Finally, the author examined the possibility of the transformation of chiral epoxyamide **1o** into 4-arylquinolin-2[*1H*]-one **5o** via the corresponding cyanohydrine derivative **4o** (**Scheme 2-6**). Treatment of *N*-aryl-α,β-unsaturated amide **1o** possessing 2-methoxyphenyl group with catalyst **IX** under the optimized conditions provided the desired epoxide **2o** in 95% yield with moderate 60% ee. From the results of **1n** and **1o**, α,β-unsaturated anilides might not be good substrates for the asymmetric epoxidation using catalyst **IX**. To demonstrate the synthetic versatility of the epoxyanilides, epoxide **2o** was converted into the target molecule **5o** in 84% by the successive treatment with $BF_3 \cdot$etherate and aqueous NaOH solution.



Scheme 2-6. Application of epoxide **2o** to synthesis of axial chiral compound **5o**.

2.2.3 Conclusion

In conclusion, the author developed a highly oxidant-resistant hydrogen bond donor organocatalyst **IX**, which effectively promoted the asymmetric epoxidation of α,β-unsaturated amides to give chiral 2-oxiranecarboxamides. Furthermore, the concise transformation of 2-oxiranecarboxamides **7** into 3,4-dihydroquinolin-2[*1H*]-ones **9a** and 4-arylquinolin-2[*1H*]-one **9b** with no racemization demonstrated the synthetic potential of chiral 2-oxiranecarboxamides **7** for the divergent synthesis of a wide range of quinolin-2[*1H*]-ones as promising antimalarial drug candidates.

2.2.4 Experimental Section

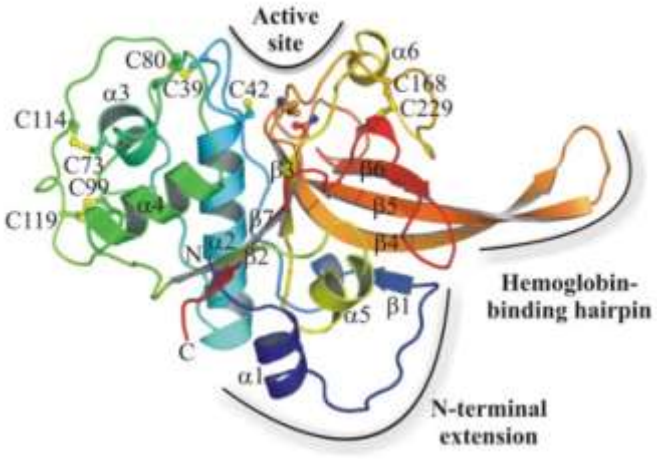
An *n*-decane solution of TBHP (0.1 mL, 5.5 M) was added to a solution of α,β-unsaturated amide **1** (0.1 mmol) and benzothiadiazine catalyst **VI** (3.2 mg, 0.01 mmol, 10 mol%) in MeCN (1.0 mL, 0.1 M); the resulting mixture was stirred at ambient temperature for the indicated time listed in the tables. The reaction mixture was then evaporated and the resulting crude residue purified by column chromatography on silica gel, with *n*-hexane/ethyl acetate as the eluent, to give the analytically pure compound **2**. The enantiomeric ratios of all of the compounds were determined by HPLC on a chiral stationary phase. For more details see supporting information.

2.3 Establishment of α selective *N*-glycosylation to improve the chemical and pharmacological properties of a cutting-edge antibiotics – antimicrobial peptides (AMPs)

2.3.1 Background

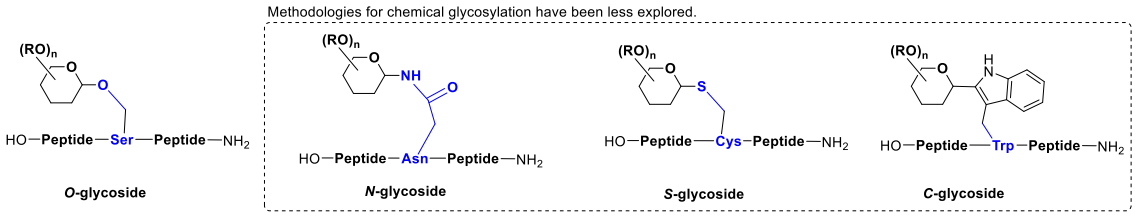
Although antibiotics have been less explored compared to other types of antimalarial drugs, they are still an important branch as they can target a variety of pathogens if designed properly. Recently, antimicrobial peptides (AMPs) have drawn considerable attention as alternatives to currently used antibiotics in the treatment and prevention of microbial infections to overcome observed antimicrobial resistance to traditional antibiotics.[73] AMPs are natural antibiotics which are produced by all known living species, ranging from bacteria, fungi, and plants to invertebrates, non-mammalian vertebrates and mammals. To date, more than 2,000 AMPs were isolated with proven records of diverse activities including antimicrobial activity, anticancer, spermicidal, chemotactic, antiviral activity, etc. They are considered as promising candidates because a single AMP has the capacity to target a variety of microorganisms simultaneously. [74]

In case of malaria, AMPs are still at an early stage, but several cutting-edge approaches with AMPs has started to emerge. A diverse range of AMPs, possessing difference in size, amino acid composition, the secondary structure, have been recently discovered as antimalarial drug candidates.[75] Antimalarial activities have been described for AMPs with biological functions concerning host hemoglobin degradation, host-cell invasion and egress, and intracellular housekeeping.[76] For instance, ankyrin peptide, a potent inhibitor of the major cysteine protease of *Plasmodium falciparum* – falcipain-2 (**Figure 2-14**)[77] – demonstrated satisfying antimalarial properties through working as cell-penetrating peptides.[78] Similarly, there are numerous reports on potential utilization of synthetic peptides which are capable of invading host-cells as antimalarial drug candidates.[79]



Figrue 2-14. Overall view of falcipain-2. Ribbon representation of falcipain-2 with the L domain on the left, the R domain on the right, and the active site cleft located on top of the molecule. The spectral color-coding is according to sequence, from dark blue (N terminus) to dark red (C terminus). Disulfide bonds and active site residues are shown in ball-and-stick models. Secondary structure elements, N and C termini, the active site cysteine (C42), and cysteine residues involved in disulfide bonds are labeled.

The antimicrobial mechanisms of AMPs depend on their biophysical properties such as the secondary structure, net charge and hydrophobicity, because these properties would significantly influence the AMP-target interaction.[80] Glycosylation, which is one of the most prevalent post-translational modifications of a protein, plays a crucial role in defining their chemical property and biological function of proteins.[81] In a similar way, peptides as well as small biomolecules could be changed and/or controlled their biological activities by connecting with a variety of glycosides, leading to a remarkable increase in diversity of AMPs. Glycosides are classified into four categories depending on the bonding mode of the anomeric carbon: *O*-, *C*-, and *S*-, *N*- glycosides (**Figure 2-15**).



Figrue 2-15. Types of AMP-glycosides

O-linked glycosides, which often include proline-rich regions, occasionally glycine-rich regions, were first described in five naturally occurring insect-derived AMPs.[82] *C*-linked glycosides, in which a carbohydrate is linked to a peptide via a carbon atom, exhibits unique resistance to metabolic hydrolysis. Although biological role of *C*-glycoslyation is still under investigation, *C*-linked proteins, such as *C*-mannosylated properdin, can interact with membrane of microorganism through its sugar moiety while stabilizing the protein at the same time. This is an important biological functionality to be further exploited as a way to modify antimicrobial peptides.[83] Recently discovered *S*-linked glycosides were described to produce by a post-translational modification of the sublancin glycopeptide and other bacteriocins.[84] *N*-linked glycosides, attached to one of the peptide residues like asparagine, have been very well studied on their biologically functions.[85] It has been reported that the functions of *N*-glycosides are related to peptide rigidity,[86] solubility,[87] propensity to aggregate,[88] conformational changes to secondary structure of peptides,[89] and their ability to influence interactions with neighboring peptides.[90] In addition to the linkage types of *N*-glycosides, glycopeptides can be further diversified on the basis of glycosidic linkage, glycan

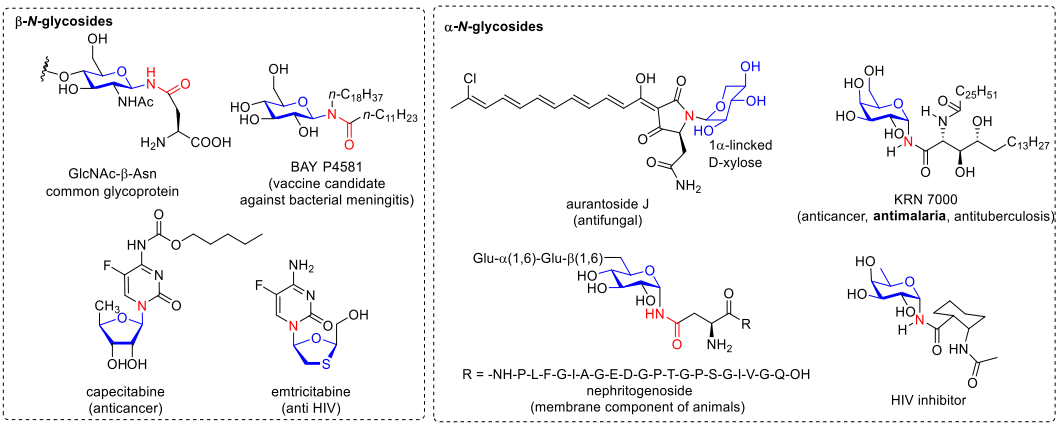
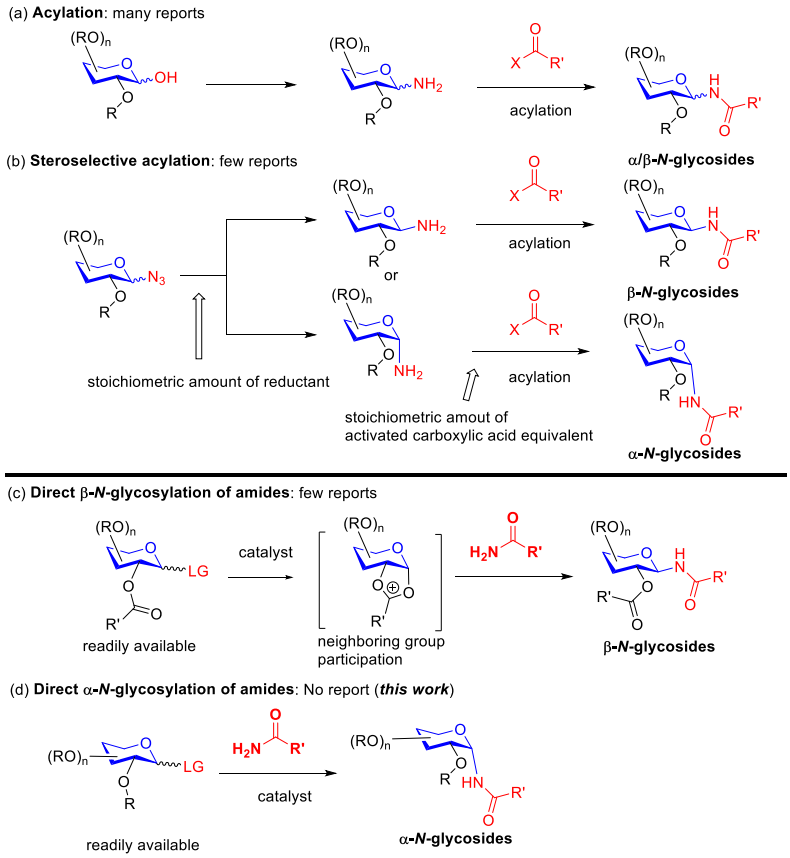


Figure 2-16. Biologically active α- and β-*N*-glycosyl amides

composition, structure, and length.[91] The presence or absence of a glycan, as well as variation in the stereochemistry of the glycosides including α- or β-linkage affects their therapeutic activities of AMPs.[92] Despite of the importance of above glycosides, methodologies for chemical glycosylation are under study, especially for *N*-, *S*-, *C*-glycosides. Thus, developing new synthetic approaches for these glycosides has become a major concern of recent research to meet the demands of new types of antimalarial drugs. Based on this background, the author focused on *N*-glycosides as target molecules, because some naturally occurring and synthetic glycosyl amides have already shown to have significant inhibition activities against various pathogens, such as malarial parasites, bacterial, fungi, and HIV virus (**Figure 2-16**)[93]

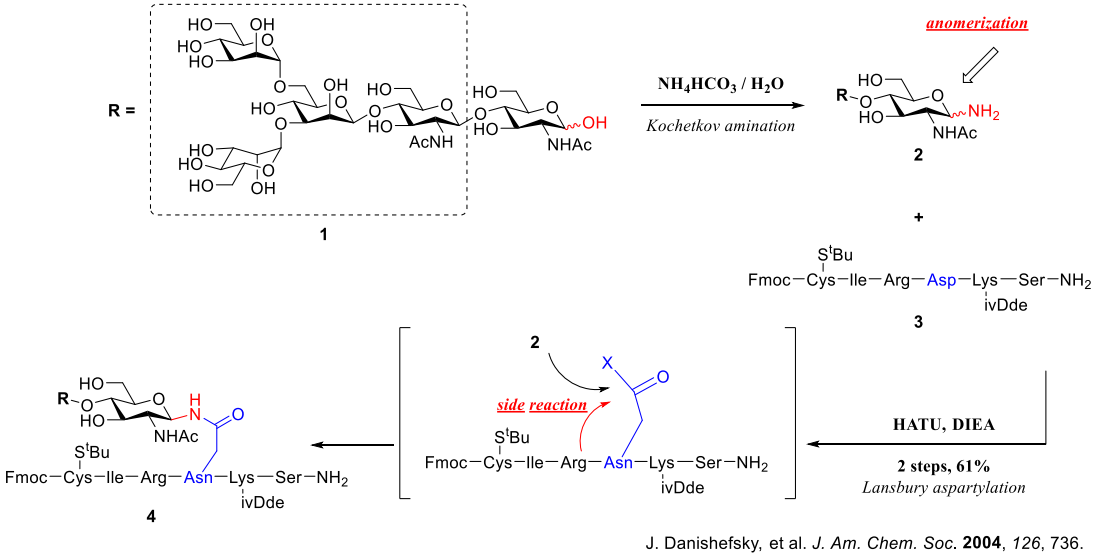
2.3.2 Research strategy

So far, the syntheses of *N*-glycosides have been much less studied than those of *O*-glycosides. The representatives were summarized in **Scheme 2-7**. A conventional synthetic method to synthesize *N*-linked glycopeptides is through the acylation of glycosylamines with activated carboxylic acid derivatives (**Scheme 2-7**, a-b, Lansbury aspartylation).[94] Recently, the direct β-*N*-glycosylation of amides has been developed by Takahashi, Yu, and our group (**Scheme 2-7**, c), which opens a new door to access to a various series of *N*-glycosides. However, selective synthesis of α-*N*-glycosides seems to be still difficult (**Scheme 2-7**, b), despite the utilities of α-*N*-glycosides shown in **Figure 2-16**. In this chapter, the author describes a direct α-*N*-glycosylation of amide, which has never been reported (**Scheme 2-7**, d).



