Carbenes-catalyzed activation of aldehyde for phenol functionalization

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**Carbenes-catalyzed Activation of Aldehyde for Phenol
Functionalization**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2019

Carbenes-catalyzed Activation of Aldehyde for Phenol Functionalization

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Master of Science

2019

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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ROBIN CHI YONGGUI

Abstract

Phthalides are a crucial kind of compounds in both of natural products and pharmaceutical molecules, which exhibit a broad spectrum of biological activities. In particular, 3-Ylidenephthalides represent satisfactory activity on anti-HIV, anti-inflammatory and anti-cancer. Consequently, a numerous of literatures have reported the methods to synthesis this series of compounds. However so far, most of these methods need to rely on transition metal catalysts. Besides, the expenses of the metal catalyst and the metal contamination of the product remain to be a pending issue.

Herein we report the first example of NHC-catalyzed activation of aldehyde for phenol functionalization, which could consider to be an eco-friendly and highly efficient method for chiral synthesis of phthalide derivatives. My topic will be divided into two parts:

Chapter I gives a brief introduction on N-Heterocyclic Carbene in organocatalysis. From it was first separated to it was applied to catalyze various kinds of reaction (Benzoin condensation, Stetter reaction and etc). Followed by its series of extended Breslow intermediates such as homoenolate, acylazolium and azolium enolate.

Chapter II introduces our initial attempt on a one-step and enantioselective approach to activate aldehyde for phenol functionalization through using N-Heterocyclic Carbene as the catalyst.

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Abbreviations

Ac	acetyl
Ar	aryl
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Bn	benzyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMSO	dimethylsulfoxide
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
ⁱ Pr	isopropyl
Mes	mesityl
OAc	acetocy
OTBS	trifluoromethanesulfonate
SET	single electron transfer
TLC	thin layer chromatography
Ts	p-toluenesulfonyl
α	alpha
β	beta

γ

gamma

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Chapter I

An Overview of N-Heterocyclic Carbenes

1.1 Introduction on N-Heterocyclic Carbene

The C-C bond-forming reactions play a significant role in chemical transformations. For this reason, organocatalysis has attracted tremendous attention.

In chemistry, a carbene is defined as a molecule containing a carbon atom with a valence of two and two unshared valence electrons. Prior to 1960, carbenes were considered to be too reactive to be isolated. However, in 1991, Arduengo and co-workers reported the unprecedented isolation and storability of crystalline N-Heterocyclic Carbene (NHC) IAd (Scheme 1.1).^[1] Since then, numerous applications of N-Heterocyclic Carbenes (NHCs) in organic synthesis have been reported constantly.

Scheme 1.1 The first isolation of stable NHC.

In the last two decades, there were many different kinds of N-Heterocyclic Carbenes (NHCs) that had been synthesised. Generally, they could be divided into four categories: thiazolylidene, triazolylidene, imidazolylidene and imidazolinylidene (Figure 1.1). These NHCs have been widely used in organocatalysis.

Fig 1.1 General structures of N-heterocyclic carbenes.

Due to the synthesis of more and more kinds of N-Heterocyclic Carbenes and their unique reactivities, N-Heterocyclic Carbenes have become common catalysts that have huge amount of applications in organic chemistry.

1.2 Umpolung acyl-anion catalyzed by NHC

The earliest investigated NHC-catalysed reaction is benzoin condensation. Based on the mechanism of the benzoin condensation, the changing of the aldehyde carbon from an electrophile to a nucleophile is promoted by N-Heterocyclic Carbene. Such conversion process is known as umpolung.^[2] The NHC-catalysed umpolung play a significant role in organocatalysis.

1.2.1 Benzoin Condensation

Upon treating certain aromatic aldehydes or glyoxals with cyanide ion, benzoin condensation is produced in a reaction called the benzoin condensation (Scheme 1.2). This phenomenon was firstly found by Wohler and Liebig in 1832.^[3] Roughly a century later, Ukai and co-workers found out that in the presence of a mild base, certain thiazolium salts could also be used to catalyse the benzoin condensation.^[4] The generally accepted mechanism of the thiazolium salt catalysed benzoin condensation was firstly proposed by R. Breslow.^[5] In this reaction pathway, N-Heterocyclic Carbene firstly react with aldehyde to form an intermediate **1**, followed by tautomerization to obtain a nucleophilic Breslow intermediate, which could be used to react with another aldehyde to generate benzoin product. (Scheme 1.3).

Scheme 1.2 General benzoin condensation catalysed by cyanide. **Scheme 1.3** Thiazolium salt catalyzed benzoin condensation proposed by Breslow.

Comparing with the original procedures, the benzoin condensation is more applicable for it works with enolizable and non-enolizable aldehydes, thus the asymmetric catalyst may be used. In 1966, the first case of stereoselective synthesis of benzoin has been achieved by Sheehan and Hunneman using a chiral thiazolium carbene catalyst.^[6] However, the best enantiomeric excess (ee) of the benzoin product that was obtained through their proposed reaction was only 22%. Since then, more and more research groups have started working on the optimization of enantioselectivity of benzoin condensation. The breakthrough came when Enders and co-workers demonstrated a thiazolium salt catalysed asymmetric benzoin condensation with a good enantioselectivity up to 95% ee (Scheme 1.4).^[7]

Scheme 1.4 Asymmetric benzoin reaction by Enders.

