Carbene-catalyzed activation of aldehydes and esters for asymmetric reactions and dynamic kinetic resolutions

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**Carbene-Catalyzed Activation of Aldehydes and Esters for
Asymmetric Reactions and Dynamic Kinetic Resolutions**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCE

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**Carbene-Catalyzed Activation of Aldehydes and Esters for
Asymmetric Reactions and Dynamic Kinetic Resolutions**

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ABSTRACT

This thesis focuses on exploring new reaction modes and new synthetic methodologies that are enabled by *N*-heterocyclic carbenes (NHCs) catalysts. It contains five parts:

Chapter 1 gives a short introduction about the history and the development of NHC catalysis based on the activation modes, and points out future challenges in the field.

Chapter 2 presents a convergent, organocatalytic asymmetric aminomethylation of α,β -unsaturated aldehydes *via* a cooperative catalysis of *N*-heterocyclic carbene (NHC) and Brønsted acid. This redox neutral strategy is suitable for the gram-scale synthesis of optically enriched β^2 -amino acids bearing various substituents.

Chapter 3 demonstrates a novel means of activating an *o*-hydroxybenzhydryl amine using the *in-situ* generated conjugated acid from NHC pre-catalyst to generate a transient *o*-QM species for enantioselective [4+2] annulation with a α -chloro aldehyde substrate. The methodology delivers highly enantioenriched chroman derivatives with very good yields and excellent distereoselectivities.

Chapter 4 reports a new mode of carbene catalysis that allows aromatic aldehydes activation and remote O-H bond functionalization. The catalytic process generates a new type of carbene-derived intermediate with an oxygen atom as the reactive center. Inexpensive achiral urea co-catalysts work cooperatively with the carbene catalysts, leading to consistent enhancement of the enantioselectivities.

Chapter 5 describes the first carbene-catalyzed dynamic kinetic resolution of α,α -disubstituted carboxylic esters with up to 99:1 er and 99% yield. The study clearly illustrates the unique power of readily available and easy to handle carboxylic esters in carbene-catalyzed reactions.

PUBLICATIONS

1. “Carbene-Catalyzed Dynamic Kinetic Resolution of Carboxylic Esters”.
Xingkuan Chen, Jacqueline Zi Mei Fong, Jianfeng Xu, Chengli Mou, Yunpeng Lu, Song Yang, Bao-An Song, and Yonggui Robin Chi*, *J. Am. Chem. Soc.*, **2016**, *138*, 7212-7215.
2. “A New Mode of Carbene-Catalyzed Aryl Aldehyde Activation and Induced OH Functionalization”.
Xingkuan Chen, Hongling Wang, Kazuki Doitomi, Chong Yih Ooi, Pengchang Zheng, Song Yang, Bao-An Song, Hajime Hirao, Yonggui Robin Chi*, *Nat. Commun.* **2016**, DOI: NCOMMS-16-16359C, accepted.
3. “Aminomethylation of Enals through Carbene and Acid Cooperative Catalysis: Concise Access to 2-Amino Acids”.
Jianfeng Xu,[†] **Xingkuan Chen**,[†] Ming Wang, Pengcheng Zheng, Bao-An Song, Yonggui Robin Chi*, *Angew. Chem., Int. Ed.*, **2015**, *54*, 5161-5165. ([†]equal to first author).
4. “Facile Access to Pyridines via DMAP –Mediated Reactions of α -Chloro Acetic Esters and Unsaturated Imines”.
Lin Hao,[†] **Xingkuan Chen**,[†] Shaojin Chen, Ke Jiang, Yonggui Robin Chi*, *Org.Chem. Front.*, **2014**, *1*, 148-150. ([†]equal to first author).
5. “Functionalization of Benzylic C(sp³)-H Bonds of Heteroaryl Aldehydes through N-Heterocyclic Carbene Organocatalysis”.
Xingkuan Chen, Song Yang, Bao-An Song, Yonggui Robin Chi*, *Angew. Chem. Int. Ed.*, **2013**, *52*, 11134-11137.

ABBREVIATIONS

Ac	acetyl
Boc	<i>tert</i> -butyloxycarbonyl
BQ	benzoquinone
Bu	butyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
IPA	isopropyl alcohol
<i>i</i> Pr	isopropyl

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	<i>N</i> -bromosuccinimide
OAc	acetoxy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
TLC	thin layer chromatography
TMS	trimethylsilyl
α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1

Introduction

1.1 N-Heterocyclic Carbenes as Organocatalysts

N-heterocyclic carbenes (NHCs) have been intensively studied and widely used by scientists as ligands in transition metal-based reactions.¹ The stable carbene was isolated by Bertrand and Arduengo in 1998. Since then due to the strong electron-donating feature, NHCs have been broadly used as powerful nucleophilic organocatalysts in a variety of chemical transformations.² Use of NHC as an organocatalyst was first discovered in the 1940s,³ but only in the last decade, with the discovery of new NHC catalysts, NHC organocatalysts have experienced an explosive development with numerous novel activation modes and have become one of the most promising organocatalysts.⁴

1.2 NHC-Catalyzed Acyl Anion Type Reactions

In organocatalysis, aldehydes are one of the most intensively used substrates. Nucleophilic NHC can react with an aldehyde substrate to generate an acyl anion equivalent. Breslow first proposed a reaction mechanism for this transformation. The acyl anion equivalent is also called Breslow intermediate, which has been widely acknowledged and has become one of the most basic activation modes in NHC catalysis.⁵ The nucleophilic Breslow intermediate can react with other aldehyde substrates (Benzoin condensation) or Michael acceptors (Stetter reaction) (Scheme 1.1). In this transformation

Scheme 1.1 “Umpolung” in NHC catalysis.

process, the polarity of the aldehyde is inverted from an electrophile to a nucleophile, which is conceptually called “umpolung” (polarity reversing). Umpolung is one of the most important modes in carbene-catalyzed reactions.

1.2.1 Benzoin Condensation

Early in 1832, Liebig and Wohler first found cyanide salt could dimerize aldehydes to hydroxyl ketones (also called the Benzoin product).^{6a} About 100 years later, Uki and co-workers found that the Benzoin condensation product could be obtained with a catalytic amount of thiazolium salts.^{6b} In 1958, Breslow first proposed a mechanism for the Benzoin condensation reaction mediated by thiazolium carbene salts (Figure 1.2).^{6c} Since then, the Benzoin condensation reaction used as a new carbon-carbon bond formation method has attracted more and more attention.⁶ Different kinds of substrates and new carbene catalysts have been developed by several research groups.

Scheme 1.2 Mechanism of the Benzoin condensation catalyzed by NHC

For example, Sheehan and co-workers first reported an asymmetric Benzoin reaction using a chiral thiazolium carbene catalyst, although the enantioselectivity of the product was not good, with only 22% ee.^{6d} In 2002, Enders group developed a new triazolium carbene catalyst, which was used in an asymmetric Benzoin reaction of aromatic aldehyde substrates. The Benzoin products were formed with high enantioselectivities, up to 95% ee (Scheme 1.3).⁷

Scheme 1.3 Highly enantioselective Benzoin condensation of aromatic aldehydes.

Benzoin condensation does not only include aldehyde homo-coupling. Additionally, cross Benzoin with two different aldehydes or aldehydes and ketones, as well as aza-Benzoin reactions with aldehydes and imines have been studied in detail by several groups recently.⁸

1.2.2 Stetter Reaction

In 1973, Stetter pioneered the Michael addition reaction of Breslow intermediate to various α,β -unsaturated compounds. Since then, the Stetter reaction has been widely used as a powerful method to synthesize many valuable 1,4-bifunctional compounds, such as 1,4-diketones, 4-keto-nitriles and 4-keto-esters.⁹ In 1996, the first asymmetric intramolecular Stetter reaction was reported by Enders and co-workers with a new triazolium carbene pre-catalyst, albeit with moderate enantioselectivities (Scheme 1.4).^{9b} Since then, a huge number of asymmetric Stetter reactions, including inter-molecular and intramolecular reactions have been intensively studied by Enders, Rovis and many others research groups.¹⁰

Scheme 1.4 The first asymmetric intramolecular Stetter reactions.

1.3 NHC-Catalyzed Homoenolate Type Reaction

Carbene-catalyzed Benzoin condensation and Stetter reaction belong to the type of a¹-d¹ Umpolung (polarity inversion of the 1st carbon from electron acceptor to electron

donor). In NHC catalysis, using other functionalized aldehydes, such as α , β -unsaturated aldehydes, will generate a new important “homoenolate intermediate”. In this case, the Breslow intermediate allows the nucleophilic properties to transfer from α carbon to the β carbon. Simultaneously, a¹-d¹ Umpolung could be transferred along the conjugated system to form the a³-d³ Umpolung. (Scheme 1.5)

Scheme 1.5 Homoenolate activation that enabled by NHC catalyst.

Homoenolate equivalent is a very reactive intermediate, which can react with many electrophiles, such as imines and ketones ([3+2] annulation), alkyl halides, and other conjugated compounds.¹¹ In 2004, Glorius and Bode independently discovered the NHC-catalyzed homoenolate activation around the same time.¹² These two groups reported the same [3+2] annulation reaction and got the same lactone products by using α,β -unsaturated aldehydes and aryl aldehydes but under different conditions. (Scheme 1.6).

Scheme 1.6 The pioneering report on NHC catalyzed homoenolate activation.