Scheme 2-7. Purpose of this work

The features and problems of the reported methods are briefly summarized below. Danishefsky and co-workers developed an elaborated strategy for synthesizing complex *N*-linked glycoproteins **4** through the acylation of aminosugar **2** with the aspartic acid residue of peptide **3** in the presence of (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) HATU as a peptide coupling reagent (**Scheme 2-8**).[95] Although aminosugar **2** could be prepared from the corresponding sugar **1** and ammonium bicarbonate (Kochetkov amination),[96] glycosylamine often undergoes anomerization, leading to low selectivity of the product.[97] Activated carboxylic acid moiety also sometimes suffers from the undesired intramolecular nucleophilic attack from a neighboring amino acid residue.

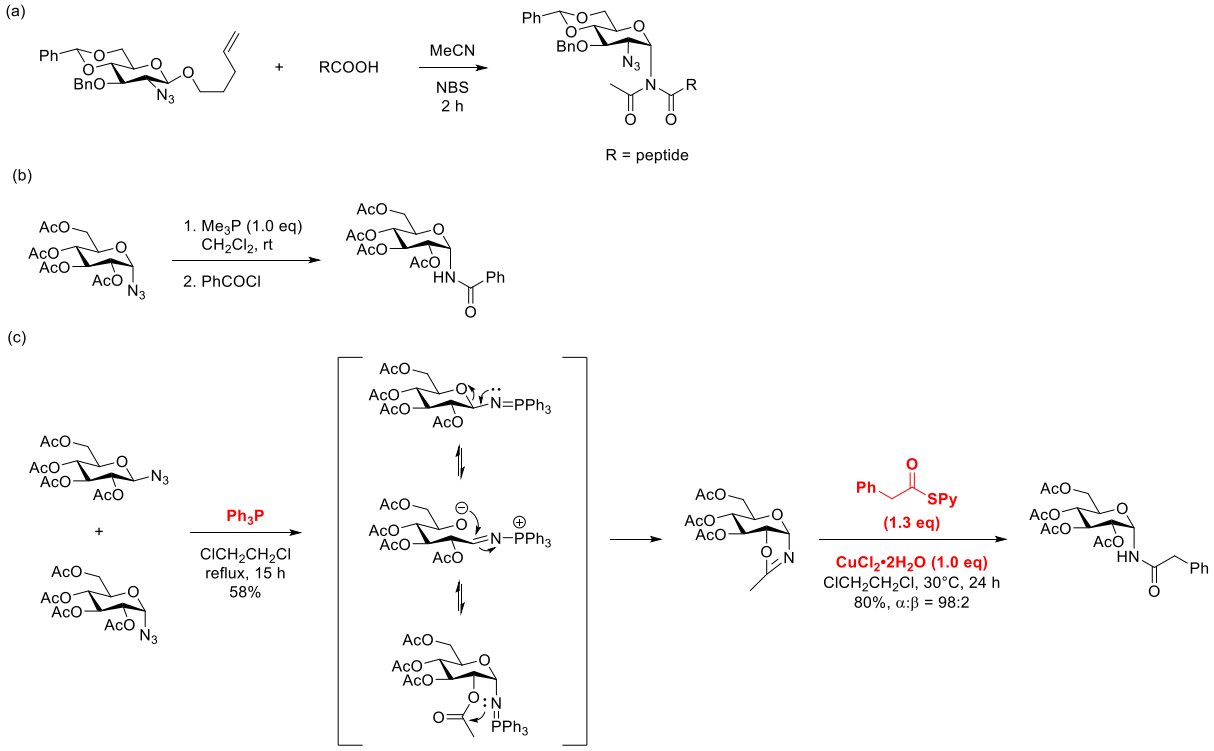


Scheme 2-8. Danishefsky's strategy for synthesizing *N*-linked glycoproteins

As illustrated above, anomerization of 1-amino glycopyranosyl derivatives is problematic, and several alternative methods were developed to avoid a free primary amine as an intermediate. For example, Fraser-Reid group reported a condensation reaction of *O*-*n*-pentenylglycosides or thioglycosides with aspartic acid in the presence of NBS (or NIS) to afford α-*N*-linked glycopeptides (**Scheme 2-9**, a)[98]. Other examples involve the reaction of α-glycosyl azide with acyl chloride in the presence of tertiary phosphine, in which anomerization remains as an unsolved problem (**Sheme 2-9**, b).[99] In 2003, DeShong's group has established a highly α-selective *N*-glycosylation reaction of glucopyranosyl isoxazoline with 2-thiopyridyl ester by employing $CuCl_2$ as the additive (**Scheme 2-9**, c).[100] Use of a stoichiometric amount of reductant, thioester as an acylating reagent, and copper salt as a promoter would be the major drawback of this method.

In 2005, Takahashi and co-workers developed the first direct *N*-glycosylation of amide with a super-armed glycosy donor using TMSOTf as the catalyst (**Scheme 2-10a**).[101] They successfully obtained the desired product with high yield and high β-selectivity, via the neighboring group participation, with several asparagine derivatives as nucleophiles. In 2010, Yu and co-workers also published the gold-catalyzed direct β–selective *N*-glycosylation reaction (**Scheme 2-10b**). These methods, however,

remained to have the capacity for further improvement concerning scope of amides and accessibility of leaving group.

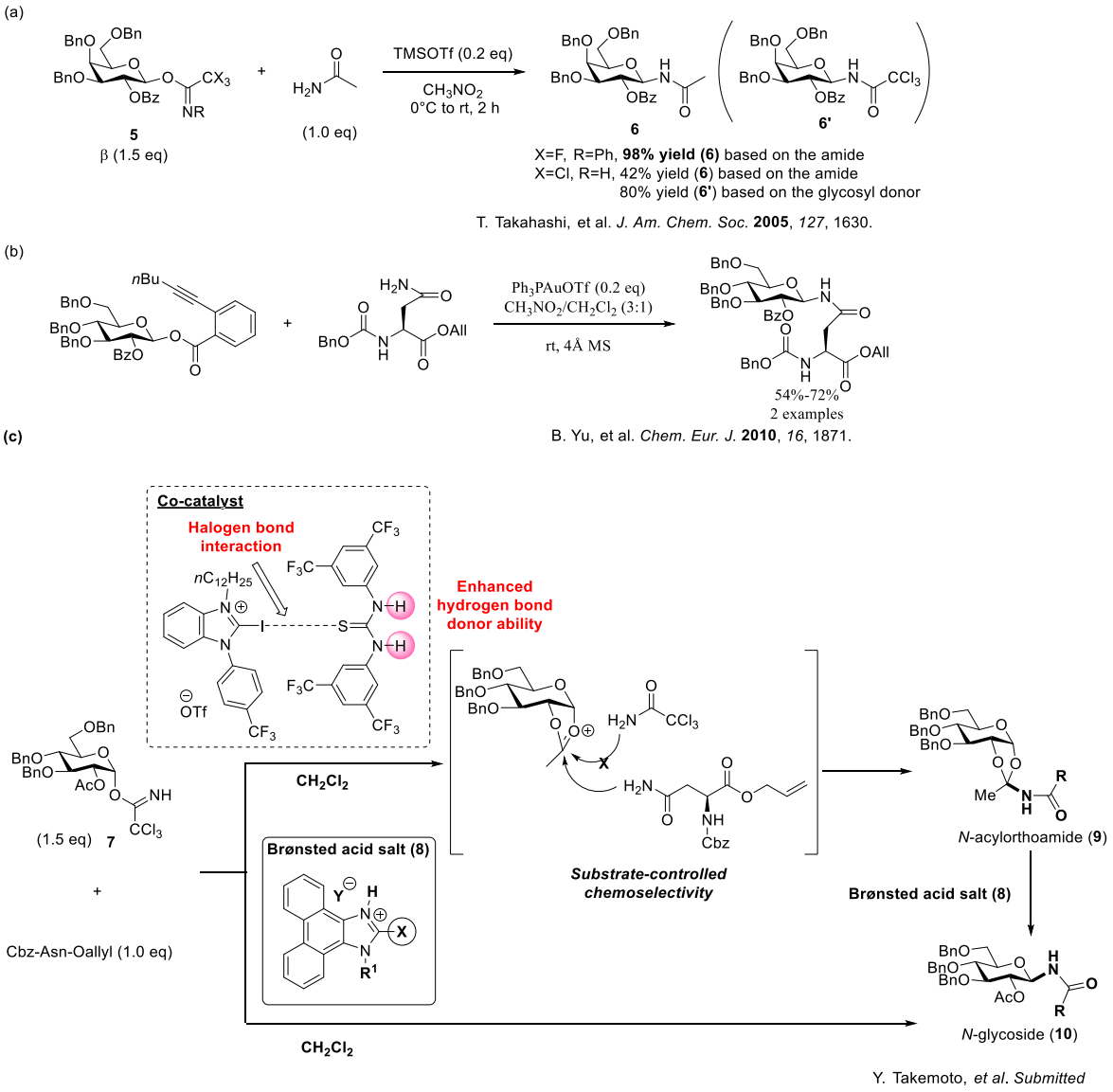


Scheme 2-9. α selective *N*-glycosylation reaction

In 2017, Takemoto revealed that the halogen bond donor (XB donor)[102]- Schreiner's thiourea[103] co-catalytic system afforded a unique glycofunctionalized adduct (*N*-acylothoamide[104] **9**) from amide and Schmidt glycosyl donor[105] which is regarded as one of the most promising and readily available glycosyl donors. More specifically, the halogen bond interaction between XB donor and thiourea catalyst contributes to the activation of the leaving group – trichloroacetoimidate moiety - of the glycosyl donor, and the generated oxonium cation is likely stabilized by the neighboring group. The subsequent nucleophilic attack to the intermediate by trichloroacetoamide generated from the leaving group generally afforded the undesired glycosyl trichloroacetamide as byproduct, especially when poor nucleophiles like amides are used. Under the mild conditions, *N*-acylorthoamides seems to be obtained in good to high yields via the substrate-controlled chemoselectivity. The same group also discovered that newly designed Brønsted acid **8** promoted not only the rearrangement of *N*-acylorthoamide **9** to the desired *N*-glycoside **10**, but also the direct β-*N*-glycosylation of amide with Schmidt donor **7**.

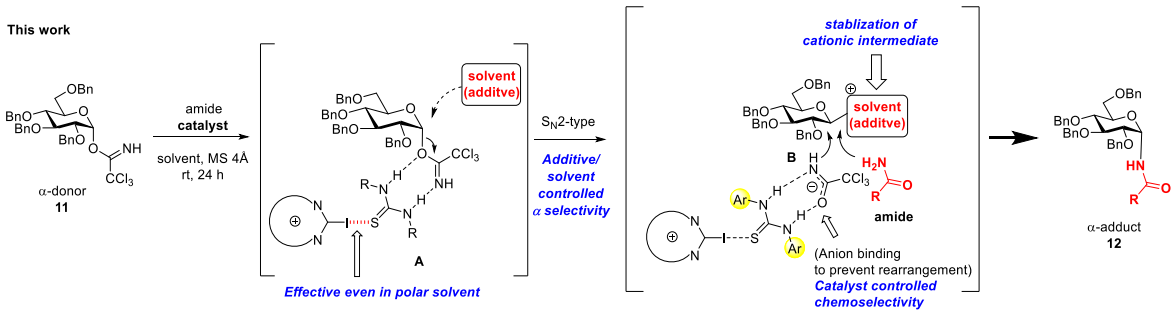
Considering the fact that a direct α-*N*-glycosylation of amide have never been reported, the author then planned to achieve it using Schmidt donor **11** without neighboring group participation. To realize the aimed reaction, suppressing the formation of the undesired glycosyl trichloroacetamide would be a crucial issue to be solved[99] (**Scheme 2-11**). The author envisioned that α-selectivity would be achieved through the dual inversion strategy involving the first S_N2 addition of an appropriate solvent and/or additive[106] to α-donor **11** and the sequential S_N2 reaction of an amide to the resulting β-linked intermediate **B,** affording the

desired α-linked product. For activation of the leaving group of **11**, the author chose the same XB-donor/thiourea co-catalytic system previously developed by our group, because of the following reasons: 1) XB interaction



Scheme 2-10. Direct β selective *N*-glycosylation reaction

would be effective in relatively polar solvent, so that the reaction could be achieved under mild conditions, and 2) tuning of both HB donor and XB donor would improve their ability of trapping the leaving group via an anion binding, so that a peptidyl amide preferentially attacks from the α-side with participation of the thiourea/leaving group complex, along with preventing the undesired rearrangement of the leaving group.

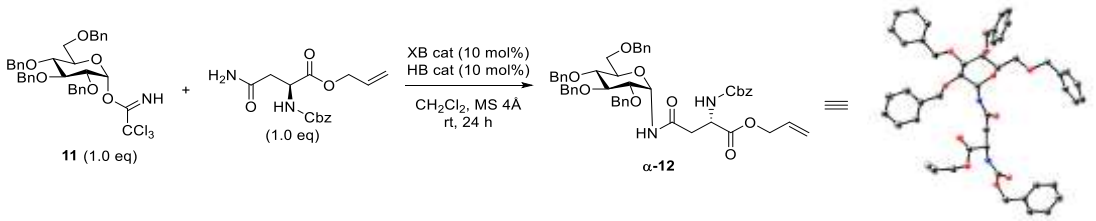


Scheme 2-11. Strategy for direct α-*N*-glycosylation of amide

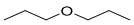
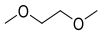
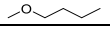
2.3.3 α selective *N*-glycosylation

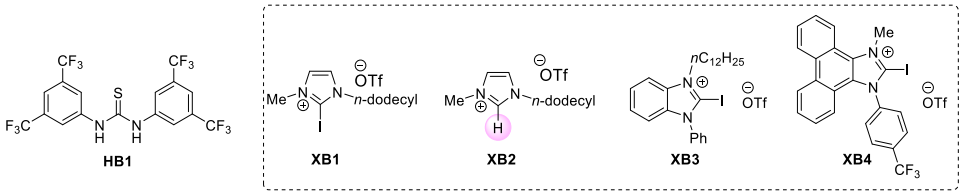
Under this strategy, the author initially screened several catalysts and solvents for developing the direct α-*N*-glycosylation using glycosyl donor **11** with asparagine derivative. (**Table 2-4**). Based on our previous work, iodoimidazolium salt as an XB donor and Schreiner thiourea were first examined in dichloromethane. As we expected, the dual catalyst system afforded the desired product **12** in 41% yield with almost no α/β selectivity (entry 3), while the reaction did not work well with each XB donor or HB donor alone (entries 1,2). When the iodine atom of **XB1** was replaced with hydrogen atom, the dual catalyst failed to promote the reaction, which indicates that the halogen bonding interaction between XB donor and HB donor plays an important role (entry 4). To increase the chemical yield, the author further investigated on the XB donor catalysts, and revealed that benzimidazolium catalyst (entry 5) and phenathoimidazolium catalyst (entry 6) can better accelerate the reaction with moderate yield, the yields being slightly increased without improving the α-selectivity. Further investigation was carried out with **XB4**, which was chosen due to the stability and synthetic simplicity, to investigate the effect of solvent on the α/β-selectivity (entries 7-12). It is well known that etheric solvents often improve α-selectivity in *O*-glycosylation.[107] A slight improvement of α/β-selectivity (α:β = 65:35) was observed when diethyl ether was used as solvent (entry 7). Encouraged by this result, the author investigated several other etheric solvents.