About a decade ago, Connon and Zeitler reported a catalyst **2** with special structure, which has a hydroxy group. Due to the presence of the hydroxyl group, this allows the formation of hydrogen bonding, which increase the selectivity significantly.^[8] As a result of the utilization of this triazolium catalyst **2**, benzoin

product was obtained with excellent yield and enantioselectivity (90% yield, >99% ee) (Scheme 1.5).

Scheme 1.5 Cannizzmann and Zeitler's work on benzoin condensation.

Benzoin condensation is not only limited to its self-coupling, the cross-benzoin reaction has also been investigated by many research groups. For an example, in 2007, You and colleagues reported a cross-azo-benzoin reaction to generate α -amino ketone products using NHC **3** (Scheme 1.6).^[9]

Scheme 1.6 You's work on cross-benzoin condensation

1.2.2 Stetter Reaction

In 1973, Stetter and co-workers demonstrated that under the presence of catalytic amount of sodium cyanide, aromatic aldehydes could be added directly to α , β -unsaturated nitriles and ketones to form the γ -oxo nitriles and γ -diketones, respectively (Scheme 1.7).^[10] Later, the application of this method was expanded to the aliphatic aldehydes by using thiazolium salts as the catalyst. In the presence of a nucleophilic catalyst, the addition of aliphatic or aromatic aldehydes to double bonds is known as the Stetter reaction. The first case of asymmetric Stetter reaction was accomplished by Enders' group in 1989 (Scheme 1.8).^[11] By using chiral NHC **4** as the catalyst, the enantioselectivity of the product was 39% with the low yield of 4%. Nevertheless, improvement was made as Enders and colleagues reported the first instance of asymmetric intramolecular Stetter reaction using NHC **5** a few years later, with an enantiomeric excess up to 74% (Scheme 1.9).^[12] Since then, this research field has been developing in an impressive trend.

Scheme 1.7 General Stetter reaction catalysed by cyanide.

Scheme 1.8 Enders' work on asymmetric Stetter reaction.

Scheme 1.9 Enders' work on intramolecular Stetter reaction.

Recently, in the laboratory of Rovis, a high-efficiency coupled reaction was completed.^[13] By utilizing chiral NHC **6a** and **6b**, the product yield was reported to be 90% and 95% respectively, with the ee of 88% and 95% respectively (Scheme 2.0). In the meantime, our group has also successfully accomplished an NHC-catalyzed coupling of enals with modified chalcones.^[14]

Scheme 2.0 NHC-catalysed coupled reaction by Rovis.

1.3 Catalysis concerning extended Breslow intermediates

As mentioned before, NHC-catalysed benzoin condensation and Stetter reaction belong to the type of a^1 - d^1 umpolung. However, in a series of reactions catalysed by NHC, α , β -unsaturated aldehydes often display unique reactivity as compared with other saturated aldehydes. Upon treating α , β -unsaturated aldehydes with NHCs, the free carbene is firstly added to carbonyl group. After proton-transfer, it becomes Breslow intermediate **7**, generally called the homoenolate equivalent (Figure 1.2). This homoenolate equivalent **7** is actually resonance, it also has another case of a resonance structure **8**, where the negative charge is located on the β position of the carbonyl group. In the nucleophilicity has transferred to the β position, such conversion process is known as a^3 - d^3 umpolung. The intermediate **8** could react with electrophiles to form β -functionalized product **9**, which undergoes tautomerization to create acylazolium **10**. Then, the nucleophile reacts with **10** to generate a product and the free carbene is regenerated.

Figure 1.2 Proposed NHC-catalysed homoenolate pathway.

The first generation of homoenolate equivalents were successfully accomplished in the laboratories of Bode^[15a] and Glorius^[15b] at same time by using thiazolium salts as precatalysts (Scheme 2.1). This successful report of NHC-catalysed homoenolate reaction has developed a new kind of organic compounds for further research.

Scheme 2.1 Generation of γ -Butyrolactones by Bode and Glorius.

Breslow intermediate could undergo a single-electron oxidation in the presence of certain oxidants. Such work was first demonstrated by Studer and co-workers in 2008 by utilizing TEMPO as the oxidant to generate esters from aldehydes (Scheme 2.2).^[16]

Scheme 2.2 Oxidation of Breslow intermediate by Studer.

In 2013, our group discovered that saturated carboxylic esters are great potential homoenolate precursors.^[17] This work is highly valuable since the non-activated β -position of a saturated ester is hard to functionalize generally. In this case, the reaction starts with the addition-elimination reaction of the free carbene to the saturated aryl ester to form acylazolium **11**. After tautomerization it becomes enolate azolium intermediate **12**, which is then transferred to form Breslow intermediate **13** through a proton-transfer pathway (Figure 1.3).