In the last decade, NHC-catalyzed homoenolate reactions have been intensively studied by Bode, Rovis, Scheidt, Chi and other research groups.¹² A series of useful reactions and methodologies have been developed. A large number of electrophiles including aldehydes, ketones and their derived imines, as well as the α,β -unsaturated ketones and imines have

been well explored. In most conditions, the homoenolate involved reactions are very efficient and smooth, the homoenolate adducts could be obtained with high yields and high enantoselectivities. (Scheme 1.7)

Scheme 1.7 Selected examples of homoenolate process with different electrophiles.

1.4 NHC-Catalyzed Enolate Type Reaction

NHC-bounded enolate intermediate is one of the most important reactive nucleophiles. Reactions that involve enolate and other electrophiles via formal [2+2], [2+3] or [2+4] type cycloaddition are very efficient methods to synthesize some important heterocyclic units. Additionally, enolate intermediate could be generated by many kinds of common substrates, such as unsaturated aldehydes, ketenes, anhydrides, esters, and other α -functionalized aldehydes.¹³ (Scheme 1.8) For example, in 2004, Bode group first developed a carbene catalyzed enolate intermediate generation method from epoxyaldehydes for synthesis of β -hydroxy esters.^{14a}

Scheme 1.8 NHC-mediated azolium enolate from different substrates

Later that same year, Rovis and co-workers reported another method to generate an enolate intermediate from α -haloaldehyde substrate. In this reaction, NHC firstly attacks the carbonyl group to form the Breslow intermediate followed by formation of the enolate intermediate via an internal redox process. Then in the presence of alcohol, the ester product is formed by tautomerization of the enolate intermediate.^{14b} Recently, our group found a new enolate precursor of carboxylate ester, which could be activated by carbene catalyst.¹⁵ Stable 4-nitrophenol esters could be activated by carbene catalyst and react with α,β -unsaturated imines (Scheme 1.9). In this transformation, NHC first reacted with ester to generate an acyl azolium intermediate. Under strong basic conditions, the α proton easily undergoes a deprotonation process and generates enolate key intermediate, that then forms the [4+2] adducts with α,β -unsaturated imines. Moreover, ester substrates can also be applied in other NHC involved activation modes such as homoenolate,^{15d} vinylogous enolate^{15e} and NHC-mediated LUMO activation.^{15f}

Scheme 1.9 Carboxylic esters as enolate precursors.

In addition, highly reactive ketenes as enolate precursors have been widely used in NHC-catalyzed reactions for synthesis of high enantiopure lactones and lactams, which were reported by Ye^{16a} and Smith^{16c} group. It should be noted that an α,β -unsaturated aldehyde is also a good enolate precursor. As discussed above, carbene reacts with enal to form the homoenolate intermediate, which can transform to the acyl azolium intermediate *via* β -protonation process. Under weak basic conditions, prior to the formation of acyl azolium intermediate, the enolate intermediate can be captured by other electrophiles. For example, Bode group firstly reported a chiral carbene-catalyzed aza-Diels-Alder reaction with enals and α,β -unsaturated imines.^{17a} Following this pioneering work, enal as an enolate intermediate precursor has been widely used in numerous NHC-catalyzed [4+2] annulation reactions. (Scheme 1.10).¹⁷

Scheme 1.10 Enolate intermediate generate form α,β -unsaturated aldehyde.

1.5 Acyl Azolium Involved Reaction in NHC Catalysis

N-heterocyclic carbene catalysis belongs to the category of covalent bond catalysis (compared to H-bond donor catalysts, such as chiral phosphoric acids and thioureas). Therefore, almost all the NHC-catalyzed reactions should be involved in the formation of NHC-bound acyl azolium intermediates. NHC-bound acyl azolium intermediate can be attacked by other nucleophilic species and then release the NHC catalyst for the new

catalytic cycle. Besides the previously mentioned enolate and homoenolate intermediates, α,β -unsaturated acyl azolium intermediate is another important intermediate in NHC-catalyzed asymmetric reactions.

In 2010, Studer and co-workers firstly reported the Michael addition reaction of 1,3-diketone to the α,β -unsaturated acyl azolium intermediate. For this reaction, in the presence of an oxidant, the nucleophilic homoenolate intermediate transformed into the electrophilic α,β -unsaturated acyl azolium intermediate (Scheme 1.11).¹⁸ Recently, Bode and co-workers proposed a Claisen-type rearrangement pathway for the annulation step based on experimental exploration and detailed mechanistic studies (Scheme 1.12).¹⁹

Scheme 1.11 NHC catalyzed α,β -unsaturated acyl azolium intermediate.

Scheme 1.12 NHC catalyzed α,β -unsaturated acyl azolium intermediate

Since then, many different electrophiles have been used in α,β -unsaturated acyl azolium involved reactions. Furthermore, many new precursors of the α,β -unsaturated acyl azolium intermediate have been explored.²⁰ For example, in 2013, our group firstly reported a straightforward method to generate α,β -unsaturated acyl azolium from α,β -unsaturated ester substrate.^{15f}

1.6 Summary and Research Design

In the last decade, there has been a very fast and intensive development on *N*-heterocyclic carbenes as organocatalysts. *N*-heterocyclic carbene as an organocatalyst has widespread application in asymmetric catalysis and natural product synthesis. Although a series of catalytic intermediates such as acyl anion, enolate, homoenolate and acyl azolium intermediates have been well studied, there are still challenges in developing new activation modes and new synthetic methodologies.

α,β -Unsaturated aldehydes are a class of widely studied substrates in NHC catalysis. However, *N*-heterocyclic carbene and Brønsted acid cooperative catalysis is rarely reported. Therefore, we aim to develop new catalytic modes for synthesis of some useful molecules with the cooperative catalysis. Moreover, the cooperative catalysis with carbene catalysts also represents challenges, especially when exclusive use of NHC catalysts can not control the enantioselectivity and can even result in deactivation of substrates. In addition, common aromatic aldehyde activation was less reported in carbene catalyzed asymmetric reactions. Aromatic moieties are common structures found in many natural products, bioactive molecules and polymeric materials. The research in the field of asymmetric carbene organic catalysis has primarily focused on the activation of carbon atoms in non-aromatic scaffolds. Here, we develop a new mode of carbene catalysis that allows aromatic aldehyde activation and remote O-H bond functionalization.

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Chapter 2

Aminomethylation of Enals Through Carbene and Acid Cooperative Catalysis: Concise Access to β^2 - Amino Acids

2.1 Introduction

β -Amino acids have become attractive synthetic targets since peptides, these motifs can exhibit well-defined secondary structural characteristics¹ and increased stability towards protease degradation.² Therefore, it is not surprising that considerable efforts have been made to the development of novel strategies for the synthesis of enantiopure β -amino acids.³ However, in contrast to β^3 -amino acids (those branched in the β -position),⁴ which are now commercially available with most natural substituents, the analogous β^2 -amino acids (those branched in the α -position), although particularly promising and widely found in natural products and pharmaceuticals,⁵ are far less accessible (Figure 2.1).⁶

Figure 2.1 β -Amino acids & examples of natural products and pharmaceuticals

Most of the widely used methods employ chiral auxiliary to efficiently set the stereochemistry,⁷ the catalytic asymmetric methods to construct β^2 -amino acids and their derivatives are still less reported.⁸ In the area of small-molecule organocatalysis, for example, in 2006, Gellman group developed a chiral secondary amine catalyzed Mannich reaction. The key step in this reaction was to prepare β^2 -amino aldehyde through enamine catalysis. After β^2 -amino aldehyde was formed an excess amount of NaBH_4 was used to reduce the aldehyde one pot to achieve β^2 -amino alcohol with very good

enantioselectivity and yield. The product, β^2 -amino alcohol, could be transformed to β^2 -amino acid with another two steps. (Scheme 2.1)^{8d,e}

Scheme 2.1 Amine catalyzed Mannich reaction

Later, List and co-workers described a catalytic asymmetric thiourea and Hantzsch ester mediated transfer hydrogenation reaction to form β^2 -nitroesters with high yields and enantioselectivities. β^2 -nitroesters could be reduced and de-protected at the same time in one step with Pd/C and H_2 to obtain β^2 -amino acid. (Scheme 2.2)^{8f} However, the development of a convergent, efficient and enantioselective route for the synthesis of β^2 -amino acids with various substitution patterns, especially with natural substituents, in multi-gram scale is still of great difficulty.

Scheme 2.2 One-pot strategy for the synthesis of β^2 -amino acid

Recently, *N*-heterocyclic carbene (NHC) has emerged as a promising organocatalyst for enantioselective chemical transformations due to its unique umpolung ability.⁹ Moreover, the combination of NHC with other catalysts such as Lewis acid¹⁰ and Brønsted acid¹¹ has provided new opportunities to develop elegant reactions for the synthesis of enantiopure molecules. For example, in 2010, Scheidt and co-workers reported the first *N*-heterocyclic carbene and Lewis acid $Mg(Ot-Bu)_2$ co-catalyzed [3+2]

annulation reaction. In this reaction, using enals and hydrazones as substrates, *N*-heterocyclic carbene and Lewis acid $\text{Mg}(\text{Ot-Bu})_2$ as co-catalysts and TBD as the base, *cis*- γ -lactams products were formed at high yields and enantioselectivities. In this cooperation process, Lewis acid $\text{Mg}(\text{Ot-Bu})_2$ was added with hydrazones and thus increased the reactivity of the hydrazone substrate. As a result of Lewis acid $\text{Mg}(\text{Ot-Bu})_2$ addition, the reaction yield, enantioselectivity and even the stereoselectivity were improved (Scheme 2.3).^{10b}

Scheme 2.3 *N*-heterocyclic carbene and Lewis acid catalysis

In 2011, Rovis and co-workers formed the asymmetric synthesis of *trans*- γ -lactams via the first NHC and Brønsted acid cooperative catalysis. In this reaction, *in situ* generated Brønsted acid dramatically improved the reaction yield. This may be due to the hydrogen bonding effect; Brønsted acid could increase the activity of the imine. (Scheme 2.4)^{11a}

Scheme 2.4 *N*-heterocyclic carbene and Brønsted acid cooperative catalysis

Notably, the synthesis of β^3 -amino acids from α -aryloxyacetaldehydes and aryl-aldehydederived imines by NHC catalysis has been reported by Scheidt and co-workers recently.^{11e} (Scheme 2.5)

Scheme 2.5 Synthesis β^3 -Amino acids with NHC catalysis.