Table 2-4. Initial screening of XB donor and solvent for direct α-*N*-glycosylation



Entry	Solvent	XB catalyst	HB catalyst	Yield of **1**[a]	α : β
1	DCM	**XB1**	—	N. R	—
2	DCM	—	**HB1**	4%	—
3	DCM	**XB1**	**HB1**	41%	49 : 51
4	DCM	**XB2**	**HB1**	N. R	—
5	DCM	**XB3**	**HB1**	55%	40 : 60
6	DCM	**XB4**	**HB1**	50%	50 : 50
7	Et_2O	**XB4**	**HB1**	41%[b]	65 :35
8	THF	**XB4**	**HB1**	50%[b]	53 : 47

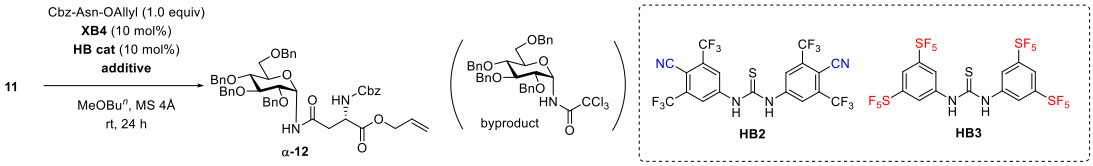
9	CPME	**XB4**	**HB1**	43%[b]	56 : 44
10		**XB4**	**HB1**	Trace[b]	—
11		**XB4**	**HB1**	40%[b]	**80 : 20**
12		**XB4**	**HB1**	54%[b]	**80 : 20**

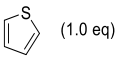
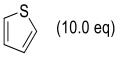
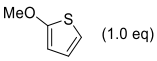
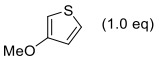
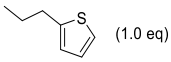
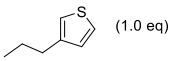
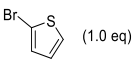
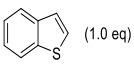


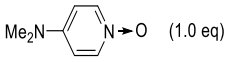
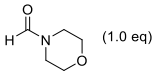
[a] Based on glycosyl acceptor. [b] 1.2 equivalent of glycosyl donor was employed.

However, THF and CPME did not improve the selectivity (entries 8 and 9), and diisopropyl ether did hardly afford the desired product (entry 10), partly because of the insolubility and bulkiness of the XB donor. The author then tried less hindered ethers as solvent, and finally found that dimethoxyethane and *n*-butyl methyl ether improved α/β-selectivity (α: β = 80:20) (entries 11 and 12). *n*-Butyl methyl ether was the solvent

Table 2-5. Effect of additives and HB donor



Entry	HB catalyst	Additive	Yield of **1**[a]	α : β	Byproduct[b]
Ref.	HB1	—	54%	80 : 20	66%
1	HB1	 (1.0 eq)	**64%**	**82 : 18**	**41%**
2	HB1	 (10.0 eq)	39%	85 : 15	54%
3	HB1	 (1.0 eq)	57%	60 : 40	50%
4	HB1	 (1.0 eq)	48%	77 : 23	60%
5	HB1	 (1.0 eq)	64%	81 : 19	47%
6	HB1	 (1.0 eq)	54%	81 : 19	55%
7	HB1	 (1.0 eq)	28%	69 : 31	55%
8	HB1	 (1.0 eq)	48%	84 : 16	60%

9	HB1	 (1.0 eq)	N.R	—	—
10	HB1	 (1.0 eq)	N.R	—	—
11	HB1	Ph_3P=O (1.0 eq)	58%	81 : 19	52%
12	HB1	R_3P^c (1.0 eq)	Trace	—	—
13	**HB2**	—	**65%**	66 : 34	**46%**
14	**HB3**	—	**74%**	**78 : 22**	**31%**
15	TMSOTf	—	<10%	—	>90%

[a] Based on glycosyl acceptor. [b] Based on glycosyl donor. [c] R = 2-thienyl

of choice in terms of chemical yield. The stereochemistry of anomeric position of the major isomer was unambiguously determined as α-isomer by an X-ray crystallographic analysis.

The author next investigated several additives and different HB donors in order to improve the α/β-selectivity and reduce the yield of undesired trichloroacetamide (Table 2-5). When 1.0 equiv of thiophene was treated, the yield increased to 64% with the decrease of byproduct yield, and the α/β-selectivity has reached 82:18 (entry 1). 10 equiv of thiophene turned out to diminish the yield which is probably ascribed to the disturbance by the access amount of additive to the catalytic activity (entry 2). Encouraged by this result, several thiophene derivatives with electron-withdrawing groups and electron-donating groups were employed (entries 3-8). Other nucleophilic additives, DMAPO, formyl amide, phosphine oxide, and phosphine were screened. Yet all of them failed to improve neither yield nor α–selectivity (entries 9-12). The yield was further improved with suppression of byproduct by using **HB2** and **HB3** with superior HB-donating ability (entries 13-14). It is worthy to note that the commonly used Lewis acid, TMSOTf, was too strong to improve the chemical yield, providing the undesired glycosyltrichloroacetamide as the major product (entry 15).

2.3.6 Conclusion

In conclusion, the author developed a novel combination of XB donor and thiourea as a dual catalyst system and successfully applied it to α-selective *N*-glycosylation reaction which cannot be achieved with common Lewis acids. Furthermore, the dual catalyst system demonstrates an unique and outstanding catalytic activity which outperforms each of catalyst. Having established the novel catalytic method for the *N*-glycosylation, the author could pave the new way for the efficient access to a wide range of *N*-glycosides and glycoproteins, in terms of yield, stereoselectivity, simple manipulation, and cost-performance, which expects to show significant inhibition activities against malarial parasites.

2.3.7 Experimental section

To a solution of additive (0.05 mmol, 1.0 eq), other reagents – glycosyl donor (0.06 mmol, 1.2 eq), glycosyl acceptor (0.05 mmol, 1.0 eq), XB donor catalyst (0.005 mmol, 0.1 eq), HB donor catalyst (0.005

mmol, 0.1 eq), MS (100.0 mg) – were added in turn. The reaction was stirred for 24 h before directly subjected to column chromatography. For more details, see supporting information.

Summary

In summary, this study integrated two different strategies – effective IP sharing and innovative IP creation – to combat malaria. In chapter 1, a new mechanism was proposed to realize an interactive and integrated IP sharing concerning a variety of research outcomes in the field of malaria drug development. An important group of stakeholders were identified to broaden the scope of IP sharing. This research intends to inform scientists to build on the success of the previous work to further develop the promising candidates into products, as well as to learn from the low value results (unpatentable and unpublishable results) to strategically conduct future research.

The strategy in chapter 2 which concerns IP creation was employed to design innovative compounds for malaria drug development. To develop effective drug candidates, two different types of natural product derivatives with prospect anti-malarial activities were designed. One type of candidates is quinolones. In this paper, a concise and effective synthetic method was developed to obtain a wide range of quinolin-2[*1H*]-ones to contribute to this research activities. The other was built on recent breakthrough on innovative antimicrobial peptides which target a wide range of pathogens. Their application to the antimalarial drugs is limited, yet it has a huge potential to widen the horizon of research dimension. To contribute to this research strategy, challenging direct α selective *N*-glycosylation reaction was planned to equip additional functionalities to antimicrobial peptides.

In conclusion, this approach is to achieve one goal – combatting malaria from different perspectives – by focusing on IP sharing and IP creation. It is to demonstrate that an integrated approach is necessary to combat diseases of poverty by focusing on malaria as an example.

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Last but not least, many thanks go to the Graduate School of Advanced Integrated Studies in Human Survivability, Kyoto University for financial support.

Supporting information

Chapter 1

Organization type	**Name**	**Malaria endemic area**	**Research activity areas**	**Publications/ patents on malaria**	**Other activities**	**Role**
University	Aberystwyth University (UK)	No	A wide range of support programs on research	Yes	education; close relationships to industry to increase business opportunities; support the development of researchers	conducting research, education program, connecting researchers to industry
University	Addis Abbaba University (Ethiopia)	Yes	A wide range of support programs on research	Yes	education;	conducting high quality research and education
Research institute	African Institute of Biomedical Science and Technology (Zimbabwe)	Yes	deliver medical products and services to fight Africa's health challenge	Yes	community activities; research collaboration	delivering services to the community, conducting research
Research institute	Armauer Hansen Research Institute (AHRI) (Ehtiopia)	Yes	NTD, malaria, AIDS, etc	yes	policy discussion; research collaboration	conducting reserch and training, active actor in glovernment policy discussion and support
NPO	Association of University Technology Managers (USA)	No	None	Yes	technology transfer	bringing research to life through technology transfer
Library	Bibliotheca Alexandrina (Egypt)	Yes	None	No	knowledge disseminating	leading institution of

						disseminating knowledge
Research institute	Biomedical Research Institute (USA)	No	Schistosomiasis, immunology, infectious diseases	No	collaborating with NIH to conduct research; research collaboration	conducting research, education program
Association	Biotechnology Industry Organization (USA)	No	healthcare, agriculture, environmental tehcnologies	No	networking with companies	providing partnering and education opportunities
Research institute	Brazilian Biosciences National Laboratory (Brazil)	Yes	Drug discovery, molecular biology	No	training, technology platform; research collaboration	conducting research, providing training, connecting partners through technology platforms
Research institute	California Institute of Technology (USA)	No	Biology, chemistry	Yes	training, technology transfer, corporate partnerships; research collaboration	conducting research, connecting researchers with corporate
University	Case Western Reserve University (USA)	No	A wide range of support programs on research	Yes	education; partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
Research institute	Center for Infectious Disease Research (USA)	No	infectious diseases	Yes	advocate; partnering with NIH; research collaboration	conducting research; partnerning with government organization

Research institute	Center for Molecular Dynamics Nepal (Nepal)	Yes	public health	Yes	policy discussion; research collaboration	conducting research; providng collaboration opportunities
Research institute	Centre for Plant Medicine Research (Ghana)	Yes	medicine, clinical research, etc	Yes	marketing, engineering; research collaboration	conducting research; evolving with industry
University	Centre of Excellence for Malaria Diagnosis, University of Lagos (Nigeria)	Yes	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	Central University of Ecuador (Ecuador)	Yes	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
Research institute	Centre Pasteur du Cameroun (Cameroon)	Yes	infectious diseases	Yes	research collaboration	conducting research; providng collaboration opportunities
University	Cheikh Anta Diop University (Senegal)	Yes	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers

						with industry and government
NPO	Council on Health Research for Development (Switzerland)	No	health	No	connecting country partnerships and policy makers with researchers	connecting different stakeholders
NGO	Drugs for Neglected Diseases initiative (Switzerland)	No	Neglected diseases	Yes	partnering with NGOs, health and development agencies, pharmaceutical companies, and othe partners	providing partnering opportunities; facillitator
Research institute	Eijkman Institute for Molecular Biology (Indonesia)	Yes	medical molecular biology and biotechnology	Yes	Research collaboration, education	leading role in conducting research; education
University	Emory University (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	Eskitis Institute, Griffith University (Australia)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and

						government
Research institute	European Commission, Directorate-General for Research and Innovation (Belgium)	No	A wide range of support programs on research	Yes	Research collaboration, education	knowledge dissemination; providng collaboration opportunities
NGO	Foundation for Innovative New Diagnostics (Switzerland)	No	Diagnostics	No	public private partnership	connecting different stakeholders to address issues on diagnostics
Research institute	Fundação Oswaldo Cruz (Brazil)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Allliance	GALVmed (UK)	No	livestock diseases	No	partnering with NGOs, health and development agencies, pharmaceutical companies, and othe partners	knowledge dissemination; providng collaboration opportunities
Research institute	Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences (China)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Icahn School of Medicine at Mount Sinai (USA)	No	health	Yes	research collaboration	conducting research; providng collaboration opportunities

Research institute	Indian Council of Medical Research (India)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Infectious Disease Research Institute (USA)	No	infectious diseases	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Institut de Recherches en Sciences de la Santé (Burkina Faso)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Institut Pasteur (France)	No	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Institut Pasteur de Madagascar (Madagascar)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Institut Pasteur de Tunis (Tunisia)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Institut Pasteur Korea (Republic of Korea)	No	health	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Institute of Molecular and Cellular Biology of Rosario (Argentina)	Yes	biological science	No	research collaboration	conducting research; providng collaboration opportunities

Research institute	International Centre for Diarrhoeal Disease Research, Bangladesh (Bangladesh)	Yes	diarrhoeal diseases	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	International Centre for Genetic Engineering and Biotechnology (India)	Yes	genetic engineering, biotechnology	Yes	training, technology transfer	conducting research; providng collaboration and training opportunities
Association	International Federation of Intellectual Property Attorneys (Switzerland)	No	None	No	partnering with IP assocations, national sections	providing partnering opportunities; facillitator
Association	International Federation of Pharmaceutical Manufacturers & Associations (Switzerland)	No	None	No	partnering with pharmaceutical companies, and other assocations	providing partnering opportunities; facillitator
NGO	International Hospital Federation (Switzerland)	No	None	No	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator
NGO	International Vaccine Institute (Republic of Korea)	No	vaccine	Yes	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator
University	James Cook University (Australia)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