Figure 1.3 Pathway for saturated esters to homoenolates.

1.4 Catalysis concerning acylazolium intermediates

The N-Heterocyclic Carbene is a very powerful synthetic tool, since it is not only involved in umpolung chemistry, but also shows capability to catalyse various other non-umpolung reactions. Notably, both NHC-bound acylazolium and azolium enolate are significant intermediates with very wide scope of applications. Due to the wide applications, increasing research has been devoted in both NHC-bound acylazolium and azolium enolate during the past decade.

1.4.1 Transesterification reactions

As mentioned before the saturated acyl azoliums are used as the precursors of the azolium enolates as they have great reactivities. Besides, they are also the remarkable intermediates for NHC-catalysed transesterification reactions (Scheme 2.3). These kind of reactions were first demonstrated by Hedrick in 2002.^[18] Shortly afterwards, Nolan and co-workers successfully introduced a transesterification process between esters and simple alcohols by using NHC **14a** or **14b**, with the usage of NHC catalysts, high production rates (93-100%) were achieved (Scheme 2.4).^[19]

Scheme 2.3 Generally NHC-catalysed transesterification reactions.

Selected examples

99% yield

95% yield

96% yield

Scheme 2.4 Nolan's work on transesterification reactions.

Dynamic kinetic resolution (DKR) has been regarded to be one of the best methodologies for the preparation of enantiopure compounds. Even in NHC-catalysed reactions, the application of DKR could be found. The first NHC-catalysed dynamic

kinetic resolution involving secondary alcohols as the starting materials was developed by Suzuki and co-workers.^[20] Vinyl acetate and various kinds of alcohols were reacted with potassium tert-butoxide in the presence of catalytic amount of chiral imidazolium salts. Through this proposed reaction scheme, optimal enantiomeric excess (up to 58%) was obtained (Scheme 2.5).

Scheme 2.5 The first NHC-catalysed dynamic kinetic resolution by Suzuki.

1.4.2 Cycloadditions involving NHC-Bound azolium enolates

In 2006, Bode's group initially introduced a [4+2] hetero-Diels-Alder reaction using an azolium enolate as the key intermediate.^[21] The products were prepared in high yield with 97% ee (Scheme 2.6). A mechanism that involves an initial addition of free carbene to the carbonyl group of the 4-oxo-2-butenate was proposed. As a result, Breslow intermediate **15** was generated. This was followed by proton transfer to give the chiral azolium enolate **16**. Then, the [4+2] cycloaddition of azolium enolate **16** to imine took place, leading to the formation of azolium-attached intermediate **17**. The formation of intermediate **17** led to the release of free carbene, while the cycloaddition product is simultaneously formed (Figure 1.4).

Selected examples

Scheme 2.6 Bode's [4+2] reaction catalysed by NHC.

Figure 1.4 Proposed mechanism of NHC-catalysed [4+2] cycloaddition.

In 2008, Ye^[22a] and Smith^[22b] independently and simultaneously introduced a valuable NHC-catalysed [2+2] cycloaddition of ketenes to imines. Ye and workmates

used a chiral triazolium salt **18** as the catalyst, coupling ketenes with N-Boc imines to afford corresponding product in moderate to good yield and with up to 99% ee. Smith's work is slightly different from Ye's as imidazolinium salt **19** and triazolium salt **20** were used due to high catalytic rate. Under such condition, treating N-Ts imines with various ketenes gives the desired product with excellent yield (up to 96%). Nonetheless, the ee value is lower than Ye's conditions (Scheme 2.7).

Ye's work:

Selected examples

72% yield
75:25 dr
96% ee

75% yield
71:29 dr
99% ee

57% yield
83:17 dr
98% ee

Smith's work:

Selected examples

96% yield
57% ee
with NHC 20

96% yield
64% ee
with NHC 20

85% yield
65% ee
with NHC 19

Scheme 2.7 Ye and Smith's work on NHC-catalysed [2+2] cycloaddition.

In the laboratory of Ye^[23], the first asymmetric NHC-catalysed [3+2] cycloaddition was achieved in 2010, with triazolium salt **21** as the precatalyst. The addition of ketenes to oxaziridines resulted in the generation of relevant products as an up to 15:1 mixture of diastereomers with good yield and high ee value (up to 95% ee) (Scheme 2.8).

Scheme 2.8 The first asymmetric NHC-catalyzed [3+2] reaction by Ye.

In 2011, a few years after Louie^[24a] discovered the first NHC-catalysed [2+2+2] cyclization of isocyanate, Ye and colleagues extended the application of this work to asymmetric synthesis and have successfully proposed the first enantioselective [2+2+2] reaction by using NHC **22** as the catalyst.^[24b] In their work, the various ketenes were treated with catalytic amount of carbene and base in dichloromethane. Carbon disulfide or isothiocyanate was added to the mixture. The desired heterocyclic compound was obtained with outstanding yield (up to 99%) with a tremendous enantioselectivity up to 97% ee (Scheme 2.9).

Scheme 2.9 Ye's report on NHC-catalysed [2+2+2] reaction.