Imines are versatile electrophiles that have been widely used in NHC catalysis.¹² However, to our best knowledge, almost all of those imines employed had aryl substituents adjacent to nitrogen. The use of formaldehyde-derived imines has never been achieved. Our attention was drawn to formaldehyde-derived imines, as products generated from these substrates can easily be converted to the synthetically useful β^2 -amino acids. Here we disclose an enantioselective NHC and (*in situ* generated) Brønsted acid cocatalyzed aminomethylation of α,β -unsaturated aldehydes (enals) to afford β^2 -amino esters (Figure 2.2). This approach is suitable for the practical synthesis of β^2 -amino acids with natural substituents through a one-pot procedure.

Figure 2.2 NHC and acid cooperative strategy synthesis of β^2 -amino acid.

N,O-acetal **2** is a useful building block that can *in situ* generate formaldehyde-derived iminium ion and methanol under Brønsted acid or Lewis acid catalysis.¹³ We envision that after deprotonation from NHC pre-catalyst, the catalytically generated conjugated acid from base is acidic enough to promote the generation of iminium ion as an electrophile and methanol as a nucleophile from *N,O*-acetals **2**. Concurrent addition of the free carbene onto enal **1** affords intermediate **I**, which can further turn to conjugated

Breslow intermediate **II** and tautomerize to homoenolate intermediate **III**. Protonation followed by deprotonation of homoenolate intermediate **III** provides NHC-bound ester enolate intermediate **V**, which then undergoes Mannich reaction, with the previously formed iminium ion to furnish intermediate **VI**. Finally, nucleophilic addition of methanol to intermediate **VI** releases the desired β^2 -amino ester product **3** and regenerates the NHC pre-catalyst (Scheme 2.6).

Scheme 2.6 Postulated catalytic cycles

2.2 Results and Discussion

Key results of our initial reaction optimization are summarized in Table 2.1. Enal **1a** and *N,O*-acetal **2** were chosen as the model substrates to test the feasibility of this proposed cooperative catalysis strategy. To our delight, when aminoindanol derived triazolium salt **A**¹⁴ was used as NHC pre-catalyst and NaOAc was used as base, the desired β^2 amino ester **3a** was isolated in 61% yield and 95:5 er (Table 2.1, entry 1). Replacing pre-catalyst **A** with triazolium salt **B**¹⁵ led to a decrease both in yield and enantioselectivity (Table 2.1, entry 2). Phenylalanine derived pre-catalyst **C**¹⁶ was also

proven to be less effective (Table 2.1, entry 3). Therefore, we chose triazolium salt **A** as the optimal pre-catalyst, and then screened a series of organic and inorganic bases. Strong organic base such as DBU was not suitable for our reaction, only affording the corresponding product in a trace amount. This is consistent with Bode's discovery (Table 2.1, entry 4).¹⁷

Table 2.1 Condition Optimization ^a

entry	NHC	base	yield (%) ^b	er ^c
1	A	NaOAc	61	95:5
2	B	NaOAc	46	91:9
3	C	NaOAc	45	86:14
4	A	DBU	trace	n.d.
5	A	DIPEA	76	95:5
6	A	Et ₃ N	77	95:5
7	A	DMAP	67	95:5
8	A	K ₂ CO ₃	50	95:5
9^d	A	Et₃N	76	95:5
10 ^{d,e}	A	Et ₃ N	41	95:5
11 ^d	A	-	trace	n.d.
12 ^d	A	3a^f	34	n.d.

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), NHC (0.02 mmol), base (0.02 mmol), DCM (1 mL), rt, 24 h. ^b

Isolated yield based on **2**. ^c Enantiomeric ratio of **3a**, determined *via* chiral phase HPLC analysis; absolute configuration of the major enantiomer was assigned by comparison of **3a** with literature (see Supporting Information). ^d This reaction was carried out at 40 °C. ^e 50 mg 4Å molecular sieve powder was added. ^f 0.02 mmol of **3a** was used as base.

A weaker organic base such as DIPEA, Et₃N or DMAP could promote this reaction smoothly. Using Et₃N obtained the best result, with 77% yield and 95:5 er (Table 2.1, entries 5-7). Inorganic base such as K₂CO₃ was also compatible with this reaction, albeit producing the product in a lower yield (Table 2.1, entry 8). Furthermore, raising the

temperature to 40 °C produced a cleaner reaction (Table 2.1, entry 9). On the other hand, adding molecular sieves to prevent the iminium ion from hydrolysis dramatically suppressed the reaction (Table 2.1, entry 10). We also tried to use *N,O*-acetal **2** or β^2 amino ester **3a** as base, but unfortunately the results were negative (Table 2.1, entries 11 and 12). This may be due to the lower basicity of benzyl substituted tertiary amine compared with triethylamine.

Scheme 2.7 Scope of Reactions^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), NHC **A** (0.02 mmol), Et₃N (0.02 mmol), DCM (1 mL), 40 °C, 24h. ^b 0.5 mmol of enal was used.

With the optimal reaction conditions in hand (Table 2.1, entry 9), we first established the generality of this NHC and Brønsted acid cocatalyzed reaction. As shown in Scheme

2.7, a broad range of enals that exhibit diverse electronic and steric properties were explored. The use of cinnamaldehyde **1a** afforded the desired product **3a** in 76% yield and 95:5 er. Enals with electron-donating substituents on their β -benzene ring, such as 4-Me and 4-OMe led to the corresponding products **3b** and **3c** in good yields and high enantioselectivities. The presence of electron-withdrawing groups (4-F, and 4-Cl) was also found to be compatible under the optimal conditions, providing products **3d** and **3e** in 66% yield, 96:4 er and 63% yield, 96:4 er, respectively. The position of the substituent on the β -benzene ring had little effect on the results as para- (4-Br), meta- (3-Br) and ortho- (2-Br) substituted cinnamaldehyde furnished the desired products **3f-h** in good yields and high enantiomeric ratios. Importantly, substrates bearing functional groups such as 4-NO₂ and 4-COOMe were well tolerated, which indicated that further transformations of those products to structurally more complex compounds were possible. It is worth noting that when 4-CHO substituted cinnamaldehyde was introduced, this reaction exclusively went through the enolate pathway, giving product **3k** in 66% yield and 96:4 er, no benzoin or aza-benzoin products were observed. Enals with sterically demanding substituents such as 1-naphthyl and 2-naphthyl were next tested, resulting in β^2 amino esters **3l** and **3m** in 76% yield, 95:5 er and 60% yield, 95:5 er, respectively. Heteroaryl substituted enals can also be readily accommodated, achieving the corresponding 2-furyl, 2-thienyl, and 3-pyridinyl substituted products **3n-p** in good yields and high enantioselectivities. β -Ester substituted β^2 -amino ester **3q**, which may have the potential to be further converted to the synthetically useful β -proline,¹⁸ was constructed as the result of introducing β -ester substituted enal to the reaction. β -Alkyl substituted enal also turned out to be a suitable substrate, forming product **3r** in an acceptable yield.

A major limitation of most synthetic approaches to β^2 -amino acids is the difficulty of introducing sensitive functional groups. Our method does not require strong acid or base

conditions, which should make this route well-suited for the synthesis of β^2 -amino esters bearing side-chain functionality. To validate the potential of our method, we next set out to synthesize β^2 -amino esters with natural substituents by employing *ent*-A as NHC pre-catalyst, as illustrated in Scheme 2.8. The use of β -aryl/heteroaryl substituted enals afforded β^2 -homophenylalanine, homotyrosine, and homotryptophan esters **4a-c** in good yields and high enantioselectivities. When β -alkyl substituted enals were used, the corresponding β^2 -homoleucine, homomethionine esters **4d** and **4e** were successfully obtained, albeit in moderate yields. Functionalities such as ester and amide on the β -carbon of enal were well tolerated, furnishing β^2 -homoaspartic acid, homoasparagine esters **4f** and **4g** in moderate yields and moderate to good enantioselectivities.

Scheme 2.8 Synthesis of β^2 -Amino Esters with Natural Substituents^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), NHC *ent*-A (0.02 mmol), Et_3N (0.02 mmol), DCM (1 mL), 40 °C, 24h. ^b 0.5 mmol of enal was used.

To demonstrate the utility of our protocol, we have converted the readily available β^2 -amino ester **3a** into *N*-Boc *ent*- β^2 -homophenylalanine **6** in gram scale (Scheme 2.9). It is worth noting that all the aminomethylation, debenzylation, and Boc protection steps could

be operated in a one-pot procedure, affording β^2 -amino ester **5** in 59% overall yield and 95:5 er, which is very appealing to large-scale synthesis, since no additional separation step is required. Simple hydrolysis of **5** finally provided *ent*- β^2 -homophenylalanine **6** in 94% yield.

Scheme 2.9 Synthesis of *N*-Boc β^2 -Homophenylalanine.