Research institute	Kenya Agricultural and Livestock Research Organization (Kenya)	Yes	livestock diseases	Yes		conduc
Research institute	Kenya Medical Research Institute (Kenya)	Yes	medical technology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Kumasi Centre for Collaborative Research (Ghana)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
NGO	Licensing Executive Society International (USA)	No	None	No	partnering with national and regional member societies	providing partnering opportunities; facillitator
Research institute	Liverpool School of Tropical Medicine (UK)	No	medicine, clinical research, etc	Yes	research collaboration	conducting research; providng collaboration opportunities
University	Mahidol University (Thailand)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	Makerere University (Uganda)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and

						government
NGO	Malaria Consortium (United Kingdom)	No	Malaria, NTD	Yes	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator
Research institute	Massachusetts General Hospital (USA)	No	A wide range of support programs on research	Yes	education	conducting research; education program; providing opportunities for partnership
University	Massachusetts Institute of Technology (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	McGill University (Canada)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	McMaster University (Canada)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
Research institute	Medical Research Council (South Africa)	Yes	medical technology	Yes	research collaboration	conducting research; providng collaboration opportunities
University	Medical Research Institute, Alexandria University (Egypt)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
NGO	Medicines for Malaria Venture (Switzerland)	No	Malaria, NTD	Yes	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator
University	Monash University (Australia)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

Research institute	Murdoch Childrens Research Institute (Australia)	No	medical technology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	National Center for Genetic Engineering and Biotechnology (Thailand)	Yes	genetic engineering, biotechnology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	National Institute for Medical Research (Tanzania)	Yes	medical technology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	National Institute of Immunology (India)	Yes	immunology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	National Institute of Industrial Property (Brazil)	Yes	A wide range of support programs on research	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	National Institute of Parasitic Diseases, Chinese Centers for Disease Control (China)	Yes	parasitic diseases	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	National Institutes of Health (USA)	No	health	Yes	research collaboration	conducting research; providng collaboration opportunities
University	National University of Singapore (Singapore)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and

						connecting researchers with industry and government
Research institute	Nigerian Institute of Medical Research (Nigeria)	Yes	medical technology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Noguchi Memorial Institute for Medical Research (Ghana)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities
University	Northeastern University (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
NGO	Operation ASHA (India)	Yes	TB	No	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator
Research institute	Papua New Guinea Institute of Medical Research (Papua New Guinea)	Yes	medical tehcnology	Yes	research collaboration	conducting research; providng collaboration opportunities
NGO	PATH (USA)	No	health	Yes	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator

NGO	Public Interest Intellectual Property Advisors (USA)	No	IP	No	partnering with other sectors; knowledge dissemination	providing partnering opportunities; facillitator
Research institute	Research Institute for Tropical Medicine (Philippines)	Yes	medicine, clinical research, etc	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Sabin Vaccine Institute (USA)	No	vaccine	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	School of Life Sciences and Technologi, Institut Teknologi Bandung (Indonesia)	Yes	life science	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Seattle Children's Research Institute (SCRI) (USA)	No	A wide range of support programs on research	Yes	partnering with other sectors; knowledge dissemination	provding partnering opportunities, conducting research
University	Social Medicine Institute, Rio de Janeiro State University (Brazil)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	Stanford University (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers

						with industry and government
Research institute	Structural Genomics Consortium (Canada)	No	genomics	No	partnering with other sectors; knowledge dissemination	provding partnering opportunities, conducting research
Research institute	Swiss Tropical and Public Health Institute (Switzerland)	Yes	Public health	Yes	partnering with other sectors; knowledge dissemination	provding partnering opportunities, conducting research
NGO	Tech Transfer Summit Ltd (UK)	No	technology transfer	No	None	provding partnering opportunities, conducting research
Research institute	Texas Children’s Hospital Center for Vaccine Development (USA)	No	A wide range of support programs on research	Yes	partnering with other sectors; knowledge dissemination	provding partnering opportunities, conducting research
University	The George Washington University (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
Research institute	Theodor Bilharz Research Institute (Egypt)	Yes	health	Yes	research collaboration	conducting research; providng collaboration opportunities

University	Tulane University (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	United States Patent and Trademark Office (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Bamako (Mali)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Bamenda (Cameroon)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	University of British Columbia (Canada)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Buea (Cameroon)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Calgary (Canada)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of California, Berkeley (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	University of California, San Diego (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of California, San Francisco (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Campinas (Brazil)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Dschang (Cameroon)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	University of Dundee (UK)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Edinburgh (UK)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Georgia (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Ghana (Ghana)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	University of Ibadan (Nigeria)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Kansas (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Mauritius (Mauritius)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Melbourne (Australia)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	University of New South Wales (Australia)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of South Carolina (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of South Florida (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Texas Southwestern Medical Center (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	University of Toronto (Canada)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Vermont (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Washington (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
University	University of Yaoundé I (Cameroon)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government

University	Université Paris-Sud (France)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
Research institute	Walter & Eliza Hall Institute of Medical Research (Australia)	No	medical technology	Yes	research collaboration	conducting research; providng collaboration opportunities
Research institute	Walter Reed Army Institute of Research (USA)	No	health	Yes	research collaboration	conducting research; providng collaboration opportunities
University	Washington University School of Medicine (USA)	No	A wide range of support programs on research	Yes	education, empowring researchers, partnering with industry	conducting research, education, empowering researchers and connecting researchers with industry and government
Company	Eisai (Japan)	No	medicines			for profit
Company	GlaxoSmithKline (GSK) (UK)	No	medicines			for profit
Company	Johnson & Johnson (USA)	No	medicines			for profit
Company	Merck KGaA (Germany)	No	medicines			for profit
Company	MSD (trade name of Merck & Co., Inc) (USA)	No	medicines			for profit

Company	Novartis (Switzerland)	No	medicines			for profit
Company	Pfizer (USA)	No	medicines			for profit
Company	Takeda (Japan)	No	medicines			for profit

Chapter 2.

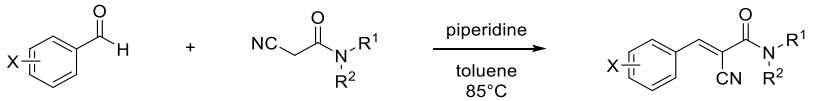
General Information

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. All the solvents and materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (230−400 mesh), and flash column chromatography was performed on silica gel (spherical/40−100 μm). Reactions and chromatography fractions were analyzed using pre-coated silica gel plate. All melting points were measured on a melting point apparatus and are uncorrected. IR spectra were measured on FTIR. Unless otherwise noted, NMR spectra were obtained in $CDCl_3$. ^1H NMR (500 or 400 MHz) spectra were measured and chemical shifts are reported in δ (ppm) relative to TMS (in $CDCl_3$), which was used as an internal reference standard. ^{13}C NMR (126 or 101 MHz) spectra were also recorded and referenced to the residual $CHCl_3$ signal. ^1H NMR multiplicities are reported as follows: br = broad; m = multiplet; s = singlet; d = doublet; t = triplet; q = quartet; sep = septet. Low-resolution and high-resolution mass spectra were obtained using an LCMS-IT-TOF fitted with an ESI. Optical rotations were recorded on a polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values were measured in 10^{-1} deg cm^2g^{-1}. Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) analysis. Unless otherwise noted, all materials and solvents were purchased and used without purification. All non-commercially available substrates were prepared according to the literature procedure as indicated below.

2.2 Design of potential antimalarial hybrid molecules and a new synthetic method to achieve them

I. Experimental protocols and spectra data

General procedure for synthesizing substrate



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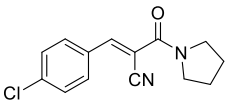
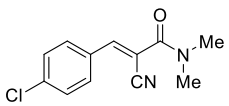
To a solution of 1.0 equivalent of starting materials in toluene (0.1 M), a catalytic amount of piperidine (0.1 equiv) was added at room temperature. After being stirred at 85 ºC for 12 to 48 hours, the reaction mixture was condensed, and the obtained crude was purified by recrystallization from ethanol or ethyl acetate.



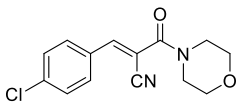
3-(4-Chlorophenyl)-2-(pyrrolidine-1-carbonyl)acrylonitrile (1a)

White solid; mp: 80–82 °C; IR (ATR): 3762, 2211, 1754, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 50 °C): 7.92 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 3.76 (br, 2H), 3.60 (br, 2H), 1.96 (br, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 50 °C): 161.0, 151.4, 151.3, 138.4, 131.4, 130.8, 129.5, 129.3, 116.0, 107.3, 48.5, 47.5, 26.7, 24.0; HRMS (ESI): Calcd. for $C_{14}H_{14}ClN_2O$ ($[M+H]^+$): 261.0789, Found: 261.0790.



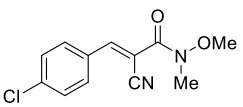
3-(4-Chlorophenyl)-2-cyano-*N, N*-dimethylacrylamide (1b)

White solid; mp: 84–86°C; IR (ATR): 3019, 2361, 1739, 1215, 909, 769, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.83 (d, *J* = 8.5 Hz, 2H), 7.71 (s, 1H), 7.45 (t, *J* = 8.5 Hz, 2H), 3.33 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 163.5, 150.7, 138.4, 131.2, 130.6, 129.4, 115.8, 107.0, 39.1, 36.5; HRMS (ESI): Calcd. for $C_{12}H_{12}ClN_2O$ ($[M+H]^+$): 235.0633, Found: 235.0615.



3-(4-Chlorophenyl)-2-(morpholine-4-carbonyl)acrylonitrile (1c)

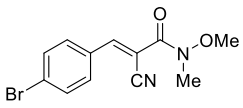
Yellow solid; mp: 87–88 °C;IR (ATR): 2967, 2923, 2858, 2210, 1744, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 50 °C): 7.83 (d, *J* = 8.7 Hz, 2H), 7.71 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 3.75 (t, *J* = 5.0 Hz, 4H), 3.69 (t, *J* = 4.1 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 50 °C): 162.7, 151.2, 151.1, 138.7, 131.3, 130.6, 129.7, 129.5, 115.8, 106.5, 66.5, 66.3; HRMS (ESI): Calcd. for $C_{14}H_{14}ClN_2O_2$ ($[M+H]^+$): 277.0738, Found: 277.0735.



3-(4-Chlorophenyl)-2-cyano-*N*-methoxy-*N*-methylacrylamide (1d)

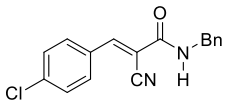
Pale yellow solid; mp: 96–97°C; IR (ATR): 2936, 2360, 1649, 1590, 1491, 1409, 1219, 1091, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 8.06 (s, 1H), 7.92 (d, *J* = 6.5 Hz, 2H), 7.46 (d, *J* = 6.5 Hz, 2H), 3.86 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$): 163.6, 152.9, 138.7, 132.0, 130.5, 129.4, 115.9, 104.5, 61.7, 33.4; HRMS (ESI): Calcd. for $C_{12}H_{12}ClN_2O_2$ ([M+H]$^+$): 251.0582, Found: 251.0571.



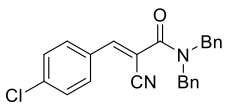
3-(4-Bromophenyl)-2-cyano-*N*-methoxy-*N*-methylacrylamide (1e)

Pale yellow solid; mp: 92–94°C; IR (ATR): 2931, 2359, 1654, 1584, 1486, 1406, 1183, 1073, 1007, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 3.87 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 163.6, 153.0, 132.5, 131.9, 130.9, 127.3, 115.7, 104.8, 61.9, 33.6; HRMS (ESI): Calcd. for $C_{12}H_{12}BrN_2O_2$ ([M+H]$^+$): 295.0077, Found: 295.0072.



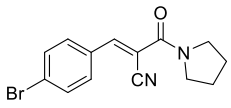
***N*-Benzyl-3-(4-chlorophenyl)-2-cyanoacrylamide (1f)**

Yellow solid; mp: 175–177°C; IR (ATR): 3415, 3004, 2359, 1714, 1420, 1362, 1223, 1092, 905cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 8.33 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.36 (m, 5H), 6.66 (s, 1H), 4.62 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): 159.0, 151.8, 139.1, 137.0, 131.8, 130.2, 129.6, 129.0, 128.0, 127.9, 116.8, 104.2, 44.5; HRMS (ESI): Calcd. for $C_{17}H_{14}ClN_2O$ ([M+H]$^+$): 297.0789, Found: 297.0769.



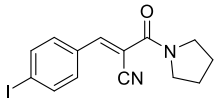
***N*,*N*-Dibenzyl-3-(4-chlorophenyl)-2-cyanoacrylamide (1g)**

Pale yellow solid; mp: 89–91°C; IR (ATR): 3410, 3004, 2360, 1713, 1420, 1362, 1222, 1092, 905 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.76 (d, *J* = 8.5 Hz, 2H), 7.64 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.38–7.30 (m, 6H), 7.24–7.08 (m, 4H), 4.64 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): 164.4, 149.1, 138.3, 135,5, 131.1, 130.6, 130.5, 129.4, 129.3, 129.2, 129.1, 128.9, 128.2, 128.0, 127.6, 127.3, 115.6, 107.0, 51.4, 48.5; HRMS (ESI): Calcd. for $C_{24}H_{20}ClN_2O$ ([M+H]$^+$): 387.1259, Found: 387.1251.



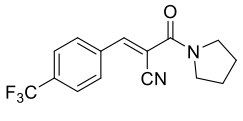
3-(4-Bromophenyl)-2-(pyrrolidine-1-carbonyl)acrylonitrile (1h)

Pale yellow solid; mp: 90–92°C; IR (ATR): 3006, 1714, 1420, 1362, 1222, 1092, 902 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.97 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 3.77 (t, *J* = 7.0 Hz, 2H), 3.62 (t, *J* = 7.0 Hz, 2H), 1.98 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.0, 151.8, 132.4, 131.5, 131.1, 126.9, 116.0, 107.1, 48.6, 47.6, 26.7, 23.9; HRMS (ESI): Calcd. for $C_{14}H_{14}BrN_2O$ ([M+H]$^+$): 305.0284, Found: 305.0270.



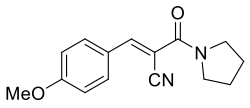
3-(4-Iodophenyl)-2-(pyrrolidine-1-carbonyl)acrylonitrile (1i)

Pale yellow solid; mp: 86–87°C; IR (ATR): 2970, 2878, 2358, 2343, 1636, 1581, 1483, 1415, 1189, 1063, 1006, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.89 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 3.75 (br, 2H), 3.59 (br, 2H), 1.97 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.0, 151.9, 138.4, 131.6, 131.3, 116.0, 107.2, 99.4, 48.6, 47.6, 26.7, 23.9; HRMS (ESI): Calcd. for $C_{14}H_{14}IN_2O$ ([M+H]$^+$): 353.0145, Found: 353.0130.