1.5 Summary

In this chapter, we firstly introduced the origin of N-Heterocyclic carbene, its ability form Breslow intermediate when treated with aldehydes. In addition, the application of Breslow intermediate is involved in various catalytic processes such as benzoin condensation and Stetter reaction were mentioned. What is more, upon treating NHC with functionalized aldehydes such as α , β -unsaturated aldehydes, the Breslow intermediate could be transformed to homoenolate due to resonance, which acts as a reactive intermediate in many reactions. We have also introduced acylazolium and azolium enolate as the derivatives of homoenolate. These derivatives have displayed tremendous catalytic activity. For example, acylazoliums is used in transesterification reactions and azolium enolates could take part in various types of cycloadditions.

Around two decades after the first successful separation of a structurally stable N-Heterocyclic carbene, the NHC-catalysed reactions have been investigated with numerous outstanding results. N-Heterocyclic carbenes currently functions as the nucleophilic catalysts, which have unique reactivity and tremendous applications. In fact, N-Heterocyclic carbene has already established its position in chemistry currently.

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Chapter II

Carbenes-catalyzed Activation of Aldehyde for Phenol Functionalization

2.1 Background

Natural products with small molecular size play a significant role in organic chemistry. Since its early investigation, it has been widely used in drug discovery.^[1] Phthalides (**22**), also known as 3H-isobenzofuran-1-ones, is one of the organic compounds used in drug discovery. The general structure of phthalides consists of two parts: γ -lactone and benzene. The lactone group acts as the key structure in many more complex derivatives, such as phenolphthalein, tetrachlorophthalide and butylphthalide (Figure 1.5). Phthalides are commonly present in various naturally occurring compounds with excellent biological activities.^[2] It has been proven that phthalides have medicinal properties, such as promoting blood circulation and heart disease prevention.

Fig 1.5 General structures of phthalides, phenolphthalein, tetrachlorophthalide and butylphthalide.

Synthesis of phthalides through biological means has been investigated extensively by many research groups. For example, the biosynthesis of isobenzofuranones was developed

by Fuska and co-workers.^[3] In this pathway, substrate **23** was first concentrated to the orsellinic acid **24** via various catalytic reactions of enzymes, such as ketoreductases, cyclases and aromatases. After the formation of **24**, methylation, oxidation, decarboxylation and redox reactions took place to form compound **25**. The product phthalide **26** is eventually generated through an intramolecular Cannizzaro reaction of **25** (Scheme 3.0).

Scheme 3.0 Fuska's work on the synthesis of phthalides.

The first abiotic synthesis of phthalides was accomplished by Wislicenus in 1893.^[4] After this pioneering work, more and more groups have begun to engage in this field. So far, there have been a lot of synthetic routes for phthalides have been proposed, such as the reduction of phthalic anhydrides and phthalaldehydic acids, thermal and photochemical rearrangements and name reactions. However, most of these methods require metal catalysts, harsh experimental conditions and expensive equipment and raw materials, which possibly made the reaction pathway hard and complicated. Besides, the high cost of the metal catalyst and the metal contamination of the product remain to be a pending issue. Herein, we report the initial carbene-catalyzed activation of aldehyde for phenol functionalization. Based on the proposed mechanism, aryl dialdehyde **27** is firstly activated by NHC in the presence of equivalent oxidant, resulting in formation of acyl

azolium intermediate **28**. This is followed by addition-elimination reaction via nucleophilic phenol compound to generate the final product (Scheme 3.1). Such mechanism could be applied to asymmetric synthesis of phthalide derivatives.

This work:

Scheme 3.1 Our work on asymmetric synthesis of phthalides.

2.2 Results and Discussion

2.2.1 Initial attempts

We first choose *o*-phthalaldehyde (**1a**) and phenol (**1b**) as the model reaction substrates in an attempt to obtain desired phthalide product **3a** (Scheme 3.2). We treat substrates with triazolium salt **A** in the presence of potassium carbonate and quinone **29** (an oxidant, Studer initially used it in NHC-catalyzed reaction). As expected, the proposed product (**3a**) is observed with fine yield (at least 70% yield).

Scheme 3.2 Our initial attempt on synthesis of phthalides.

2.2.2 Optimization of reaction condition

After confirming the feasibility of the reaction, chiral NHCs is used in a hope to get enantioselective product. In this case, various chiral NHC catalysts are investigated as shown in Table 2.1. Based on the table, we could that the usage of triazolium salt **C** as the precatalyst, leads to the significant increase in enantiomeric excess of the product (up to 81%) (Table 2.1 entry 2).

Table 2.1 Screening of various NHCs for the reaction of **1a** with **1b**.^[a]

entry	NHCs	yield (%)	ee (%)
1	B	5	14
2	C	58	81
3	D	53	64
4	E	60	13
5	F	50	10
6	G	15	55

^[a] Reaction condition: **1a** (0.1mmol), **2a** (0.1mmol), NHC (10 mol%), K₂CO₃ (40 mol%) and 1eq. **29** in DCM (1ml). ^[b] Isolated yield. ^[c] Determined by chiral phase HPLC analysis.