2.3 Conclusion

In summary, we have developed a NHC and Brønsted acid cocatalyzed aminomethylation of α,β -unsaturated aldehydes to afford β^2 -amino esters in good yields and high enantioselectivities. The catalytically generated conjugated acid from triethylamine not only plays the role of being the proton source to form enolate intermediate, but also assists the *in situ* generation of iminium ion (as electrophile) and methanol (as nucleophile). As the reaction condition is mild and the functional group tolerance is good, seven β^2 -amino esters with natural substituents were successfully synthesized using this protocol. These β^2 -amino esters can be easily converted to the corresponding *N*-Boc protected β^2 -amino acids in gram scale through simple deprotection and hydrolysis steps.

2.4 Experimental and Methods Section

Materials and Instrumentation

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker BBFO (400 MHz) spectrometer. Chemical shifts were recorded in parts per

million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker BBFO (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *er* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp. High pressure reactions were carried out in Paar-high pressure reactors (125 mL). Enals, which are not commercially available, were prepared following the literatures procedures.¹⁹ *N,O*-acetal was synthesized according to reported method.²⁰

General procedure for the catalytic synthesis of products 3 and 4:

Chiral NHC pre-catalyst **A** (0.02 mmol) was added to a 10 mL dry Schlenk reaction tube equipped with a magnetic stir bar. The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). CH_2Cl_2 (1.0 mL), Et_3N (0.02 mmol), enal **1** (0.2 mmol), and *N,O*-acetal **2** (0.1 mmol) were then added successively and the reaction mixture was allowed to stir for 24 hours at 40 °C. After completion of the reaction,

monitored by TLC, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography directly using hexane/EtOAc (most use 9/1) as eluent to afford the desired product **3**. When preparing product **4**, chiral NHC pre-catalyst *ent*-**A** was used.

Note: The racemic catalyst that was used for the preparation of the corresponding racemic products for HPLC analysis was synthesized by mixing chiral pre-catalyst **A** and *ent*-**A** in a 1:1 ratio.

One-pot procedure for the gram scale synthesis of **5**²⁰:

Chiral NHC pre-catalyst **A** (2 mmol, 838.4 mg) was added to a 250 mL dry round bottom flask equipped with a magnetic stir bar. The flask was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). CH_2Cl_2 (100 mL), Et_3N (2 mmol, 202.4 mg, 281 μL), cinnamaldehyde **1a** (15 mmol, 1.98 g, 1.88 mL), and *N,O*-acetal **2** (10 mmol, 2.41 g) were then added successively and the reaction mixture was allowed to stir for 24 hours at $40\text{ }^\circ\text{C}$. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to afford the crude product **3a**, which was used directly for the next step.

To a Parr's high pressure reactor equipped with a magnetic stir bar, the above crude product **3a** (~ 10 mmol), wet 5% Pd/C (5.09 g, which can be recycled and reused after filtration), and MeOH (30 mL) were added. The reactor was filled with H_2 to reach a pressure of 9.6 atm and stirred at room temperature for 24 hours. The reaction mixture was then passed through a short pad of celite, and then washed with MeOH extensively.

The filtrate was concentrated under reduced pressure to afford crude free amine **8**, which was used directly for the next step.

To a 250 mL dry round bottom flask equipped with a magnetic stir bar, the above crude free amine **8** (~ 10 mmol), CH₂Cl₂ (100 mL), DIPEA (10 mmol, 1.29 g, 1.74 mL) and (Boc)₂O (15 mmol, 3.27 g, 3.45 mL) were added. The reaction mixture was then stirred at room temperature for 24 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography directly using hexane/EtOAc = 4/1 as eluent to afford the desired product **5** (1.74 g, 5.93 mmol, 59% overall yield for three steps).

Transformation of **5 to **6**²¹:**

To a 250 mL round bottom flask equipped with a magnetic stir bar, the above β^2 -amino ester **5** (1.74 g, 5.93 mmol), THF (100 mL), H₂O (18 mL) and LiOH•H₂O (8.9 mmol, 374 mg) were added. The reaction mixture was then stirred at room temperature for 24 hours. After completion of the reaction, the reaction mixture was acidified to pH 3 with 1N HCl aqueous solution and extracted with CH₂Cl₂ (3 × 100 mL), the combined CH₂Cl₂ layers were washed with brine and dried over Na₂SO₄. After evaporation of the solvent, the reaction residue was subjected to column chromatography directly using hexane/EtOAc = 2/1 as eluent to afford the pure product **6** (1.56 g, 5.57 mmol, 94% yield).

Transformation of 6 to 7²⁵:

To a solution of (*S*)-**6** (28 mg, 0.1 mmol) in DMF (0.5 mL) HOBT (20 mg, 0.15 mmol) and EDCI (29 mg, 0.15 mmol) were added under a nitrogen atmosphere. The mixture was stirred for 10 minutes at room temperature and cooled down to 0 °C. (*R*)-1-phenylethylamine (15 μ L, 0.12 mmol) and Et₃N (55 μ L) were then added. The mixture was stirred for 20 hours at room temperature, diluted with DCM (10 mL), washed with 1N HCl aqueous solution (4 $\times$ 10mL), neutralized with NaHCO₃ saturated solution, dried over Na₂SO₄ and finally evaporated under reduced pressure to give crude (*S,R*)-**7** as a white solid (29 mg, 76% yield). From crude NMR, compared with reference 7, the dr value of (*S,R*)-**7** is approximately 16:1, so the er value of (*S*)-**6** is approximately 94:6.

Determination of absolute configuration:

$[\alpha]^{21}_D = +22.6$ ($c = 1.0$, CHCl₃)
lit⁴: $[\alpha]^{25}_D = +22.7$ ($c = 1.1$, CHCl₃)

$[\alpha]^{21}_D = -21.7$ ($c = 1.0$, CHCl₃)

$[\alpha]^{21}_D = -0.9$ ($c = 1.0$, CHCl₃)
lit⁵: $[\alpha]^{22}_D = -1$ ($c = 1.09$, CHCl₃)
lit⁶: *R*-isomer, $[\alpha]^{22}_D = +0.9$ ($c = 1.11$, CHCl₃)

$[\alpha]^{21}_D = -14.4$ ($c = 0.5$, CHCl₃)
lit⁷: *R*-isomer, $[\alpha]^{27}_D = +12.0$ ($c = 0.5$, CHCl₃)

2.5 Characterization of Products.

(S)-Methyl 2-benzyl-3-(dibenzylamino)propanoate (3a): 28.4 mg, 76% yield. ^1H NMR

(400 MHz, CDCl_3) δ 7.32-7.15 (m, 13H), 7.06 (d, $J = 7.2$ Hz, 2H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.55 (s, 3H), 3.43 (d, $J = 13.2$ Hz, 2H), 3.02-2.95 (m, 1H), 2.82 (dd, $J_1 = 12.4$ Hz, $J_2 = 8.8$ Hz, 1H), 2.76 (d, $J = 7.2$ Hz, 2H), 2.51 (dd, $J_1 = 12.4$ Hz, $J_2 = 5.6$ Hz, 1H); ^{13}C NMR

(100 MHz, CDCl_3) δ 174.9, 139.2, 139.0, 129.0, 128.7, 128.4, 128.1, 126.9, 126.3, 58.4, 55.9, 51.4, 46.9, 36.4; IR ν_{max} (neat, cm^{-1}): 2800, 1738, 1452, 1163, 750, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_2\text{H}^+$ 374.2120, found 374.2114. $[\alpha]_D^{21} = +22.6$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: i -PrOH/hexane = 2:98; retention times: 13.9 min (major), 16.3 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(4-methylbenzyl)propanoate (3b): 27.9 mg, 72%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.22 (m, 10H), 7.03 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 8.0$ Hz, 2H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.56 (s, 3H), 3.42 (d, $J = 13.6$ Hz, 2H), 3.00-2.93 (m, 1H), 2.81 (dd, $J_1 = 12.8$ Hz, $J_2 = 9.2$ Hz, 1H), 2.71

(d, $J = 7.6$ Hz, 2H), 2.51 (dd, $J_1 = 12.8$ Hz, $J_2 = 6.0$ Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.0, 139.1, 136.1, 135.7, 129.1, 129.0, 128.5, 128.1, 126.9, 58.4, 55.8, 51.4, 46.9, 36.0, 21.0; IR ν_{max} (neat, cm^{-1}): 2800, 1732, 1452, 1161, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{29}\text{NO}_2\text{H}^+$ 388.2277, found 388.2278. $[\alpha]_D^{21} = +21.4$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: i -PrOH/hexane = 2:98; retention times: 14.5 min (major), 18.8 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(4-methoxybenzyl)propanoate (3c): 27.8 mg, 69% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.21 (m, 10H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 3.77 (s, 3H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.56 (s, 3H), 3.42 (d, $J = 13.6$ Hz,

2H), 2.98-2.91 (m, 1H), 2.81 (dd, $J_1 = 12.4$ Hz, $J_2 = 8.8$ Hz, 1H), 2.70 (d, $J = 7.6$ Hz, 2H),

2.51 (dd, $J_1 = 12.8$ Hz, $J_2 = 5.6$ Hz, 1H); ^{13}C NMR (100

MHz, CDCl_3) δ 175.0, 158.1, 139.1, 131.2, 129.6, 128.9,

128.1, 126.9, 113.8, 58.4, 55.8, 55.2, 51.4, 47.0, 35.7; IR

ν_{max} (neat, cm^{-1}): 2801, 1732, 1512, 1248, 754, 698; HRMS

(ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{29}\text{NO}_3\text{H}^+$ 404.2226, found 404.2229. $[\alpha]_{\text{D}}^{21} = +14.8$ ($c = 1.0$ in

CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system:

i -PrOH/hexane = 2:98; retention times: 16.0 min (minor), 17.2 min (major)].