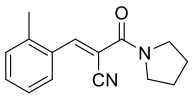
2-(Pyrrolidine-1-carbonyl)-3-{4-(trifluoromethyl)phenyl}acrylonitrile (1j)

Pale yellow solid; mp: 80–81°C; IR (ATR): 3854, 3745, 3736, 3629, 3004, 2360, 2343, 1711, 1419, 1360, 1220, 1092, 913, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 8.02 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.00 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): 160.5, 151.1, 135.4, 133.2 (q, *J* = 32.7 Hz), 130.2, 126.0, 123.4 (q, *J* = 274 Hz), 115.5, 109.3, 48.5, 47.6, 26.6, 24.0; HRMS (ESI): Calcd. for $C_{15}H_{14}F_3N_2O$ ($[M+H]^+$): 295.1053, Found: 295.1036.



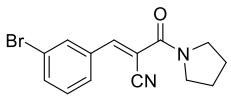
3-(4-Methoxyphenyl)-2-(pyrrolidine-1-carbonyl)acrylonitrile (1k)

Yellow solid; mp: 120–122°C; IR (ATR): 2971, 2881, 2208, 1636, 1603, 1511, 1415, 1263, 1220, 1179, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.95 (s, 1H), 7.93 (dd, *J* = 6.9, 1.7 Hz, 2H), 6.87 (dd, *J* = 6.9, 2.0 Hz, 2H), 3.88 (s, 3H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 1.97 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): 162.9, 162.1, 152.8, 132.7, 125.1, 117.0, 114.5, 102.9, 55.5, 48.6, 47.6, 26.7, 24.1; HRMS (ESI): Calcd. for $C_{15}H_{17}N_2O_2$ ($[M+H]^+$): 257.1285, Found: 257.1272.



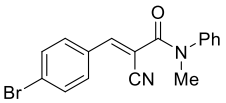
2-(Pyrrolidine-1-carbonyl)-3-(*p*-tolyl)acrylonitrile (1l)

Colorless oil; IR (ATR): 2974, 2360, 1637, 1420, 1220, 914, 772, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 8.26 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.38 (m, 1H), 7.29 (m, 2H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.04 (s, 3H), 1.98 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): 161.3, 151.7, 138.7, 131.6, 131.3, 130.7, 128.0, 126.4, 116.0, 108.2, 48.5, 47.5, 26.6, 24.0, 19.0; HRMS (ESI): Calcd. for $C_{15}H_{17}N_2O$ ($[M+H]^+$): 241.1335, Found: 241.1320.



3-(3-Bromophenyl)-2-(pyrrolidine-1-carbonyl)acrylonitrile (1m)

Pale yellow solid; mp: 83–85°C; IR (ATR): 3004, 2360, 1711, 1647, 1420, 1361, 1221, 1092, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.98 (s, 1H), 7.88 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.76 (t, *J* = 7.0 Hz, 2H), 3.61 (t, *J* = 7.0 Hz, 2H), 1.98 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): 160.6, 151.2, 134.9, 134.1, 132.9, 130.6, 128.3, 123.1, 115.6, 108.2, 48.6, 47.6, 26.6, 24.0; HRMS (ESI): Calcd. for $C_{14}H_{14}BrN_2O$ ($[M+H]^+$): 305.0284, Found: 305.0266.

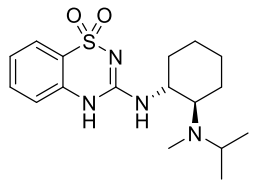


3-(4-Bromophenyl)-2-cyano-*N*-methyl-*N*-phenylacrylamide (1n)

Pale yellow solid; mp: 101–102°C; IR (ATR): 3859, 3682, 2214, 1726, 1651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.91 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.54 (d,

J = 8.6 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 2H), 3.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 162.9, 151.6, 142.6, 132.3, 131.4, 131.0, 129.9, 128.3, 127.1, 126.9, 114.6, 107.9, 39.1; HRMS (ESI): Calcd. for $C_{17}H_{14}BrN_2O$ ($[M+H]^+$): 341.0284, Found: 341.0286.

Catalyst **VII** was prepared according to the literature procedure.[1]

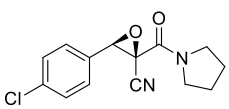


3-[{(1*R*,2*R*)-2-(isopropylmethylamino)cyclohexyl}amino]-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (VII)

Pale yellow amorphous solid; IR (ATR): 2369, 2347, 2253, 912, 744, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.30 (br, 1H), 3.43 (br, 1H), 2.96 (m, 1H), 2.63 (m, 1H), 2.37 (s, 3H), 2.24 (m, 1H), 1.85–1.60 (m, 3H), 1.50–1.16 (m, 6H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H) (One N-H proton peak was not observed); ^{13}C NMR (126 MHz, $CDCl_3$): 153.2, 136.2, 132.3, 132.1, 124.1, 124.0, 117.2, 116.9, 64.7, 41.0, 33.3, 30.8, 26.9, 25.0, 24.5, 19.6; HRMS (ESI): Calcd. for $C_{17}H_{27}N_4O_2S$ ($[M+H]^+$): 351.1849, Found: 351.1827.

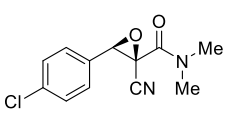
General procedure for the synthesis of epoxides 2

An *n*-decane solution of TBHP (0.1 mL, 5.5 M) was added to a solution of α,β-unsaturated amide **1** (0.1 mmol) and benzothiadiazine catalyst **VI** (3.5 mg, 0.01 mmol, 10 mol%) in MeCN (1.0 mL, 0.1 M). The resulting mixture was stirred at ambient temperature for the indicated time listed in the tables. The reaction mixture was then evaporated and the resulting crude residue purified by column chromatography on silica gel, with *n*-hexane/ethyl acetate as the eluent, to give the analytically pure coumpound **2**. The enantiomeric ratios of all of the compounds were determined by HPLC on a chiral stationary phase.



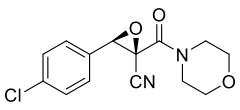
(2*S*,3*R*)-3-(4-Chlorophenyl)-2-(pyrrolidine-1-carbonyl)oxirane-2-carbonitrile (2a)

Colorless oil; IR (ATR): 2976, 2882, 2365, 1669, 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.43 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 1H), 3.75 (m, 2H), 3.57 (m, 2H), 2.05 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): 158.6, 136.2, 129.1, 127.8, 113.7, 62.7, 55.3, 47.2, 46.6, 26.2, 23.7 (One carbon peak is missing due to overlapping); HRMS (ESI): Calcd. for $C_{14}H_{14}ClN_2O_3$ ($[M+H]^+$): 277.0738, Found: 277.0737; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 84% *ee*, (minor) 10.6 min, (major) 14.1 min; $[\alpha]^{25}_D$ +76.6 (*c* 2.48, $CHCl_3$, 84% *ee*).



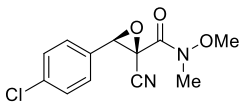
(2*S*,3*R*)-3-(4-Chlorophenyl)-2-cyano-*N*,*N*-dimethyloxirane-2-carboxamide (2b)

White solid; mp: 90–92°C; IR (ATR): 3020, 2364, 1711, 1419, 1362, 1219, 1091, 771, 750, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.43 (s, 1H), 3.25 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 160.3, 136.3, 129.1, 129.0, 127.8, 113.6, 63.1, 55.0, 36.9, 36.1; HRMS (ESI): Calcd. for $C_{12}H_{12}ClN_2O_2$ ($[M+H]^+$): 251.0582, Found: 251.0585; HPLC [Chiralpak IC, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 74% *ee*, (minor) 14.4 min, (major) 16.8 min; $[\alpha]^{25}_D$ +41.4 (*c* 2.06, $CHCl_3$, 74% *ee*).



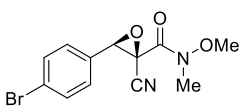
(2*S*,3*R*)-3-(4-Chlorophenyl)-2-(morpholine-4-carbonyl)oxirane-2-carbonitrile (2c)

Yellow oil; IR (ATR): 2974, 2925, 2861, 2249, 1669, 1439 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.44 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 4.46 (s, 1H), 3.93–3.45 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$): 159.1, 136.4, 129.2, 128.7, 127.8, 113.6, 66.3, 63.1, 53.8, 46.2, 43.2; HRMS (ESI): Calcd. for $C_{14}H_{14}ClN_2O_3$ ($[M+H]^+$): 293.0687, Found: 293.0690; HPLC [Chiralpak IC, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 60% *ee*, (minor) 15.7 min, (major) 17.0 min; $[\alpha]^{25}_D$ +36.0 (*c* 2.25, $CHCl_3$, 60% *ee*).



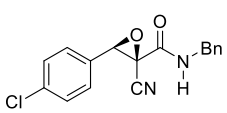
(2*S*,3*R*)-3-(4-Chlorophenyl)-2-cyano-*N*-methoxy-*N*-methyloxirane-2-carboxamide (2d)

White solid; mp: 105–107°C; IR (ATR): 3006, 2364, 1714, 1420, 1362, 1221, 1092, 914, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.44 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 4.38 (s, 1H), 3.85 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.6, 136.2, 129.1, 128.9, 128.0, 113.6, 62.5, 61.8, 54.0, 33.0; HRMS (ESI): Calcd. for $C_{12}H_{12}ClN_2O_3$ ($[M+H]^+$): 267.0531, Found: 267.0524; HPLC [Chiralpak IA, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 265 nm]; retention time: 46% *ee*, (minor) 8.9 min, (major) 11.4 min; $[\alpha]^{25}_D$ +9.4 (*c* 1.68, $CHCl_3$, 46% *ee*).



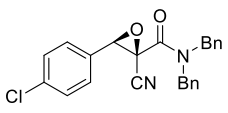
(2*S*,3*R*)-3-(4-Bromophenyl)-2-cyano-*N*-methoxy-*N*-methyloxirane-2-carboxamide (2e)

White solid; mp: 86–88°C; IR (ATR): 3629, 2360, 1711, 1419, 1362, 1221, 1071, 986, 913, 823, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.61 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.37 (s, 1H), 3.85 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.5, 132.0, 129.5, 128.2, 124.5, 113.6, 62.5, 61.8, 53.9, 33.0; HRMS (ESI): Calcd. for $C_{12}H_{12}BrN_2O_3$ ($[M+H]^+$): 311.0026, Found: 311.0012; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 42% *ee*, (minor) 9.4 min, (major) 12.4 min; $[\alpha]^{25}_D$ +35.8 (*c* 0.98, $CHCl_3$, 42% *ee*).



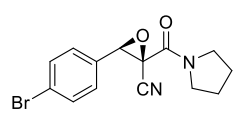
(2*S*,3*R*)-*N*-Benzyl-3-(4-chlorophenyl)-2-cyanooxirane-2-carboxamide (2f)

White solid; mp: 154–156°C; IR (ATR): 3006, 2359, 1711, 1420, 1361, 1220, 1092, 904, 772, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.42 (d, *J* = 8.5 Hz, 2H), 7.38–7.33 (m, 5H), 7.29 (d, *J* = 6.5 Hz, 2H), 6.61 (br, 1H), 4.51 (m, 2H), 4.32 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.0, 136.6, 136.4, 129.2, 129.0, 128.2, 128.2, 128.0, 128.0, 113.0, 63.9, 55.3, 44.0; HRMS (ESI): Calcd. for $C_{17}H_{14}ClN_2O_2$ ($[M+H]^+$): 313.0738, Found: 313.0725; HPLC [Chiralpak IA, hexane/EtOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 53% ee, (major) 14.8 min, (minor) 16.7 min; $[\alpha]^{25}_D$ –74.0 (*c* 2.88, $CHCl_3$, 53% ee).



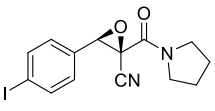
(2*S*,3*R*)-*N*,*N*-Dibenzyl-3-(4-chlorophenyl)-2-cyanooxirane-2-carboxamide (2g)

White solid; mp: 85–87°C; IR (ATR): 3006, 2362, 1361, 1419, 1361, 1220, 1092, 903, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.44–7.30 (m, 8H), 7.22–7.18 (m, 6H), 4.75–4.53 (m, 4H), 4.45 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.1, 136.3, 134.5, 132.9, 129.2, 129.1, 129.0, 128.6, 128.4, 128.3, 128.1, 127.7, 127.3, 113.7, 63.4, 55.3, 49.8, 48.3; HRMS (ESI): Calcd. for $C_{24}H_{20}ClN_2O_2$ ($[M+H]^+$): 403.1203, Found: 403.1208; HPLC [Chiralpak IC, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 33% *ee*, (minor) 9.9 min, (major) 16.0 min; $[\alpha]^{25}_D$ +15.0 (*c* 1.83, $CHCl_3$, 33% *ee*).



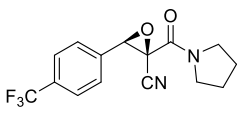
(2*S*,3*R*)-3-(4-Bromophenyl)-2-(pyrrolidine-1-carbonyl)oxirane-2-carbonitrile (2h)

Yellow solid; mp: 75–77°C; IR (ATR): 3003, 2360, 1712, 1419, 1361, 1220, 1092, 913, 772, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.59 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.43 (s, 1H), 3.71 (m, 2H), 3.57 (m, 2H), 2.05 (m, 2H), 1.92 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): 158.6, 132.0, 129.6, 128.1, 124.4, 113.7, 62.8, 55.2, 47.2, 46.6, 26.2, 23.7; HRMS (ESI): Calcd. for $C_{14}H_{14}BrN_2O_2$ ($[M+H]^+$): 321.0233, Found: 321.0227; HPLC [Chiralpak AD, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 84% *ee*, (minor) 11.0 min, (major) 14.8 min; $[\alpha]^{25}_D$ +52.2 (*c* 2.82, $CDCl_3$, 84% *ee*).



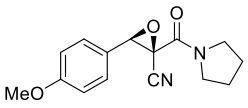
(2*S*,3*R*)-3-(4-Iodophenyl)-2-(pyrrolidine-1-carbonyl)oxirane-2-carbonitrile (2i)

White solid; mp: 104–106°C; IR (ATR): 3005, 2361, 1713, 1419, 1362, 1221, 1092, 905, 772, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.79 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.42 (s, 1H), 3.75 (m, 2H), 3.70 (m, 2H), 2.05 (m, 2H), 1.94 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): 158.6, 137.9, 130.3, 128.2, 113.7, 96.3, 62.9, 55.1, 47.2, 46.6, 26.2, 23.7; HRMS (ESI): Calcd. for $C_{14}H_{14}IN_2O_2$ ($[M+H]^+$): 369.0095, Found: 369.0089; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 265 nm]; retention time: 84% *ee*, (minor) 11.5 min, (major) 15.5 min; $[\alpha]^{25}_D$ +48.5 (*c* 2.96, $CHCl_3$, 84% *ee*).