Then, we proceed to explore the effects of different bases and solvents on the enantioselectivity of the reaction. As indicated in Table 2.2, a wide range of bases are studied, taking into consideration of both transformation rate and enantioselectivity, TMEDA (Table 2.2 entry 3) and LiOH·H₂O (Table 2.2 entries 8, 9) seem to be the best organic base and inorganic base for this reaction respectively. It is worth noting that both entry 8 and entry 9 give corresponding product with exciting ee value, but when compared with entry 9, the yield when PhCF₃ is used is not as satisfactory. Nevertheless, in subsequent research work we have concluded that PhCF₃ serves as the better solvent, which shows potential on controlling the enantiomeric excess.

Table 2.2 Screening of various bases for the reaction of **1a** with **1b**.

entry	base	solvent	yield (%)	ee (%)
1	DBU	DCM	20	72
2	Et ₃ N	DCM	74	89
3	TMEDA	DCM	96	86
4	4-Methyl-morpholine	DCM	59	90
5	pyridine	DCM	42	96
6	Cs ₂ CO ₃	DCM	18	54
7	Li ₂ CO ₃	DCM	35	96

8	LiOH·H ₂ O	DCM	93	92
9	LiOH·H ₂ O	PhCF ₃	66	94

Reaction condition: **1a** (0.1mmol), **2a** (0.2mmol), NHC (10 mol%), K₂CO₃ (40 mol%) and 1eq. **29** in DCM (1ml). All the yields are isolated yields. Enantiomeric excesses were determined via chiral phase HPLC analysis.

In order to further investigate the application of the reaction, we conducted a series of substrate screening work (Table 2.3). Under the optimum condition, this process is tolerant to a wide range of electron-withdrawing (3b, 3f, 3i) or electron-donating (3d, 3g) groups as well as large steric hindrance groups on the phenol ring. Besides that, heterocyclic hydroxyl compounds are also investigated, affording phthalide derivatives with good yields (54-80%) and excellent enantioselectivity (86-99% ee).

Table 2.3 Substrate scope of aryl dialdehydes **2a** and phenols **2b**.

Reaction condition: **2a** (0.1mmol), **2b** (0.1mmol), NHC **C** (10 mol%), LiOH·H₂O (40 mol%) and 1eq. **29** in PhCF₃ (1ml). All the yields are isolated yields by silica gel column chromatography. Enantiomeric excesses are assessed by chiral phase HPLC analysis.

2.3 Summary

In conclusion, phthalides are crucial kind of organic compounds, and widely applied in the field of medicinal chemistry. We have accomplished an NHC-catalysed activation of aldehyde for phenol functionalization. Such mechanism could be utilized for enantioselective synthesis of phthalide derivatives by using chiral triazolium salts as the precatalysts. Compared with other works, this method is considered to be greener and highly efficient due to the simple generation, high catalytic activity and metal-free reaction condition (environmental protection). Further work is currently in progress to extend the activation of aldehyde for other groups functionalization, such as amides and acids.

2.4 Experimental Section

2.4.1 General Information.

All commercially available substrates are purchased from Sigma-Aldrich or TCI. As our reaction is not sensitive to the air or water, so all the samples are set up at normal condition without any further drying treatment. ¹H NMR spectra are collected by Bruker AV 300, 400 MHz NMR equipments. Chemical shifts (δ) for ¹H NMR spectra are recorded, which is specified in parts per million (ppm). The signal from SiMe₄ and CDCl₃ were defined as 0.00 and 7.26 on the δ scale respectively. Spin-spin splitting patterns are assigned as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublets of doublet) or m (multiplets). Carbon NMR spectra are analyzed on Bruker AV 300, 400 MHz NMR equipments. IR spectra are recorded on a Shimadzu FT-IR Spectrometer. X-ray single crystal diffraction is conducted on Bruker X8 APEX X-ray Diffractometer. Optical rotations are assessed on a Jasco P-1030 polarimeter as below: [α]_D^t (*c* in g per 100 mL solvent).

2.4.2 General process for the catalytic reaction of aldehydes **2a** with phenols **2b** to generate products **3**

The aryl dialdehydes **2a** (0.1mmol) and phenols **2b** (0.1mmol) are added to a 4ml clear flask equipped with a magnetic stir bar. Solvent PhCF_3 (1ml), catalyst **C** (0.01mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.04mmol) are introduced at room temperature (rt). The reaction mixture is stirred at rt for 12h. After the reaction has completed (monitored by TLC analysis), the crude product is obtained by concentration. Then, purification using column chromatography on silica gel (hexane/EtOAc) is carried out to afford the corresponding products **3**.

2.4.3 Stereochemistry confirmation of **3a** by single-crystal X-ray diffraction analysis

Product **3a** is a colorless crystal and was obtained through the evaporation of its dichloromethane/hexane mixture.