(S)-Methyl 3-(dibenzylamino)-2-(4-fluorobenzyl)propanoate (3d): 25.8 mg, 66% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.23 (m, 10H), 7.01-6.98 (m,

2H), 6.90 (t, $J = 8.8$ Hz, 2H), 3.64 (d, $J = 13.6$ Hz, 2H), 3.55 (s,

3H), 3.45 (d, $J = 13.2$ Hz, 2H), 2.96-2.89 (m, 1H), 2.80 (dd, $J_1 =$

12.4 Hz, $J_2 = 8.8$ Hz, 1H), 2.74-2.67 (m, 2H), 2.51 (dd, $J_1 = 12.4$

Hz, $J_2 = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 161.5 ($J_{\text{C-F}} = 242$ Hz), 139.0,

134.8 ($J_{\text{C-F}} = 3$ Hz), 130.0 ($J_{\text{C-F}} = 8$ Hz), 128.9, 128.2, 127.0, 115.1 ($J_{\text{C-F}} = 21$ Hz), 58.6,

55.8, 51.4, 47.0, 35.5; IR ν_{max} (neat, cm^{-1}): 2803, 1732, 1510, 1228, 754, 698; HRMS

(ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{26}\text{FNO}_2\text{H}^+$ 392.2026, found 392.2028. $[\alpha]_{\text{D}}^{21} = +12.7$ ($c = 1.0$

in CHCl_3); HPLC analysis: 96:4 er, [CHIRALPAK IC column; 0.5 mL/min; solvent

system: i -PrOH/hexane = 2:98; retention times: 12.2 min (major), 14.2 min (minor)].

(S)-Methyl 2-(4-chlorobenzyl)-3-(dibenzylamino)propanoate (3e): 25.7 mg, 63% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.31-7.24 (m, 10H), 7.18 (d, $J =$

8.4 Hz, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 3.63 (d, $J = 13.6$ Hz, 2H),

3.56 (s, 3H), 3.45 (d, $J = 13.6$ Hz, 2H), 2.95-2.88 (m, 1H), 2.80

(dd, $J_1 = 12.4$ Hz, $J_2 = 8.4$ Hz, 1H), 2.75-2.67 (m, 2H), 2.51 (dd,

$J_1 = 12.4$ Hz, $J_2 = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 139.0, 137.7, 132.1,

130.0, 128.9, 128.5, 128.2, 127.0, 58.6, 55.8, 51.4, 46.8, 35.7; IR $\nu_{\max}$ (neat, cm^{-1}): 2801, 1732, 1492, 1161, 752, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{26}\text{ClNO}_2\text{H}^+$ 408.1730, found 408.1729. $[\alpha]_D^{21} = +10.8$ ($c = 1.0$ in CHCl_3); HPLC analysis: 96:4 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 12.5 min (minor), 13.3 min (major)].

(S)-Methyl 2-(4-bromobenzyl)-3-(dibenzylamino)propanoate (3f): 33.9 mg, 75% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.35-7.24 (m, 12H), 6.91 (d, $J = 8.0$ Hz, 2H), 3.64 (d, $J = 13.6$ Hz, 2H), 3.56 (s, 3H), 3.45 (d, $J = 13.6$ Hz, 2H), 2.95-2.88 (m, 1H), 2.80 (dd, $J_1 = 12.8$ Hz, $J_2 = 8.8$ Hz, 1H), 2.75-2.65 (m, 2H), 2.51 (dd, $J_1 = 12.8$ Hz, $J_2 = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 139.0, 138.2, 131.4, 130.5, 128.9, 128.2, 127.0, 120.1, 58.6, 55.8, 51.5, 46.7, 35.7; IR $\nu_{\max}$ (neat, cm^{-1}): 2801, 1732, 1489, 1161, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{26}\text{BrNO}_2\text{H}^+$ 452.1225, found 452.1221. $[\alpha]_D^{21} = +8.5$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 12.9 min (minor), 14.0 min (major)].

(S)-Methyl 2-(3-bromobenzyl)-3-(dibenzylamino)propanoate (3g): 32.5 mg, 72%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.21 (m, 12H), 7.09 (t, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 3.65 (d, $J = 13.6$ Hz, 2H), 3.57 (s, 3H), 3.46 (d, $J = 13.2$ Hz, 2H), 2.95-2.88 (m, 1H), 2.81 (dd, $J_1 = 12.4$ Hz, $J_2 = 8.8$ Hz, 1H), 2.76-2.66 (m, 2H), 2.51 (dd, $J_1 = 12.4$ Hz, $J_2 = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 141.6, 139.0, 131.8, 129.9, 129.4, 128.9, 128.2, 127.3, 127.0, 122.4, 58.6, 55.9, 51.5, 46.7, 36.0; IR $\nu_{\max}$ (neat, cm^{-1}): 2801, 1738, 1450, 1161, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{26}\text{BrNO}_2\text{H}^+$ 452.1225, found 452.1228. $[\alpha]_D^{21} = +21.4$ ($c = 1.0$ in CHCl_3); HPLC

analysis: 97:3 er, [CHIRALPAK OJ-H column; 1.0 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 15.7 min (major), 30.4 min (minor)].

(S)-Methyl 2-(2-bromobenzyl)-3-(dibenzylamino)propanoate (3h): 36.6 mg, 81%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 8.0$ Hz, 1H), 7.31-7.21 (m, 10H), 7.16 (t, $J = 8.0$ Hz, 1H), 7.08-7.03 (m, 2H), 3.65 (d, $J = 13.6$ Hz, 2H), 3.55 (s, 3H), 3.50 (d, $J = 13.2$ Hz, 2H), 3.22-3.15 (m, 1H), 3.01 (dd, $J_1 = 13.6$ Hz, $J_2 = 4.8$ Hz, 1H), 2.88-2.74 (m, 2H),

2.56 (dd, $J_1 = 12.8$ Hz, $J_2 = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 138.9, 138.5, 132.9, 130.9, 129.0, 128.2, 128.1, 127.3, 126.9, 124.5, 58.3, 55.9, 51.4, 46.7, 36.8; IR ν_{max} (neat, cm^{-1}): 2801, 1732, 1450, 1163, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{26}\text{BrNO}_2\text{H}^+$ 452.1225, found 452.1220. $[\alpha]_{\text{D}}^{21} = +6.0$ ($c = 1.0$ in CHCl_3); HPLC analysis: 97:3 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 12.8 min (major), 14.1 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(4-nitrobenzyl)propanoate (3i): 23.0 mg, 55% yield.

^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, $J = 8.8$ Hz, 2H), 7.32-7.25 (m, 10H), 7.17 (d, $J = 8.8$ Hz, 2H), 3.63 (d, $J = 13.2$ Hz, 2H), 3.56 (s, 3H), 3.52 (d, $J = 13.6$ Hz, 2H), 2.96-2.88 (m, 2H), 2.85-2.78 (m, 2H), 2.56 (dd, $J_1 = 12.8$ Hz, $J_2 = 6.4$ Hz,

1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 147.2, 146.6, 138.9, 129.5, 128.9, 128.3, 127.1, 123.6, 58.9, 55.9, 51.6, 46.4, 35.9; IR ν_{max} (neat, cm^{-1}): 2851, 1732, 1520, 1346, 750, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_4\text{H}^+$ 419.1971, found 419.1970. $[\alpha]_{\text{D}}^{21} = +8.4$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 54.8 min (major), 64.1 min (minor)].

(S)-Methyl 4-(2-(((dibenzylamino)methyl)-3-methoxy-3-oxopropyl)benzoate (3j): 31.5

mg, 73% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 8.4 Hz, 2H), 7.33-7.22 (m, 10H), 7.11 (d, J = 8.4 Hz, 2H), 3.89 (s, 3H), 3.64 (d, J = 13.6 Hz, 2H), 3.55 (s, 3H), 3.46 (d, J = 13.6 Hz, 2H), 3.00-2.92 (m, 1H), 2.86-2.75 (m, 3H), 2.53 (dd, J_1 = 12.4 Hz, J_2 = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 167.0, 144.7, 139.0, 129.7, 128.9, 128.7, 128.3, 128.2, 127.0, 58.7, 55.9, 52.0, 51.5, 46.6, 36.3; IR ν_{max} (neat, cm^{-1}): 2847, 1720, 1435, 1281, 754, 700; HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{29}\text{NO}_4\text{H}^+$ 432.2175, found 432.2172. $[\alpha]_D^{21}$ = +18.2 (c = 1.0 in CHCl_3); HPLC analysis: 96:4 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 33.2 min (minor), 44.6 min (major)].

(S)-Methyl 3-(dibenzylamino)-2-(4-formylbenzyl)propanoate (3k): 26.5 mg, 66%

yield. ^1H NMR (400 MHz, CDCl_3) δ 9.95 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.31-7.24 (m, 10H), 7.19 (d, J = 8.0 Hz, 2H), 3.64 (d, J = 13.6 Hz, 2H), 3.55 (s, 3H), 3.48 (d, J = 13.6 Hz, 2H), 2.99-2.93 (m, 1H), 2.90-2.77 (m, 3H), 2.55 (dd, J_1 = 12.8 Hz, J_2 = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.9, 174.4, 146.6, 138.9, 134.8, 129.9, 129.4, 128.9, 128.2, 127.1, 58.7, 55.9, 51.5, 46.5, 36.4; IR ν_{max} (neat, cm^{-1}): 2801, 1734, 1701, 1607, 1215, 754, 700; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_3\text{H}^+$ 402.2069, found 402.2063. $[\alpha]_D^{21}$ = +10.9 (c = 1.0 in CHCl_3); HPLC analysis: 96:4 er, [CHIRALPAK IC column; 1.0 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 22.0 min (major), 25.2 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(naphthalen-1-ylmethyl)propanoate (3l): 32.2 mg, 76%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.96-7.94 (m, 1H), 7.84-7.82 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.46-7.44 (m, 2H), 7.34-7.20 (m, 12H), 3.62 (d, J = 13.6 Hz, 2H), 3.53 (s,

3H), 3.51 (d, $J = 13.6$ Hz, 2H), 3.28-3.24 (m, 1H), 3.18-3.14 (m, 2H), 2.94-2.89 (m, 1H),

2.63 (dd, $J_1 = 12.4$ Hz, $J_2 = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 138.9, 135.2, 133.9, 131.7, 128.9, 128.8, 128.2, 127.2, 127.0, 126.7, 126.0, 125.5, 125.4, 123.5, 58.5, 56.2, 51.4, 45.8, 33.6; IR ν_{max} (neat, cm^{-1}): 2800, 1734, 1443,

1158, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{29}\text{NO}_2\text{H}^+$ 424.2277, found 424.2271.