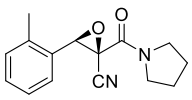
(2*S*,3*R*)-2-(Pyrrolidine-1-carbonyl)-3-{4-(trifluoromethyl)phenyl}oxirane-2-carbonitrile (2j)

White solid; mp: 89–91°C; IR (ATR): 3005, 2364, 1712, 1419, 1361, 1220, 1092, 905, 772, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.72 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 4.54 (s, 1H), 3.76 (m, 2H), 3.74 (m, 2H), 2.06 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): 158.4, 134.5, 132.1 (q, *J* = 32.7 Hz), 127.0, 125.8, 123.7 (q, *J* = 274 Hz), 113.5, 62.5, 55.3, 47.3, 46.7, 26.2, 2.7; HRMS (ESI): Calcd. for $C_{15}H_{14}F_3N_2O_2$ ($[M+H]^+$): 311.1002, Found: 311.0986; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 238 nm]; retention time: 80% *ee*, (minor) 9.9 min, (major) 13.8 min; $[\alpha]^{25}_D$ +45.3 (*c* 2.23, $CHCl_3$, 80% *ee*).



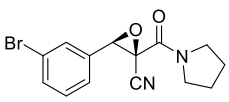
(2*S*,3*R*)-3-(4-Methoxyphenyl)-2-(pyrrolidine-1-carbonyl)oxirane-2-carbonitrile (2k)

Yellow oil; IR (ATR): 3004, 2364, 1712, 1419, 1361, 1220, 1092, 904, 772, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.38 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 4.39 (s, 1H), 3.83 (s, 3H), 3.75 (m, 2H), 3.70 (m, 2H), 2.03 (m, 2H), 1.93 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): 161.0, 159.1, 145.3, 127.9, 122.3, 114.2, 63.4, 55.4, 55.3, 47.2, 46.6, 26.2, 23.7; HRMS (ESI): Calcd. for $C_{15}H_{17}N_2O_3$ ($[M+H]^+$): 273.1234, Found: 273.1211; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 82% *ee*, (minor) 13.2 min, (major) 15.1 min; $[\alpha]^{25}_D$ +86.2 (*c* 1.0, $CHCl_3$, 82% *ee*).



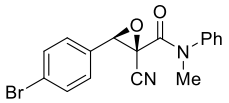
(2*S*,3*R*)-2-(Pyrrolidine-1-carbonyl)-3-(*p*-tolyl)oxirane-2-carbonitrile (2l)

Colorless oil; IR (ATR): 2360, 1739, 1654, 1374, 1219, 911, 772, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.32 (m, 2H), 7.24 (m, 2H), 4.56 (s, 1H), 3.80 (m, 2H), 3.57 (m, 2H), 2.47 (s, 3H), 2.05 (m, 2H), 1.96 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): 159.1, 136.6, 130.3, 129.6, 129.3, 126.2, 125.1, 114.0, 62.2, 55.1, 47.1, 46.7, 26.2, 23.7, 18.8; HRMS (ESI): Calcd. for $C_{15}H_{17}N_2O_2$ ($[M+H]^+$): 257.1285, Found: 257.1267; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 80% *ee*, (major) 8.2 min, (minor) 9.0 min; $[\alpha]^{25}_D$ –0.3 (*c* 1.91, $CHCl_3$, 80% *ee*).



(2*S*,3*R*)-3-(3-Bromophenyl)-2-(pyrrolidine-1-carbonyl)oxirane-2-carbonitrile (2m)

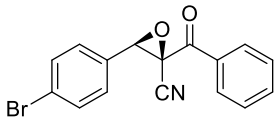
White solid; mp: 107–109°C; IR (ATR): 3019, 2364, 2342, 1739, 1215, 771, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.60 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.44 (s, 1H), 3.76 (m, 2H), 3.57 (m, 2H), 2.06 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): 158.5, 133.2, 132.8, 130.3, 129.6, 124.9, 122.8, 113.6, 62.4, 55.2, 47.3, 46.7, 26.2, 23.7; HRMS (ESI): Calcd. for $C_{14}H_{14}BrN_2O_2$ ($[M+H]^+$): 321.0233, Found: 321.0211; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 254 nm]; retention time: 82% *ee*, (minor) 10.1 min, (major) 12.2 min; $[\alpha]^{25}_D$ +51.7 (*c* 1.0, $CHCl_3$, 82% *ee*).



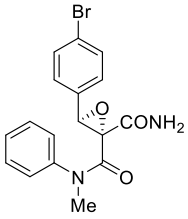
(2*S*,3*R*)-3-(4-Bromophenyl)-2-cyano-*N*-methyl-*N*-phenyloxirane-2-carboxamide (2n)

White solid; mp: 183–185°C; IR (ATR): 3860, 3743, 2979, 2366, 1677, 1423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.57–7.44 (m, 4H), 7.41 (m, 1H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 4.35 (s, 1H), 3.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 160.4, 140.6, 131.8, 130.2, 129.2, 129.2, 127.9, 127.2, 124.3, 113.2, 63.9, 54.8, 38.7; HRMS (ESI): Calcd. for $C_{17}H_{14}BrN_2O_2$ ($[M+H]^+$): 357.0233, Found: 357.0239; HPLC [Chiralpak IB, hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 265 nm]; retention time: 52% *ee*, (minor) 10.7 min, (major) 14.2 min; $[\alpha]^{25}_D$ –2.6 (*c* 1.03, $CHCl_3$, 52% *ee*).

Derivatization of epoxide 4

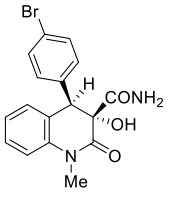


(2*S*,3*R*)-2-Benzoyl-3-(4-bromophenyl)oxirane-2-carbonitrile (5) To a solution of Weinreb amide **4g** (17.1 mg, 0.05 mmol) in THF (0.5 mL) was added PhMgCl (0.15 mmol, 0.075 mL, 2.0 M solution in THF) dropwise at –78 ºC. After being stirred at the same temperature for 3 hours, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and warmed up to room temperature. The reaction mixture was extracted with ethyl acetate three times, and concentrated under reduced pressure. The obtained crude residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 5/1 to 3/1) to furnish ketone **5** (10.1 mg, 62%). White solid; ^1H NMR (500 MHz, $CDCl_3$): 8.04 (m, 2H), 7.69 (m, 1H), 7.64 (m, 2H), 7.55 (m, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 4.38 (s, 1H); $[\alpha]^{25}_D$ +80.5 (*c* 1.0, $CHCl_3$, 42% *ee*).



1. (2*S*,3*R*)-2-Benzoyl-3-(4-bromophenyl)oxirane-2-carbonitrile (4n)

To a solution of epoxide **2n** (67.1 mg, 0.19 mmol) in MeCN (4.0 mL) was added solid sodium carbonate (201 mg, 1.9 mmol) and 37% aqueous hydrogen peroxide solution (1.0 mL, ca. 10 mmol). After being stirred at room temperature for 12 h, the reaction mixture was extracted with ethyl acetate three times, and concentrated under reduced pressure. The obtained crude residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 1/1 to EtOAc) to furnish the title compound (41.9 mg, 59%). White solid; mp: 171–173°C; IR (ATR): 2984, 2369, 1740, 1448, 1374, 1241, 1099, 1048, 939, 914, 847, 773, 635, 608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.45–7.36 (m, 7H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.52 (br, 1H), 5.16 (br, 1H), 4.46 (s, 1H), 3.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 166.2, 164.7, 141.5, 131.4, 131.0, 129.6, 128.3, 128.0, 128.0, 122.7, 64.7, 63.9, 38.2; HRMS (ESI): Calcd. for $C_{17}H_{16}BrN_2O_3$ ($[M+H]^+$): 375.0339, Found: 375.0319.



2. (2*S*,3*R*)-2-Benzoyl-3-(4-bromophenyl)oxirane-2-carbonitrile (5n)

To a solution of **4n** (41.9 mg, 0.11 mmol) in MeCN (1.1 mL) was added sulfuric acid

(61.1 μL, 1.1 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was poured into crushed ice. The precipitated solid was collected and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 5/1 to 1/1, then EtOAc) to furnish the title compound (28.0 mg, 67%). White solid; mp: 213–215°C; IR (ATR): 2985, 1739, 1448, 1373, 1238, 1098, 1046, 938, 915, 848, 773, 634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 7.51 (d, *J* = 7.5 Hz, 2H), 7.33 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.00 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.85 (d, *J* = 6.5 Hz, 1H), 6.49 (br, 1H), 5.21 (br, 1H), 4.91 (s, 1H), 4.42 (s, 1H), 3.55 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 170.8, 168.4, 140.1, 134.7, 132.5, 131.6, 128.2, 127.2, 126.0, 123.6, 122.2, 114.8, 52.4, 31.2 (One carbon peak is missing due to overlapping); HRMS (ESI): Calcd. for $C_{17}H_{16}BrN_2O_3$ ($[M+H]^+$): 375.0339, Found: 375.0334; HPLC [Chiralpak IB, hexane/*i*-PrOH = 85/15, 1 mL/min, λ = 254 nm]; retention time: 96% *ee*, (minor) 14.1 min, (major) 15.1 min; $[\alpha]^{25}_D$ +136.5 (*c* 0.54, $CHCl_3$, 96% *ee*).

II. Cartesian coordinates and total energies for the proposed transition state structures

All of the theoretical optimizations were performed using Gaussian 09 at the B3LYP/6-31G* level. Once the stationary points were obtained at the B3LYP/6-31G* level, the harmonic vibrational frequencies were calculated at the same level to estimate the Gibbs free energy. All of the Gibbs free energy values reported in this paper were calculated for a temperature of 298.15 K.

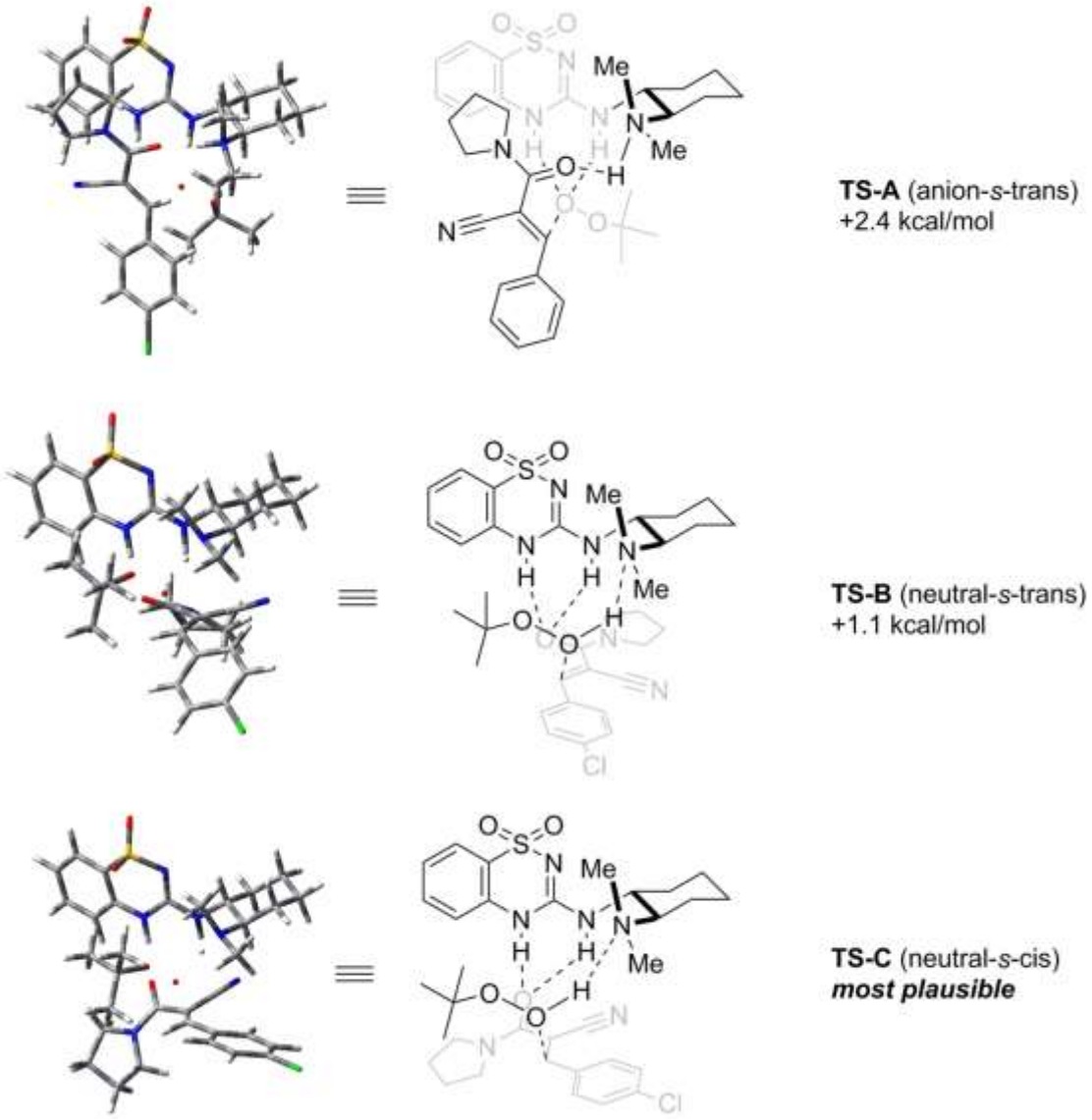


Figure S1. A preliminary calculation for the transition state.