2.4.4 Characterization of products.

(R)-3-phenoxyisobenzofuran-1(3H)-one (3a): Yellow solid, 66% yield

¹H NMR (400 MHz, CDCl₃) δ 7.97 – 7.93 (m, 1H), 7.79 (ddd, J = 8.7, 5.1, 1.9 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.41 – 7.34 (m, 2H), 7.27 – 7.22 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.87 – 6.85 (m, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 168.12, 156.64, 144.53, 134.66, 131.18, 129.78, 126.86, 125.64, 123.75, 123.72, 117.11, 99.66;

IR ν_{max} (film, cm⁻¹): 1786, 1635, 1244, 972; **[α]_D²¹** = -246.4 (c = 2.2 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₄H₁₀O₃]⁺ 227.0703, found 227.0708;

HPLC analysis: 98:2 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 16.7 min (minor), 18.7 min (major)]

(R)-3-(2-bromophenoxy)isobenzofuran-1(3H)-one (3b): Off-white solid, 76% yield

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.81 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.62 (dd, J = 8.0, 1.5 Hz, 1H), 7.50 (dd, J = 8.2, 1.4 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.10 – 7.05 (m, 1H), 6.75 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 168.03, 153.55, 144.29, 134.86, 133.57, 131.39, 128.97, 126.82, 125.65, 124.23, 119.69, 114.08, 100.97;

IR ν_{max} (film, cm⁻¹): 2093, 1776, 1636, 1267, 1184, 961; **[α]_D²¹** = -168.5 (c = 1.5 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₄H₁₀BrO₃]⁺ 304.9808, found 304.9810;

HPLC analysis: >99.5:0.5 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 42.2 min (major), 46.5 min (minor)].

(R)-3-(4-(tert-butyl)phenoxy)isobenzofuran-1(3H)-one (3c): Yellow solid, 67% yield

¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 7.6 Hz, 1H), 7.77 (td, *J* = 7.4, 1.0 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.41 – 7.36 (m, 2H), 7.20 – 7.15 (m, 2H), 6.83 (s, 1H), 1.33 (s, 9H);

¹³C NMR (100 MHz, CDCl₃) δ 168.17, 154.44, 146.62, 144.61, 134.60, 131.11, 126.89, 126.57, 125.58, 123.72, 116.60, 99.93, 34.29, 31.44;

IR ν_{max} (film, cm⁻¹): 2089, 1780, 1734, 1635, 1240, 1053, 972; **$[\alpha]_{\text{D}}^{21}$** = –163.4 (*c* = 2.2 in CHCl₃);

HRMS (ESI, *m/z*): calcd. for [C₁₈H₁₉O₃]⁺ 283.1329, found 283.1230;

HPLC analysis: 97:3 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 16.0 min (minor), 20.8 min (major)]

(R)-3-(4-methoxyphenoxy)isobenzofuran-1(3H)-one (3d): Yellow solid, 74% yield

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 7.6 Hz, 1H), 7.77 (td, *J* = 7.5, 1.1 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.20 – 7.15 (m, 2H), 6.90 – 6.86 (m, 2H), 6.75 (s, 1H), 3.80 (s, 3H);

¹³C NMR (100 MHz, CDCl₃) δ 168.21, 156.04, 150.45, 144.52, 134.58, 131.11, 126.94, 125.57, 123.74, 118.84, 114.72, 100.80, 55.66;

IR ν_{max} (film, cm⁻¹): 2091, 1790, 1637, 1265, 1234, 1047, 970, 744; **$[\alpha]_{\text{D}}^{21}$** = –162.2 (*c* = 0.6 in CHCl₃);

HRMS (ESI, *m/z*): calcd. for [C₁₅H₁₃O₄]⁺ 257.0808, found 257.0808;

HPLC analysis: 98:2 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 23.1 min (minor), 34.5 min (major)]

(R)-3-(4-ethylphenoxy)isobenzofuran-1(3H)-one (3e): Yellow solid, 76% yield

¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 7.6 Hz, 1H), 7.77 (td, J = 7.4, 1.0 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.21 – 7.14 (m, 4H), 6.82 (s, 1H), 2.64 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃) δ 168.20, 154.69, 144.58, 139.73, 134.60, 131.11, 129.01, 126.87, 125.57, 123.73, 117.11, 100.06, 28.09, 15.75;

IR ν_{max} (film, cm⁻¹): 2090, 1782, 1638, 1238, 1049, 970; **$[\alpha]_D^{21}$** = -203.5 (c = 2.4 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₆H₁₄O₃]⁺ 255.1016, found 255.1016;

HPLC analysis: 95:5 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 20.1 min (minor), 24.2 min (major)]

(R)-3-(4-fluorophenoxy)isobenzofuran-1(3H)-one (3f): Yellow solid, 74% yield

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 7.6 Hz, 1H), 7.79 (t, J = 7.4 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.20 (dd, J = 9.1, 4.2 Hz, 2H), 7.04 (t, J = 8.5 Hz, 2H), 6.77 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 167.98, 160.22, 157.82, 152.54, 152.51, 144.23, 134.69, 131.24, 126.75, 125.62, 123.72, 118.87, 118.79, 116.32, 116.09, 100.15;

¹⁹F NMR (376 MHz, CDCl₃) δ -119.66;

IR ν_{max} (film, cm⁻¹): 2096, 1780, 1738, 1643, 1260, 976; **$[\alpha]_D^{21}$** = -223.5 (c = 1.8 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₄H₁₀FO₃]⁺ 245.0608, found 245.0608;

HPLC analysis: 99:1 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 35.2 min (minor), 41.3 min (major)].