$[\alpha]_D^{21} = +27.2$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 19.0 min (major), 22.7 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(naphthalen-2-ylmethyl)propanoate (3m): 25.4 mg,

60% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.79-7.77 (m, 1H), 7.74-7.71 (m, 2H), 7.51 (s, 1H), 7.44-7.41 (m, 2H), 7.29-7.19 (m, 11H), 3.67 (d, $J = 13.6$ Hz, 2H), 3.55 (s, 3H), 3.44 (d, $J = 13.6$ Hz, 2H), 3.12-3.05 (m, 1H), 2.92 (d, $J = 7.2$ Hz, 2H), 2.86

(dd, $J_1 = 12.8$ Hz, $J_2 = 9.2$ Hz, 1H), 2.56 (dd, $J_1 = 12.4$ Hz, $J_2 = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 139.1, 136.7, 133.5, 132.2, 129.0, 128.2, 128.0, 127.6, 127.5, 127.2, 127.1, 127.0, 125.9, 125.4, 58.5, 56.0, 51.4, 46.8, 36.6; IR ν_{max} (neat, cm^{-1}): 2800, 1734, 1442, 1158, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{29}\text{NO}_2\text{H}^+$ 424.2277, found 424.2280. $[\alpha]_D^{21} = +22.1$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 22.0 min (major), 29.5 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(furan-2-ylmethyl)propanoate (3n): 25.1 mg, 69% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.22 (m, 11H), 6.23-6.22 (m, 1H), 5.92-5.91 (m, 1H), 3.65 (d, $J = 13.6$ Hz, 2H), 3.62 (s, 3H), 3.45 (d, $J = 13.6$ Hz, 2H), 3.11-3.04 (m, 1H), 2.82-2.76 (m, 3H), 2.52 (dd, $J_1 = 12.4$ Hz, $J_2 = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3)

δ 174.6, 153.0, 141.2, 139.0, 129.0, 128.2, 127.0, 110.1, 106.1, 58.4, 55.5, 51.6, 43.9,

28.7; IR $\nu_{\max}$ (neat, cm^{-1}): 2801, 1734, 1450, 1159, 750, 698;

HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_3\text{H}^+$ 364.1913, found

364.1911. $[\alpha]_{\text{D}}^{21} = +15.9$ ($c = 1.0$ in CHCl_3); HPLC analysis:

94:6 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system:

i -PrOH/hexane = 2:98; retention times: 14.9 min (major), 17.2 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(thiophen-2-ylmethyl)propanoate (3o): 24.3 mg, 64%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.22 (m, 10H), 7.10-7.09

(m, 1H), 6.87-6.85 (m, 1H), 6.69-6.68 (m, 1H), 3.66 (d, $J = 13.6$ Hz,

2H), 3.60 (s, 3H), 3.46 (d, $J = 13.6$ Hz, 2H), 3.00 (s, 3H), 2.83-2.77

(m, 1H), 2.58-2.54 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5,

141.5, 139.0, 129.0, 128.2, 127.0, 126.8, 125.4, 123.7, 58.5, 55.6, 51.6, 47.2, 30.3; IR $\nu_{\max}$

(neat, cm^{-1}): 2801, 1736, 1450, 1169, 750, 698; HRMS (ESI, m/z): calcd. for

$\text{C}_{23}\text{H}_{25}\text{NO}_2\text{SH}^+$ 380.1684, found 380.1685. $[\alpha]_{\text{D}}^{21} = +15.3$ ($c = 1.0$ in CHCl_3); HPLC

analysis: 96:4 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: i -PrOH/hexane

= 2:98; retention times: 17.3 min (major), 20.8 min (minor)].

(S)-Methyl 3-(dibenzylamino)-2-(pyridin-3-ylmethyl)propanoate (3p): 25.1 mg, 67%

yield. ^1H NMR (400 MHz, CDCl_3) δ 8.43-8.42 (m, 1H), 8.32 (s,

1H), 7.35-7.22 (m, 11H), 7.16-7.13 (m, 1H), 3.65 (d, $J = 13.6$ Hz,

2H), 3.56 (s, 3H), 3.49 (d, $J = 13.2$ Hz, 2H), 2.94-2.88 (m, 1H),

2.85-2.68 (m, 3H), 2.55 (dd, $J_1 = 12.4$ Hz, $J_2 = 6.4$ Hz, 1H); ^{13}C

NMR (100 MHz, CDCl_3) δ 174.3, 150.1, 147.8, 138.9, 136.1, 134.7, 128.9, 128.2, 127.1,

123.3, 58.7, 55.9, 51.5, 46.6, 33.4; IR $\nu_{\max}$ (neat, cm^{-1}): 2803, 1734, 1450, 1161, 750, 700;

HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_2\text{H}^+$ 375.2073, found 375.2067. $[\alpha]_{\text{D}}^{21} = +12.7$ (c

= 1.0 in CHCl_3); HPLC analysis: 93:7 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 10:90; retention times: 21.1 min (major), 29.1 min (minor)].

(S)-4-Ethyl 1-methyl 2-((dibenzylamino)methyl)succinate (3q): 19.6 mg, 53% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.33-7.20 (m, 10H), 4.08 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 3.59 (d, J = 13.6 Hz, 2H), 3.52 (d, J = 13.2 Hz, 2H), 3.17-3.10 (m, 1H), 2.72 (dd, J_1 = 12.4 Hz, J_2 = 6.8 Hz, 1H), 2.62-2.51 (m, 3H), 1.62 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 172.0, 138.8, 128.9, 128.2, 127.0, 60.6, 58.4, 54.9, 51.8, 40.3, 34.3, 14.1; IR ν_{max} (neat, cm^{-1}): 2800, 1730, 1630, 1167, 752, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_4\text{H}^+$ 370.2018, found 370.2012. $[\alpha]_D^{21}$ = -3.1 (c = 1.0 in CHCl_3); HPLC analysis: 91:9 er, [CHIRALPAK ODH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 19.5 min (major), 23.4 min (minor)].

(S)-Methyl 2-((dibenzylamino)methyl)hexanoate (3r): 12.6 mg, 37% yield. ^1H NMR

(400 MHz, CDCl_3) δ 7.30-7.21 (m, 10H), 3.68 (d, J = 13.6 Hz, 2H), 3.63 (s, 3H), 3.39 (d, J = 13.6 Hz, 2H), 2.79-2.66 (m, 2H), 2.43 (dd, J_1 = 12.0 Hz, J_2 = 4.8 Hz, 1H), 1.45-1.11 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.8, 139.2, 128.9, 128.1, 126.9, 58.4, 56.2, 51.3, 44.8, 30.1, 29.5, 22.6, 13.9; IR ν_{max} (neat, cm^{-1}): 2799, 1728, 1452, 1217, 754, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}_2\text{H}^+$ 340.2277, found 340.2273. $[\alpha]_D^{21}$ = +17.2 (c = 1.0 in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK OJH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 11.1 min (major), 14.4 min (minor)].

(R)-Methyl 2-benzyl-3-(dibenzylamino)propanoate (4a): 27.6 mg, 74% yield. ^1H NMR

(400 MHz, CDCl_3) δ 7.30-7.17 (m, 13H), 7.06 (d, $J = 6.8$ Hz, 2H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.55 (s, 3H), 3.43 (d, $J = 13.6$ Hz, 2H), 3.02-2.95 (m, 1H), 2.82 (dd, $J_1 = 12.8$ Hz, $J_2 = 9.2$ Hz, 1H), 2.76 (d,

$J = 7.6$ Hz, 2H), 2.51 (dd, $J_1 = 12.8$ Hz, $J_2 = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 139.2, 139.0, 129.0, 128.7, 128.4, 128.1, 126.9, 126.3, 58.4, 55.9, 51.4, 46.9, 36.4; IR ν_{max} (neat, cm^{-1}): 2801, 1732, 1452, 1163, 746, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_2\text{H}^+$ 374.2120, found 374.2119. $[\alpha]_D^{21} = -21.7$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 13.8 min (minor), 16.2 min (major)].

(R)-Methyl 3-(dibenzylamino)-2-(4-(methoxymethoxy) benzyl)propanoate (4b): 27.7

mg, 64% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.23 (m, 10H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 5.13 (s, 2H), 3.66 (d, $J = 13.6$ Hz, 2H), 3.56 (s, 3H), 3.46 (s,

3H), 3.42 (d, $J = 13.2$ Hz, 2H), 2.96-2.91 (m, 1H), 2.80 (dd, $J_1 = 12.8$ Hz, $J_2 = 9.2$ Hz, 1H), 2.70 (d, $J = 7.2$ Hz, 2H), 2.50 (dd, $J_1 = 12.4$ Hz, $J_2 = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 155.7, 139.1, 132.6, 129.7, 129.0, 128.1, 126.9, 116.2, 94.5, 58.5, 55.9, 55.8, 51.4, 47.0, 35.6; IR ν_{max} (neat, cm^{-1}): 2801, 1734, 1510, 1152, 750, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{31}\text{NO}_4\text{H}^+$ 434.2331, found 434.2330. $[\alpha]_D^{21} = -2.9$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 26.0 min (minor), 27.8 min (major)].