TS-A (anion-*s*-trans)

Zero-point vibrational energy 2001319.1 (Joules/Mol)
478.32673 (Kcal/Mol)

Zero-point correction= 0.762262 (Hartree/Particle)

Thermal correction to Energy= 0.807972

Thermal correction to Enthalpy= 0.808917

Thermal correction to Gibbs Free Energy= 0.681975

Sum of electronic and zero-point Energies= -2846.710298

Sum of electronic and thermal Energies= -2846.664587

Sum of electronic and thermal Enthalpies= -2846.663643

Sum of electronic and thermal Free Energies= -2846.790585

E(RB3LYP) = -2847.47255971

Imaginary frequency = 96i

0 1

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C	0.94067800	-1.72765900	0.97432600
C	-0.17240300	-1.33327300	1.86993100
C	-1.24869500	-3.64204500	1.89620500
H	-1.57636000	-3.83905200	0.87009500
H	-0.26762000	-4.10488800	2.03056700
O	-0.18486500	-0.18975500	2.40114200
O	1.47872300	0.58035900	-0.39362200
H	-5.99251100	-1.87159000	-2.25389100
C	-4.92899200	-2.07309200	-2.33413700
C	-2.16508500	-2.52164200	-2.50969200
C	-4.03528900	-1.26109400	-1.63496900
C	-4.44343600	-3.11904500	-3.11283100
C	-3.06342000	-3.34525800	-3.18103700
C	-2.65056000	-1.45892300	-1.73394100
H	-5.13161900	-3.75976300	-3.65578100
H	-2.67738200	-4.16917200	-3.77456500
H	-1.09696800	-2.70881000	-2.56195500
S	-4.61343900	-0.01952700	-0.50073000
N	-1.77156800	-0.57950800	-1.08999700
H	-0.77689700	-0.76076800	-1.17635800
N	-3.39081100	1.08915300	-0.52494900
C	-2.14880200	0.67169200	-0.64700500
N	-1.12870000	1.51564200	-0.36468900
H	-0.14063500	1.18883300	-0.48027900
O	-4.68188300	-0.63115200	0.84156700
O	-5.82578600	0.60095300	-1.03843300
C	-1.38243700	2.87293700	0.09419800
C	-0.33171700	4.82933300	1.34662300

C	-1.83872900	5.28667100	-0.62817500
C	-0.60096600	5.75287200	0.14672100
C	-1.67686700	3.83217300	-1.08228500
C	-0.16617000	3.37231800	0.89305400
H	-1.17705200	4.91147500	2.04146500
H	-2.72873800	5.38124300	0.01031600
H	0.27352500	5.75452700	-0.51892500
H	-0.85429500	3.75887200	-1.80518300
H	0.72091100	3.27408100	0.25748400
H	-2.27594200	2.84993100	0.72967900
H	0.56283900	5.16585200	1.88415700
H	-2.01007100	5.93177500	-1.49771600
H	-0.72586600	6.78104300	0.50576800
H	-2.58086200	3.47087700	-1.58065800
N	0.13080600	2.43735500	2.06883500
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H	-0.64526400	1.67922300	3.86073600
H	-1.84279400	2.50570500	2.85039800
H	-0.64206700	3.47392000	3.76131200
C	1.54890200	2.55726900	2.52917100
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C	1.61398400	2.12972000	-2.89240300
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H	0.89707100	1.30632900	-2.83383500
H	1.95461200	2.21520900	-3.93038300
C	3.56021100	0.61854000	-2.38412800
H	2.91207100	-0.25728700	-2.31911500
H	4.43280700	0.45272500	-1.74689100
H	3.90332900	0.72722000	-3.41951000
C	3.72367200	3.08801300	-1.88080000
H	3.17911300	3.97765900	-1.54341300

H	4.14628300	3.30159100	-2.86849200
H	4.54882900	2.90250300	-1.18524000
C	3.43977700	-1.20785700	0.53942500
C	6.13212800	-1.66132500	-0.12070200
C	4.46417300	-0.36950700	1.01912700
C	3.81073700	-2.28443700	-0.28854800
C	5.14407300	-2.51174700	-0.61753900
C	5.80157100	-0.58418900	0.70004200
H	4.20446900	0.46862600	1.65897200
H	3.06051200	-2.95745500	-0.68320400
H	5.41642200	-3.34680300	-1.25417100
H	6.57795700	0.06902900	1.08395700
Cl	7.81629300	-1.95331000	-0.53015400
C	-2.30960800	-1.72600700	2.98880400
H	-2.77988400	-0.84870500	2.54072000
H	-1.93808600	-1.45319500	3.98529500
C	-3.24827900	-2.93609000	3.03130700
H	-3.93077800	-2.89366800	2.17618900
H	-3.85194400	-2.95621900	3.94348500
C	-2.29189500	-4.13196100	2.91137500
H	-2.78165300	-5.05198700	2.57882400
H	-1.81104300	-4.33548500	3.87638500
H	0.03745800	1.43754700	1.75334100

TS B (neutral-*s*-trans)

Zero-point vibrational energy 1996853.4 (Joules/Mol)
477.25941 (Kcal/Mol)

Zero-point correction= 0.760561 (Hartree/Particle)
Thermal correction to Energy= 0.806547
Thermal correction to Enthalpy= 0.807491
Thermal correction to Gibbs Free Energy= 0.678935
Sum of electronic and zero-point Energies= -2846.710700
Sum of electronic and thermal Energies= -2846.664714
Sum of electronic and thermal Enthalpies= -2846.663770
Sum of electronic and thermal Free Energies= -2846.792326

E(RB3LYP) = -2847.47126103

Imaginary frequency = 141i

0 1

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C	-0.40025300	2.63682200	0.14695700
C	-1.28940400	4.54601200	-1.28133200
H	-1.56984900	3.98979400	-2.17659100
H	-2.19445300	4.68803800	-0.67546100
O	0.42337500	2.30096500	1.02794300
O	-1.23957400	-0.95948500	0.91199700
H	-0.81150100	-1.78618100	-0.31141500
H	6.83809500	-0.67944300	1.19381100
C	6.01213100	-0.02169400	1.44560800
C	3.84318400	1.65827000	2.03269800
C	4.76531800	-0.24991700	0.86283600
C	6.17298000	1.03689100	2.33503600
C	5.08156900	1.86362300	2.63163700
C	3.67769700	0.59346700	1.13301200
H	7.13836800	1.21750300	2.79794000
H	5.20239300	2.68947200	3.32750200
H	3.00197100	2.31593300	2.23262000
S	4.46183900	-1.67329000	-0.16253000
N	2.45644200	0.40085100	0.49278000
H	1.65286700	0.95731600	0.80966400
N	3.23563100	-1.15594900	-1.13974700
C	2.31188900	-0.37166900	-0.62233100
N	1.10922400	-0.26535900	-1.25815900
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C	0.80231800	-0.98107200	-2.48657400
C	-0.82751500	-2.48285600	-3.70403300
C	0.57778600	-0.82474100	-5.01743600
C	-0.76459600	-1.56025200	-4.93504100
C	0.85903000	-0.05538700	-3.72060300
C	-0.57288600	-1.68058300	-2.41754600
H	-0.07666500	-3.27849200	-3.80553000
H	1.38518200	-1.54876500	-5.19814100

H	-1.57983400	-0.82690200	-4.87390400
H	0.12503100	0.75164600	-3.59906800
H	-1.35098400	-0.91414300	-2.32507800
H	1.58804100	-1.73314700	-2.59566100
H	-1.80932500	-2.96599700	-3.66827700
H	0.57918700	-0.13454700	-5.86911800
H	-0.93751400	-2.15559500	-5.83926900
H	1.85363700	0.40248800	-3.74685200
N	-0.72227600	-2.50575600	-1.14300100
C	0.40308000	-3.44887900	-0.86322300
H	0.16536400	-3.99127000	0.05186500
H	1.33458900	-2.90575400	-0.71602600
H	0.50415800	-4.15661200	-1.68970400
C	-2.02911400	-3.22390400	-1.07649700
H	-2.03466100	-4.07855400	-1.75461700
H	-2.83251200	-2.53160700	-1.33275100
N	-0.26159500	3.83287600	-0.49137600
H	-2.17073900	-3.56076700	-0.04907000
C	-2.03700200	1.68212600	-1.51247000
N	-2.38385400	1.57005400	-2.62629700
O	0.05635800	-1.02830300	1.56456300
C	-0.03907300	-1.58619000	2.89902600
C	-0.84644300	-0.66283400	3.81813200
H	-1.89725100	-0.64541900	3.51801100
H	-0.44359500	0.35509300	3.77904400
H	-0.79495500	-1.01360700	4.85536700
C	1.42887500	-1.64727500	3.34085900
H	1.85411600	-0.64153400	3.41672200
H	2.03242000	-2.22079100	2.63061800
H	1.50069100	-2.12337700	4.32510500
C	-0.65995600	-2.98777400	2.85966600
H	-1.65735000	-2.94510200	2.41296000
H	-0.75292100	-3.39670800	3.87188800
H	-0.03126100	-3.67365000	2.28071600
C	-3.42929400	0.40502500	0.91188900
C	-6.06650900	-0.51979600	1.20874700
C	-4.07871400	0.43401900	2.15931500
C	-4.14901900	-0.09860600	-0.18638200

C	-5.45555800	-0.56216900	-0.04341100
C	-5.38649900	-0.01675200	2.31644600
H	-3.55373400	0.83169700	3.02258500
H	-3.70242900	-0.11490000	-1.17269300
H	-6.00017100	-0.94403500	-0.90060400
H	-5.87291200	0.02143200	3.28530800
Cl	-7.71549700	-1.10064200	1.39062600
C	0.85401800	4.72657600	-0.11759100
H	1.74345400	4.48359100	-0.71480000
H	1.10777400	4.57816800	0.93301000
C	0.32523600	6.12968900	-0.43621200
H	1.12911600	6.83639800	-0.66216700
H	-0.23560500	6.52157100	0.42109300
C	-0.62014900	5.88644400	-1.62110500
H	-0.04411000	5.78897800	-2.54914500
H	-1.35383900	6.68468200	-1.76693300

TS-C (neutral-*s*-cis)

Zero-point vibrational energy 2000471.3 (Joules/Mol)
478.12411 (Kcal/Mol)

Zero-point correction= 0.761939 (Hartree/Particle)
Thermal correction to Energy= 0.807385
Thermal correction to Enthalpy= 0.808329
Thermal correction to Gibbs Free Energy= 0.682411
Sum of electronic and zero-point Energies= -2846.714835
Sum of electronic and thermal Energies= -2846.669390
Sum of electronic and thermal Enthalpies= -2846.668446
Sum of electronic and thermal Free Energies= -2846.794364

E(RB3LYP) = -2847.47677443

Imaginary frequency = 87i

0 1

C	-2.05485900	1.58819200	-0.13805100
H	-1.85599500	2.39495600	0.55325600
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C	-0.05313200	2.44773100	-1.41182700
C	-1.34284600	4.56892400	-0.89363900
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H	-1.66428200	4.61290100	0.15649400
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O	-1.17298400	0.33686600	1.24996500
H	-1.03534600	-1.21013600	0.80081900
H	6.78909700	-0.86762100	0.87005800
C	6.14419900	-0.18468100	0.32605600
C	4.42927800	1.52489300	-1.09134600
C	4.79450700	-0.50562400	0.17505500
C	6.63573700	0.99734700	-0.21956100
C	5.76944300	1.85119700	-0.91514300
C	3.93120700	0.32884800	-0.55047700
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H	-0.23829100	-5.22028800	-3.64108700
H	-2.05626100	-5.91423900	-2.02592300

H	1.39074000	-3.44577100	-2.87126000
N	-1.20760800	-2.28653800	0.85133900
C	-0.22478600	-2.82339300	1.84452700
H	-0.41027900	-2.32373600	2.79518000
H	0.79384400	-2.60606100	1.52612900
H	-0.36748700	-3.90007800	1.95983400
C	-2.59208900	-2.35529200	1.41237600
H	-2.80732600	-3.36286700	1.77070900
H	-3.30804000	-2.06584000	0.64157300
N	-0.12115000	3.75743000	-1.03680400
H	-2.64503200	-1.63852400	2.23161700
C	-1.33541400	0.56054000	-2.24730300
N	-1.38249700	-0.31291000	-3.02599400
O	0.21383300	0.73670300	1.30676600
C	0.52552300	1.37888400	2.57041500
C	2.00141400	1.75937800	2.40717100
H	2.13661000	2.41017500	1.53642000
H	2.62122400	0.86779900	2.28388700
H	2.34762200	2.29720300	3.29697700
C	0.34990200	0.38649500	3.72617500
H	1.01613000	-0.47112400	3.58825000
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C	-4.01269800	1.07925200	1.29085900
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C	-5.42617200	-0.08597100	-0.80555000
C	-5.29106200	0.58171300	1.52179000
H	-3.46013000	1.52422000	2.11167300
H	-3.73109700	0.36692100	-2.02205800
H	-5.98660000	-0.52786400	-1.62268100
H	-5.74453200	0.65006900	2.50508900
Cl	-7.60618300	-0.64002900	0.74297700

C	1.07762800	4.60523300	-1.18966400
H	1.47434400	4.49377500	-2.20563100
H	1.86315500	4.29067900	-0.49544200
C	0.56185800	6.02684400	-0.92337000
H	1.14456300	6.78292300	-1.45757100
H	0.61635400	6.25846800	0.14735600
C	-0.90633000	5.95973300	-1.37416900
H	-0.97059700	6.01488200	-2.46756500
H	-1.52732200	6.75854300	-0.95771900

V. References

[1] T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem*. *Eur*. *J*. **2011**, *17*, 10470.

[2] C. De Fusco, C. Tedesco, A. Lattanzi *J*. *Org*. *Chem*. **2011**, *76*, 676

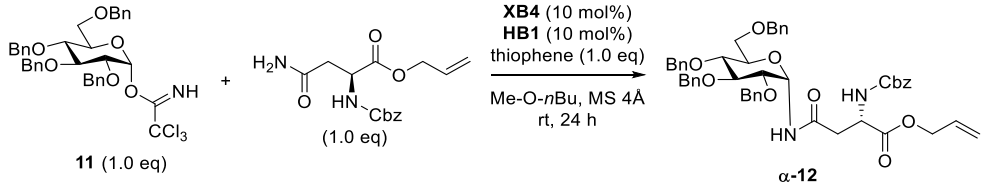
2.3 Establishment of α selective *N*-glycosylation to improve the chemical and pharmacological properties of a cutting-edge antibiotics – antimicrobial peptides (AMPs)

I. General information

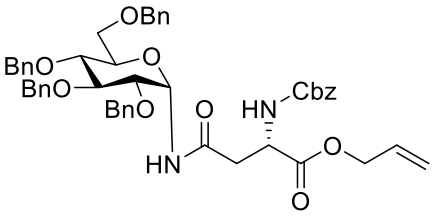
All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. All the solvents and materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (230−400 mesh), and flash column chromatography was performed on silica gel (spherical/40−100 μm). Reactions and chromatography fractions were analyzed using pre-coated silica gel plate. All melting points were measured on a melting point apparatus and are uncorrected. IR spectra were measured on FTIR. Unless otherwise noted, NMR spectra were obtained in $CDCl_3$. ^1H NMR (500 or 400 MHz) spectra were measured and chemical shifts are reported in δ (ppm) relative to TMS (in $CDCl_3$), which was used as an internal reference standard. ^{13}C NMR (126 or 101 MHz) spectra were also recorded and referenced to the residual $CHCl_3$ signal. ^1H NMR multiplicities are reported as follows: br = broad; m = multiplet; s = singlet; d = doublet; t = triplet; q = quartet; sep = septet. Low-resolution and high-resolution mass spectra were obtained using an LCMS-IT-TOF fitted with an ESI. Unless otherwise noted, all materials and solvents were purchased and used without purification. All non-commercially available substrates were prepared according to the literature procedure as indicated below.