(R)-3-(3-methoxyphenoxy)isobenzofuran-1(3H)-one (3g): Yellow solid, 65% yield

¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 7.6 Hz, 1H), 7.78 (td, J = 7.5, 1.0 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.29 – 7.24 (m, 1H), 6.86 – 6.83 (m, 2H), 6.77 (t, J = 2.4 Hz, 1H), 6.69 (dd, J = 8.3, 2.4 Hz, 1H), 3.82 (s, 3H);

¹³C NMR (100 MHz, CDCl₃) δ 168.09, 160.86, 157.74, 144.44, 134.65, 131.16, 130.22, 126.77, 125.59, 123.73, 109.45, 108.93, 103.35, 99.53, 55.41;

IR ν_{max} (film, cm⁻¹): 2092, 1782, 1634, 1238, 970, 737; **$[\alpha]_D^{21}$** = -225.4 (c = 1.6 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₅H₁₃O₄]⁺ 257.0808, found 257.0809;

HPLC analysis: 94:8 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 22.7 min (minor), 30.9 min (major)]

(R)-3-(3-allylphenoxy)isobenzofuran-1(3H)-one (3h): Yellow solid, 71% yield

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 7.6 Hz, 1H), 7.79 (td, J = 7.5, 1.2 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.43 – 7.40 (m, 1H), 7.31 – 7.21 (m, 2H), 7.11 (td, J = 7.4, 1.2 Hz, 1H), 6.80 (s, 1H), 5.99 (ddt, J = 16.7, 10.1, 6.4 Hz, 1H), 5.09 – 4.97 (m, 2H), 3.52 – 3.33 (m, 2H);

¹³C NMR (100 MHz, CDCl₃) δ 168.15, 154.77, 144.70, 136.52, 134.65, 131.14, 130.42, 129.63, 127.82, 126.86, 125.62, 123.80, 123.69, 115.80, 115.75, 100.24, 34.23;

IR ν_{max} (film, cm⁻¹): 2090, 1784, 1636, 1240, 972, 741; **$[\alpha]_D^{21}$** = -198.1 (c = 2.7 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₇H₁₅O₃]⁺ 267.1016, found 267.1013;

HPLC analysis: 93:7 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 20.1 min (minor), 24.2 min (major)]

(R)-3-(4-nitrophenoxy)isobenzofuran-1(3H)-one (3i): Yellow solid, 60% yield

¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.25 (m, 2H), 7.98 (dt, J = 7.6, 1.0 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.76 – 7.70 (m, 2H), 7.35 – 7.30 (m, 2H), 6.94 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 167.40, 161.04, 143.60, 143.56, 135.00, 131.64, 126.44, 125.92, 123.79, 116.85, 98.19;

IR ν_{max} (film, cm⁻¹): 2091, 1636, 1261, 1083, 955; **$[\alpha]_D^{21}$** = -261.5 (c = 2.2 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₄H₁₀NO₅]⁺ 272.0553, found 272.0554;

HPLC analysis: 96:4 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 15.4 min (minor), 16.3 min (major)].

(R)-3-(isoquinolin-5-yloxy)isobenzofuran-1(3H)-one (3j): Off-white solid, 54% yield

¹H NMR (400 MHz, CDCl₃) δ 9.26 (s, 1H), 8.51 (d, J = 5.7 Hz, 1H), 7.98 (dt, J = 7.6, 1.0 Hz, 1H), 7.86 – 7.76 (m, 4H), 7.71 (td, J = 7.4, 1.2 Hz, 1H), 7.65 (dt, J = 5.7, 1.0 Hz, 1H), 7.54 (dd, J = 8.9, 2.5 Hz, 1H), 7.01 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 167.86, 155.08, 151.70, 144.11, 142.22, 134.85, 132.62, 131.42, 129.34, 128.63, 126.63, 125.80, 123.80, 123.51, 120.20, 110.81, 99.15;

IR ν_{max} (film, cm⁻¹): 2091, 1782, 1630, 1261, 970; **$[\alpha]_D^{21}$** = -245.6 (c = 1.0 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₇H₁₂NO₃]⁺ 278.0812, found 278.0813;

HPLC analysis: 98:2 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 16.1 min (minor), 17.1 min (major)].