(R)-tert-Butyl 3-(2-(((dibenzylamino)methyl)-3-methoxy-3-oxopropyl)-1H-indole-1-

carboxylate (4c): 33.3 mg, 65% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.11 (br, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.31-7.19 (m, 13H), 3.67 (d, $J = 13.6$ Hz, 2H), 3.59 (s, 3H), 3.46 (d, $J = 13.6$

Hz, 2H), 3.13-3.06 (m, 1H), 2.91-2.79 (m, 3H), 2.60 (dd, $J_1 = 12.4$ Hz, $J_2 = 5.6$ Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.2, 149.7, 139.0, 135.5, 130.4, 129.0, 128.2, 127.0, 124.3, 123.2, 122.4, 118.8, 118.1, 115.2, 83.4, 58.5, 56.1, 51.6, 44.9, 28.2, 25.8; IR ν_{max} (neat, cm^{-1}): 2801, 1730, 1452, 1159, 748, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_4\text{H}^+$ 513.2753, found 513.2748. $[\alpha]_{\text{D}}^{21} = -11.0$ ($c = 1.0$ in CHCl_3); HPLC analysis: 90:10 er, [CHIRALPAK ODH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 13.3 min (major), 14.3 min (minor)].

(R)-Methyl 2-(((dibenzylamino)methyl)-4-methylpentanoate (4d): 15.3 mg, 45% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.21 (m, 10H), 3.71 (d, $J = 13.6$ Hz, 2H), 3.63 (s, 3H), 3.37 (d, $J = 13.2$ Hz, 2H), 2.82-2.73 (m, 2H), 2.42-2.35 (m, 1H), 1.50-1.39 (m, 2H), 1.22-1.15 (m, 1H), 0.85 (d, $J =$

6.4 Hz 3H), 0.82 (d, $J = 6.4$ Hz 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.9, 139.2, 128.9, 128.1, 126.9, 58.4, 56.9, 51.3, 42.9, 39.6, 26.3, 23.0, 22.0; IR ν_{max} (neat, cm^{-1}): 2802, 1728, 1450, 1215, 756, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{22}\text{H}_{29}\text{NO}_2\text{H}^+$ 340.2277, found 340.2282. $[\alpha]_{\text{D}}^{21} = -20.0$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK OJH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 9.3 min (minor), 11.1 min (major)].

(R)-Methyl 2-(((dibenzylamino)methyl)-4-(methylthio)butanoate (4e): 14.7 mg, 41%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.22 (m, 10H), 3.65 (s, 3H), 3.63 (d, $J = 13.6$ Hz, 2H), 3.46 (d, $J = 13.6$ Hz, 2H), 2.89-2.82

(m, 1H), 2.75 (dd, $J_1 = 12.8$ Hz, $J_2 = 8.8$ Hz, 1H), 2.48 (dd, $J_1 = 12.4$ Hz, $J_2 = 6.0$ Hz, 1H), 2.38-2.33 (m, 2H), 2.04 (s, 3H), 1.85-1.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.0, 139.0, 128.9, 128.2, 127.0, 58.4, 55.7, 51.5, 43.6, 31.8, 29.5, 15.4; IR ν_{max} (neat, cm^{-1}): 2801, 1732, 1450, 1261, 752, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{27}\text{SNO}_2\text{H}^+$ 358.1841, found 358.1834. $[\alpha]^{21}_{\text{D}} = -6.9$ ($c = 1.0$ in CHCl_3); HPLC analysis: 92:8 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 17.9 min (major), 19.7 min (minor)].

(R)-4-Benzyl 1-methyl 2-((dibenzylamino)methyl)succinate (4f): 22.0 mg, 51% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.35-7.21 (m, 15H), 5.10-5.03 (m, 2H), 3.60 (s, 3H), 3.58 (d, $J = 14.4$ Hz, 2H), 3.50 (d, $J = 13.6$ Hz, 2H), 3.19-3.10 (m, 1H), 2.72 (dd, $J_1 = 12.8$ Hz, $J_2 = 7.2$ Hz, 1H), 2.67-2.57 (m, 2H), 2.53 (dd, $J_1 = 12.4$ Hz, $J_2 = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 171.8, 138.8, 135.8, 129.0, 128.9, 128.5, 128.2, 128.1, 127.0, 66.4, 58.4, 54.9, 51.8, 40.3, 34.2; IR ν_{max} (neat, cm^{-1}): 2800, 1736, 1452, 1263, 754, 700; HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{29}\text{NO}_4\text{H}^+$ 432.2175, found 432.2169. $[\alpha]^{21}_{\text{D}} = +11.0$ ($c = 1.0$ in CHCl_3); HPLC analysis: 92:8 er, [CHIRALPAK ODH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 43.5 min (major), 49.8 min (minor)].

(R)-Methyl 4-amino-2-((dibenzylamino)methyl)-4-oxobutanoate (4g): 20.1 mg, 59%

yield. ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.24 (m, 10H), 5.43 (br, 1H), 5.30 (br, 1H), 3.68 (s, 3H), 3.59 (d, $J = 13.6$ Hz, 2H), 3.53 (d, $J = 13.6$ Hz, 2H), 3.25-3.18 (m, 1H), 2.73 (dd, $J_1 = 12.8$ Hz, $J_2 = 7.2$ Hz, 1H), 2.53 (dd, $J_1 = 12.4$ Hz, $J_2 = 8.0$ Hz, 1H), 2.48-2.36 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 173.3, 138.9, 129.0, 128.2, 127.1, 58.4, 55.2, 51.9, 40.6, 35.6; IR ν_{max} (neat, cm^{-1}): 2800, 1730, 1682, 1450, 1074, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3\text{H}^+$ 341.1865, found 341.1859. $[\alpha]^{21}_{\text{D}} = -1.5$ ($c = 1.0$ in CHCl_3); HPLC

analysis: 20:80 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 50:50; retention times: 24.6 min (minor), 30.8 min (major)].

(S)-Methyl 2-benzyl-3-((tert-butoxycarbonyl)amino)propanoate (5): 1.74 g, 59%

overall yield for three steps. ^1H NMR (400 MHz, CDCl_3) δ 7.29-

7.14 (m, 5H), 4.88 (br, 1H), 3.64 (s, 3H), 3.39-3.25 (m, 2H), 2.99-

2.80 (m, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6,

155.7, 138.3, 128.8, 128.5, 126.5, 79.3, 51.7, 47.3, 41.5, 35.8, 28.3; IR ν_{max} (neat, cm^{-1}):

2978, 1717, 1499, 1167, 754, 700; HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_4\text{H}^+$ 294.1705,

found 294.1710. $[\alpha]_D^{21} = -0.9$ ($c = 1.0$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK

ODH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 13.9

min (major), 15.0 min (minor)].

(S)-2-Benzyl-3-((tert-butoxycarbonyl)amino)propanoic acid (6): 1.56 g, 94% yield. ^1H

NMR (400 MHz, CDCl_3) δ 9.10 (br, 1H), 7.30-7.18 (m, 5H), 6.65 &

4.99 (br, 1H), 3.38-2.63 (m, 5H), 1.42 & 1.38 (s, 9H); ^{13}C NMR (100

MHz, CDCl_3) δ 179.1 & 178.0, 157.9 & 155.9, 138.2, 128.9, 128.5,

126.6, 81.1 & 79.7, 47.5 & 47.1, 42.0 & 41.3, 35.9 & 35.7, 28.3 & 28.2; IR ν_{max} (neat,

cm^{-1}): 2928, 1713, 1368, 1167, 737, 700; HRMS (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{H}^+$

280.1549, found 280.1555. $[\alpha]_D^{21} = -14.4$ ($c = 0.5$ in CHCl_3).

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Chapter 3

N-Heterocyclic Carbene and in-situ Generated Brønsted Acid Co-catalyzed Formal Diels–Alder Reaction

3.1 Introduction

Ortho-quinone methide (*o*-QM) is an extremely reactive intermediate, which was generated through the temporary destruction of a stable phenolic aromatic system.¹ The structure is similar to *o*-quinones, however one of the carbonyl oxygen atoms is replaced by a methylene unit and thus *o*-QMs are much more polarized and reactive. Moreover, the strong thermodynamic process that drives the *o*-QMs to undergo rearomatization also accounts for their high reactivity. Therefore, simple *o*-QMs are not stable enough to be isolated under normal circumstances; they can react quickly with nucleophiles or undergo dimerization among other reactions.² Its widespread application in biological processes and demonstration of phenomenal successes in various natural product syntheses constantly builds a rapport for the significance of *o*-QM.² Indeed, the defined reaction patterns of *o*-QM, combined with chiral auxiliaries or catalysts, has provided solutions to many challenging syntheses of asymmetric chroman-cored structures; the core of many natural products and synthetic analogs that play important roles in lipophilic antioxidation, vasodilation, HIV transcriptase suppression, immunomodulation and especially antineoplastic action³.