II. Experimental protocols and spectra data

1. General procedure for the synthesis of glycosyl amide **12**



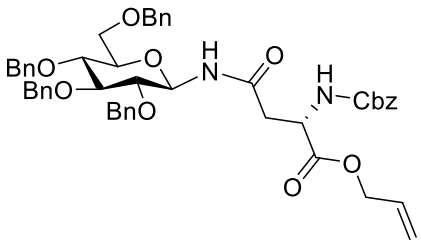
To a solution of thiophene (4.2 mg, 0.05 mmol, 1.0 eq) in methyl butyl ether (1 ml), glycosyl donor **11** (41.1 mg, 0.06 mmol, 1.2 eq), glycosyl acceptor (15.3 mg, 0.05 mmol, 1.0 eq), **XB4** catalyst (3.3 mg, 0.005 mmol, 0.1 eq), **HB1** catalyst (2.5 mg, 0.005 mmol, 0.1 eq), MS (100.0 mg) – were added in turn. The reaction was stirred for 24 h before directly subjected to column chromatography. The desired product was obtained α/β mixture (26.5mg, α/β = 82:18, 64%). Further purification was performed with PLC to obtain pure α-isomert and β-isomer for analytical data.



Allyl *N*2-((benzyloxy)carbonyl)-*N*4-((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)-*L*-

asparaginate (α-12)

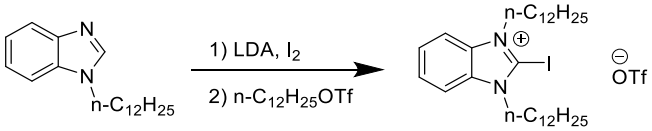
White solid; mp 110–112 °C (EtOAc/*n*-hexane); IR (ATR): 3320, 2952, 1726, 1688, 1498 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.31–7.26 (m, 25H), 7.12 (d, *J* = 3.5 Hz, 2H), 6.31 (d, *J* = 6.5 Hz, 1H), 6.00 (d, *J* = 8.5 Hz, 1H), 5.85 (m, 1H), 5.69, (dd, J_1 = 6.0, J_2 = 5.5 Hz, 1H), 5.31 (d, *J* = 17.0 Hz, 1H), 5.19 (d, *J* = 10.5 Hz, 1H), 5.09 (m, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 2H), 4.61 (d, *J* = 6.0 Hz, 3H), 4.57 (d, *J* = 9.0 Hz, 2H), 4.49 (d, *J* = 10.5 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.79 (m, 1H), 3.71 (m, 2H), 3.63 (m, 2H), 3.58 (m, 1H), 2.99 (d, *J* = 12.0 Hz, 1H), 2.77 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): 170.5, 156.2, 138.4, 138.0, 137.9, 137.1, 136.1, 131.5, 128.6, 128.5, 128.4 (3C), 128.2, 128.1 (2C), 128.0, 127.9 (2C), 127.8 (2C), 127.7 (2C), 118.6, 81.9, 77.5, 76.8, 75.5, 75.0 (2C), 74.9, 73.5, 72.7, 71.2, 68.1, 67.1, 66.4, 50.7, 38.0; HRMS (ESI): Calcd. for $C_{49}H_{53}N_2O_{10}$ ($[M+H]^+$): 829.3695, Found: 829.3650; $[\alpha]^{25}_D$ +44.3 (*c* 0.54, $CHCl_3$).



Allyl *N*2-((benzyloxy)carbonyl)-*N*4-((2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)-*L*-asparaginate (β-12)

White solid; mp 168–171 °C (EtOAc/*n*-hexane); IR (ATR): 3734, 3648, 2354, 1698, 1558, 1540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.35–7.18 (m, 25H), 7.03 (d, *J* = 4.0Hz, 2H), 5.88 (d, *J* = 9.5 Hz, 1H), 5.80 (m, 1H), 5.25 (m, 2H), 5.15, (d, *J* = 10.0 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 5.00 (d, *J* = 7.5 Hz, 1H), 4.89 (dd, J_1 = 8.5 Hz, J_2 = 9.0 Hz, 1H), 4.83 (m, 2H), 4.72 (d, *J* = 4.5 Hz, 1H), 4.70 (d, *J* = 3.0 Hz, 1H), 4.55 (m, 2H), 4.49 (m, 2H), 4.40 (d, *J* = 10.0 Hz, 1H), 4.34 (m, 1H), 3.62 (m, 3H), 3.37 (d, *J* = 5.0 Hz, 1H), 3.22 (m, 1H), 2.70 (d, *J* = 20.0 Hz, 1H), 2.39 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) (Two non-aromatic carbon peaks are overlapped): 170.5, 170.0, 156.1, 138.2, 137.9, 137.8, 137.6, 136.2, 131.6, 129.1, 128.8, 128.5 (2C), 128.4 (2C) 128.1, 127.9 (2C), 127.8 (2C), 118.6, 86.1, 78.8, 78.6, 77.4, 77.2, 76.7, 76.2, 75.3, 75.0, 74.4, 73.5, 67.8, 67.0, 66.3, 50.3, 37.6; HRMS (FAB): Calcd. for $C_{49}H_{53}N_2O_{10}$ ($[M+H]^+$): 829.3695, Found: 829.3704. $[\alpha]^{25}_D$ +1.9 (*c* 1.44, $CHCl_3$).

2. The procedure for the synthesis of **XB3**

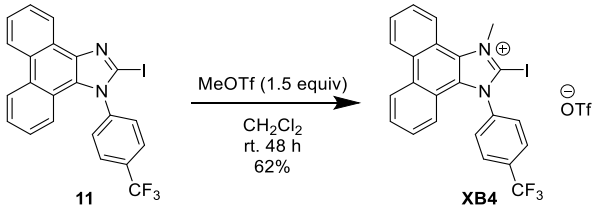


XB3

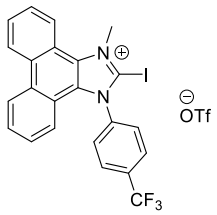
To a stirred solution of *N*-dedecylbenzimidazole[S1] (9.40 g, 32.8 mmol) in THF (120 mL) was carefully added freshly prepared lithium diisopropylamide (ca. 1.5 M solution in THF) at –78 ˚C, and the reaction mixture was stirred at the same temperature for 1 hour. Then, a THF solution (80 mL) of iodine (9.16 g, 36.1 mmol) was added dropwise to the mixture at –78 ˚C, and the resulting mixture was slowly allowed to warm up to room temperature before being quenched with aqueous $Na_2S_2O_3$

solution. After extraction with EtOAc (50 mL ×3), the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude solid, which was purified by column chromatography (EtOAc/*n*-hexane = 1/10) to furnish *N*-dodecyl-2-iodobenzimidazole (8.10 g, 60%) as purple solid. To a solution of *N*-dodecyl-2-iodobenzimidazole (2.00 g, 4.85 mmol) in DCM (10 mL) was added *n*-dodecyl triflate[S2] (2.46 g, 7.72 mmol), and the reaction mixture was stirred at ambient temperature for 10 h. After the solvent was evaporated under reduced pressure, the resulting solid was recrystallized from ether to afford the desired product **XB3** (2.04 g, 58%) as colorless solid; mp 107 –108 °C (ether); IR (ATR): 2920, 2852, 1278, 1237, 1221, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.74–7.71 (m, 2H), 7.62–7.59 (m, 2H), 4.51 (t, *J* = 6.1 Hz, 4H), 1.95–1.87 (m, 4H), 1.43–1.41 (m, 4H), 1.38–1.34 (4m, 4H), 1.29–1.25 (m, 28H), 0.87 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 133.2, 127.2, 120.4 (q, *J* = 321.1 Hz), 112.9, 111.3, 50.4, 31.8, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 26.6, 22.6, 14.1; HRMS (FAB): calcd for $C_{31}H_{54}N_2I^+$ ([M–OTf]$^+$): 581.3332, found: 581.3333.

3. The procedure for the synthesis of **XB4**



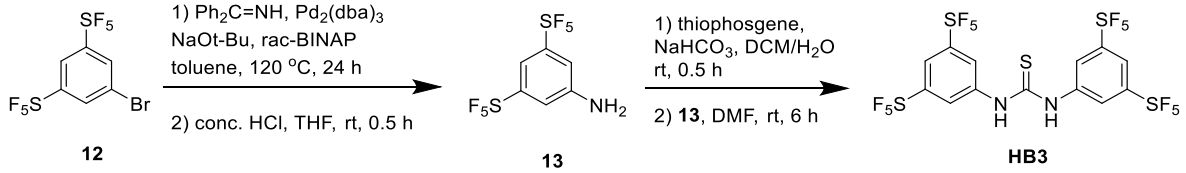
To a solution of compound **11**[S3] (244 mg, 0.5 mmol) in DCM (10 mL) was added MeOTf (123 mg, 0.75 mmol), and the reaction mixture was stirred at ambient temperature for 48 h. After the solvent was evaporated under reduced pressure, the resulting solid was recrystallized from toluene to afford the desired product **XB4** (203 mg, 62%) as colorless solid.



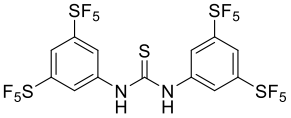
2-Iodo-3-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-phenanthro[9,10-*d*]imidazol-3-ium trifluoromethanesulfonate (XB4)

White solid; mp 269.9–271.9 °C (DCM); IR (ATR): 1728, 1687, 1498 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 9.11 (d, *J* = 8.1 Hz, 1H), 9.05 (d, *J* = 8.7 Hz, 1H), 8.84 (d, *J* = 7.5 Hz, 1H), 8.34 (d, *J* = 8.1 Hz, 2H), 8.11 (d, *J* = 8.1 Hz, 2H), 7.98-7.91 (m, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 4.70 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ: 170.4, 141.60, 132.3 (q, *J* = 33.5 Hz), 130.0, 129.3, 129.2, 128.9, 128.8, 128.5 (q, *J* = 3.4 Hz), 128.4 (2C), 128.3, 124.9, 124.8, 123.6 (q, *J* = 271.3), 122.9, 121.1, 120.7 (q, *J* = 323.0 Hz), 120.4, 119.5, 59.8; HRMS (FAB): calcd for $C_{23}H_{15}F_3N_2I^+$ ([M–OTf]$^+$): 503.0232, found: 503.0230; *Anal*. Calcd for $C_{24}H_{15}F_6IN_2O_3S$ C, 44.19; H, 2.32; N, 4.29. Found: C, 43.92; H, 2.58; N, 4.01.

4. The procedure for the synthesis of **HB3**



To a mixture of 3,5-bis(pentafluorothio)bromobenzene (818 mg, 2.0 mmol), $Pd_2(dba)_3$ (58.0 mg, 0.06 mmol), *rac*-BINAP (118 mg, 0.18 mmol), and NaO*t*-Bu (284 mg, 3.0 mmol) in anhydrous toluene (20 mL) was added benzophenone imine (0.48 mL, 2.52 mmol) under argon atmosphere at room temperature, and the reaction mixture was stirred at 120 ºC (oil bath temperature) for 24 hours, before being quenched with water (20 mL) at room temperature. The resulting mixture was then extracted with EtOAc (50 mL ×3), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude solid. To this crude imine (1.28 g) in THF (6.6 mL) was added concentrated HCl solution (0.3 mL), and the mixture was stirred at room temperature for 30 minutes, when the consumption of imine was monitored by TLC analysis. After being quenched with saturated aqueous $NaHCO_3$ solution, the mixture was then extracted with EtOAc (10 mL ×3), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was purified by column chromatography (EtOAc/*n*-hexane = 1/10) to furnish the title compound **13** (597 mg, 86%) as pale yellow solid; mp 62.0–64.2 °C (EtOAc/*n*-hexane); IR (ATR): 3424, 3206, 1612, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.47 (s, 1H), 7.15 (s, 2H), 4.15 (brs, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.2 (quintet, *J* = 18.7 Hz), 147.0, 114.7 (quintet, *J* = 4.3 Hz), 113.2 (quintet, *J* = 4.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: 82.7 (quintet, *J* = 150.3 Hz), 62.6 (d, *J* = 150.3 Hz); HRMS (FAB): calcd for $C_6H_6F_{10}NS_2^+$ ($[M+H]^+$): 345.9782, found: 345.9785.



1,3-Bis(3,5-bis(pentafluoro-l6-sulfanyl)phenyl)thiourea (HB3)

To a vigorously stirred mixture of 3,5-bis(pentafluorothio)aniline **13** (150 mg, 0.43 mmol) in DCM (4.0 mL) and saturated aqueous $NaHCO_3$ solution (4.0 mL) was added thiophosgene (0.083 mL, 1.09 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 0.5 hour. The resulting mixture was then extracted with DCM (5.0 mL ×3), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude isothiocyanate as pale yellow solid (quant), which was used for the next reaction without further purification. To this crude isothiocyanate (112 mg, 0.29 mmol) in DMF (1.0 mL) was added 3,5-bis(pentafluorothio)aniline **13** (100 mg, 0.29 mmol), and the mixture was stirred at room temperature for 6 hours, before being quenched with the addition of crushed ice (ca. 20 mL). The formed precipitate was collected by filtration, and washed with water three times to give **HB3**•DMF

complex, which was further purified by column chromatography (EtOAc/*n*-hexane/HCOOH = 10/90/1) to furnish the title compound (134 mg, 63%) as colorless solid; mp 122.1–125.7 °C (EtOAc/*n*-hexane); IR (ATR): 3214, 1537, 1453 cm^{-1}; ^{1}H NMR (acetone-d_6) δ: 10.08 (s, 2H), 8.48 (s, 4H), 8.13 (s, 2H); ^{13}C NMR (126 MHz, acetone-d_6) δ: 182.1, 153.5 (quintet, J = 19.2 Hz), 141.6, 126.29 (quintet, J = 4.3 Hz), 120.7 (quintet, J = 4.8 Hz).; ^{19}F NMR (376 MHz, acetone-d_6) δ: 81.3 (quintet, J = 150.3 Hz), 62.4 (d, J = 138.7 Hz).; HRMS (FAB): calcd for $C_{13}H_9F_{20}N_2S_5^+$ ($[M+H]^+$): 732.9050, found: 732.9048.

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