(R)-3-(naphthalen-1-yloxy)isobenzofuran-1(3H)-one (3k): Red brownish solid, 57% yield

¹H NMR (400 MHz, CDCl₃) δ 8.19 – 8.14 (m, 1H), 8.00 (dt, J = 7.6, 1.0 Hz, 1H), 7.88 – 7.79 (m, 3H), 7.74 – 7.69 (m, 1H), 7.66 – 7.61 (m, 1H), 7.55 – 7.45 (m, 4H), 7.00 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 168.14, 152.64, 144.68, 134.79, 134.55, 131.27, 127.70, 126.87, 126.67, 125.95, 125.77, 125.74, 125.64, 123.80, 123.45, 121.50, 109.87, 100.05;

IR ν_{max} (film, cm⁻¹): 2092, 1782, 1634, 1258, 1088, 970; **$[\alpha]_D^{21}$** = -170.4 (c = 1.9 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₈H₁₃O₃]⁺ 277.0859, found 277.0860;

HPLC analysis: 99:1 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 26.1 min (minor), 26.8 min (major)]

(R)-3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)isobenzofuran-1(3H)-one (3l): Off-white solid, 60% yield

¹H NMR (400 MHz, CDCl₃) δ 7.95 (dd, J = 7.6, 1.0 Hz, 1H), 7.78 (td, J = 7.5, 1.1 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.21 – 7.12 (m, 2H), 6.89 (dd, J = 7.4, 1.3 Hz, 1H), 6.80 (s, 1H), 2.81 – 2.77 (m, 2H), 2.72–2.68 (m, 2H), 1.81–1.75 (m, 4H);

¹³C NMR (100 MHz, CDCl₃) δ 168.26, 154.87, 144.87, 139.20, 134.62, 131.07, 127.19, 126.92, 126.08, 125.60, 124.52, 123.65, 112.32, 100.29, 77.31, 77.00, 76.68, 29.54, 23.33, 22.67, 22.62;

IR ν_{max} (film, cm⁻¹): 2090, 1786, 1734, 1635, 1269, 972; **$[\alpha]_D^{21}$** = -137.2 (c = 1.6 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₈H₁₇O₃]⁺ 281.1127, found 281.1127;

HPLC analysis: 98:2 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 13.9 min (minor), 14.4 min (major)]

(R)-3-(naphthalen-2-yloxy)isobenzofuran-1(3H)-one (3m): White solid, 70% yield

¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 7.6 Hz, 1H), 7.84 – 7.74 (m, 5H), 7.71 – 7.65 (m, 2H), 7.52– 7.48 (m, 1H), 7.45 – 7.41 (m, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.98 (s, 1H);

¹³C NMR (100 MHz, CDCl₃) δ 168.16, 154.44, 144.49, 134.71, 134.14, 131.22, 130.28, 129.85, 127.67, 127.38, 126.79, 126.74, 125.67, 124.90, 123.81, 118.72, 111.73, 99.69;

IR $\nu_{\max}$ (film, cm⁻¹): 2090, 1786, 1736, 1636, 1242, 974; **$[\alpha]_D^{21}$** = -307.7 (c = 2.7 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₈H₁₃O₃]⁺ 277.0859, found 277.0861;

HPLC analysis: 99:1 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 17.3 min (minor), 19.4 min (major)]

(R)-3-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)isobenzofuran-1(3H)-one (3n): White solid, 75% yield

¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 7.7 Hz, 1H), 7.83 – 7.74 (m, 1H), 7.67 (m, 4H), 7.46 (d, J = 1.7 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.05 (s, 2H);

¹³C NMR (100 MHz, CDCl₃) δ 167.88, 164.32, 152.61, 147.94, 144.52, 134.81, 131.25, 126.62, 126.43, 125.80, 123.69, 122.18, 109.79, 108.17, 102.04, 93.22;

IR $\nu_{\max}$ (film, cm⁻¹): 2091, 1643, 1260, 1151, 972; **$[\alpha]_D^{21}$** = -143.3 (c = 0.5 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₈H₁₇O₃]⁺ 281.1127, found 281.1130;

HPLC analysis: 98:2 *er*, [CHIRALPAK IA column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 32.1 min (minor), 40.8 min (major)]

(R)-5,6-dimethoxy-3-phenoxyisobenzofuran-1(3H)-one (3o): Yellow solid, 80% yield

¹H NMR (400 MHz, CDCl₃) δ 7.40-7.34 (m, 2H), 7.32 (s, 1H), 7.29-7.26 (m, 2H), 7.13 (t, J = 7.4 Hz, 1H), 7.09 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H);

¹³C NMR (100 MHz, CDCl₃) δ 168.33, 156.61, 155.18, 151.95, 138.88, 129.73, 123.60, 118.99, 117.03, 106.03, 104.93, 99.05, 56.53, 56.41;

IR $\nu_{\max}$ (film, cm⁻¹): 2091, 1788, 1664, 1400, 1361, 1246, 974; **$[\alpha]_D^{21}$** = -242.5 (c = 3.3 in CHCl₃);

HRMS (ESI, m/z): calcd. for [C₁₆H₁₅O₅]⁺ 287.0914, found 287.0915;

HPLC analysis: 98:2 *er*, [CHIRALPAK IB column; 0.6 mL/min; solvent system: *i*-PrOH/hexane 5:95; retention times: 16.8 min (minor), 18.7 min (major)].

2.5 References

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