In the past, *o*-QM was treated as an extremely unstable species that reacts unselectively and decomposes easily, likely due to the harsh conditions applied to generate *o*-QM. Only until recently, Schneider and Rueping group reported activating an *o*-hydroxybenzhydryl alcohol with chiral phosphoric acid (CPA) to facilitate the cleavage of a hydroxyl for the generation of *o*-QM in mild reaction conditions (Figure 3.1a).⁴ Shortly after, Sun and co-workers also utilized similar reaction conditions to generate β,β -disubstituted *o*-QM for nucleophilic addition (Figure 3.1a).⁵ Alternatively, generation of *o*-QM under basic conditions has also been demonstrated by Scheidt group with chiral *N*-heterocyclic carbene catalysis (Figure 3.1b).⁶ They subjected *o*-

silylbenzhydryl bromide with a fluoride source to generate a phenolate-type intermediate and through the release of a bromide ion, *o*-QM was generated as an intermediate for a [3+4] annulation.

In NHC organocatalysis,⁷ the active catalyst (i.e. the carbene species) is typically generated by activating a pre-catalyst (normally an azolium or triazolium salt) with a base. Such activation generates a conjugated acid as the side product. Herein, we pioneered a study of using the conjugated acid, generated from NHC pre-catalyst, as a co-catalyst to stimulate the *o*-QM species generation. In particular, NHC is used as a catalyst to give azolium enolate intermediate that can undergo an inverse electron demand formal Diels-Alder with the transient *o*-QM generated (Figure 3.1c).

Figure 3.1 Acid/base catalyzed *o*-QM intermediate generation and our synthetic strategy

3.2 Results and Discussions

Primary results of the reaction optimization using *o*-hydroxybenzhydryl alcohol **1a** and α -chloro aldehyde **2a** as the model substrates are summarized in table 3.1. To our delight,

the annulation conducted using mesityl-substituted indanol-derived NHC pre-catalyst **C1** (first reported by Bode)⁸ give rise to the desired product with an excellent enantiomeric ratio (99:1 er, entry 1). When trichlorophenyl-substituted indanol-derived NHC pre-catalyst **C2** was used,⁹ the yield of the desired product reduced significantly, without affecting the enantioselectivity (entry 2). During the investigation, *o*-hydroxybenzhydryl alcohol species turned out to be rather unstable and decompose readily. Hence, effort has been devoted to seeking an alternative substrate that could demonstrate indefinite stability without compromising the inherent reaction reactivity and selectivity. Amongst the different substrates that are stable indefinitely, the methoxide **1b** and tosylate **1c** substrates formed undesired ester as the main product, bearing the supposed good leaving group (entry 3 & 4). However, the stable *o*-hydroxybenzhydryl amine **1d**¹⁰ substrate performed comparatively relative to its alcohol counterpart **1a** (entry 5). Using

Table 3.1 Condition Optimization^a

entry	subst	NHC	base	yield (%) ^b	er ^c
1	1a	C1	TEA	44 ^d	99:1
2	1a	C2	TEA	34 ^d	99:1
3	1b	C1	TEA	--	--
4	1c	C1	TEA	--	--
5	1d	C1	TEA	41	99:1
6	1d	C1	DABCO	34	99:1
7	1d	C1	DBU	11	98:2
8	1d	C1	K ₃ PO ₄	23	98:2
9	1d	C1	Cs ₂ CO ₃	18	99:1
10	1d	C1	NaOAc	48	99:1
11	1d	C1	NaOAc	61 ^e	99:1
12	1d	C1	NaOAc	82 ^{e,f}	99:1

^a Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), CH₂Cl₂ (1 mL), rt, 24 h. ^b Isolated yield based on **1a**. ^c Enantiomeric

ratio of **3a**, determined *via* chiral phase HPLC analysis. ^d With 100 mg 4 Å MS. ^e slowly add **1a** in 30 min. ^f 40 °C.

the amine substrate, we continued to screen different bases including a diverse species of organic bases (entry 6 & 7) and inorganic bases (entry 8-10). The choice of base seems to have a negligible effect on the enantioselectivity, but it could significantly impact the yield of the reaction. The use of sodium acetate was found to give the optimal yield. At the same time, we have also realized that elevating the reaction temperature (at 40 °C) and adding the *o*-QM precursor part by part dramatically increases the yield of the reaction, without compromising the enantioselectivity (entry 11 & 12).

Using the optimized reaction conditions (Table 3.1, entry 12), we proceeded to examine the generalizability of the reaction through expanding the scope of α -chloro aldehyde (Table 3.2). A range of β -aryl- α -chloro aldehydes (**2b-2g**) with different substituents and substitution positions were first examined. These substitutions were all

Table 3.2 Scope of Diels-Alder Reactions with aldehyde **2**^a

^a Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), CH₂Cl₂ (1 mL), 40 °C. ^b Isolated yield based on **1d**. ^c Enantiomeric ratio of **3**, determined *via* chiral phase HPLC analysis. Most of products > 20:1 dr, except for **3c**, **3e** (>15:1 dr); **3f** (>14:1 dr).

well tolerated (71-84% yields, good dr and mostly >99:1 er). On the other hand, switching

the aryl substituent to a naphthyl substituent gave a high yield of the desired product **3h** (92% yield). However, when α -phenyl- α -chloro aldehyde **2i** was used, the resulted product had a slightly diminished yield (64%). On the other hand, various α -chloro alkyl aldehydes **2j-2l** performed well under the optimized reaction condition (81-86% yield, excellent er).

Table 3.3 Scope of Diels-Alder Reactions with *o*-hydroxybenzhydrl amines **1**^a

^a Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), CH₂Cl₂ (1 mL), 40 °C. ^b Isolated yield based on **1**. ^c Enantiomeric ratio of **3**, determined *via* chiral phase HPLC analysis. Most of product > 20:1 dr, except **3s** (>16:1 dr).

Following that, we continued to look at the scope of *o*-hydroxybenzhydrl amine substrates (Table 3.3 & 3.4). One could easily figure that the stereoelectronic property of the aryl substituents would have a direct relationship with the efficiency of the piperidine dissociation and play an important role in the *o*-QM generation. Indeed, the aryl substituents that are capable of delocalizing the charge (**3w**), inductively donating electrons (**3n**) and donating electrons through the π -system (**3a** & **3x**), assisted the substrate to behave pleasantly (78-91% yields). Having said so, the aryl substituents bearing the opposite effects (**3m**, **3o-3s**, **3u**) were also well tolerated (61-75%). Notably,

the N,N-dimethylaniline substituted substrate **3t** ended with a slightly lower yield compared to the other electron donating species substituted substrates. This, we supposed

Table 3.4 Scope of Diels-Alder Reactions with *o*-hydroxybenzhydryl amines **1**^a

^a Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), CH₂Cl₂ (1 mL), 40 °C. ^b Isolated yield based on **1**. ^c Enantiomeric ratio of **3**, determined *via* chiral phase HPLC analysis. All the products > 20:1 dr.

is due to the ability of the amine pendant to neutralize the conjugated acid essential for the pre-*o*-QM substrate activation. Further investigation revealed that the pre-*o*-QM aryl core is also flexible enough to be substituted with other electron rich aromatic species, including N, N-dimethylaniline (**3y**, **3z** & **3za**), methoxybenzene (**3zb**), dimethoxybenzene (**3zc**), and naphthalene (**3zd** and **3ze**) to give the anticipated product in moderate to good yield (36-73% yields). One should note that, regardless of the aryl substituents and the pre-*o*-QM core used, the enantioselectivity of the reaction always remain remarkable (mostly > 99:1 er).

3.3 Mechanistic Study.

A postulated reaction pathway is briefly illustrated in Figure 3.2. Firstly, in the presence of 1 equiv. base of NaOAc, chiral triazolium pre-catalyst **C1** was deprotonated to form the free carbene and generate the conjugated acid (HOAc) simultaneously. Free carbene attacked the aldehyde to generate Breslow intermediate **II**. And then the α chlorine atom

served as a leaving group under basic conditions to generate enolate intermediate **IV**, at same time forming NaCl and acetic acid. Amine substrate as an organic base can attack acetic acid to form an acetic salt, which salt containing a good leaving group can easily form *o*-QM intermediate under basic conditions. Then, the enolate intermediate **IV** generated from aldehyde acts as a nucleophile and the *o*-QM intermediate acts as an electrophile, thus forming an enantioselective formal [4+2] cyclization products. According to the X-ray analysis of the product, we found that product **3** has *cis* configuration. Based on the observed formation of *cis*-products and literature reports¹¹, we speculate that the reaction proceeds *via* a concerted mechanism. In addition, further experimental and computational investigations are underway and will lead to an improved understanding of the mechanism and stereochemical outcome.

Figure 3.2 Proposed Reaction Pathway.

3.4 Summary.

In summary, we have demonstrated a novel way of activating an *o*-hydroxybenzhydryl amine, using the conjugated acid generated from NHC pre-catalyst, to generate a transient

o-QM species for enantioselective [4+2] annulation with a α -chloro aldehyde substrate. The presented methodology delivers highly enantioenriched chroman-derivatives with very good yields and excellent distereoselectivities. We anticipate that the method will contribute a versatile platform for the synthesis of a wide variety of biological, important chroman-derived products and empower the development of therapeutics with enhanced biological properties.

3.5 Experimental Section

3.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker BBFO (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker BBFO (100 MHz) spectrometer. IR spectra were recorded on a Shimadzu IR Prestige-21FT-IR spectrometer as neat thin films between KBr plates. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer. The determination of enantiomeric excess was performed *via* chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{rt}$ (c in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate. Visualization was performed using a UV lamp.

3.5.2 Preparation of substrates

A typical method for synthesis of diarylmethylamines **1d**¹⁰:

To a solution of sesamol (1.0g, 7.24 mmol) in EtOH (2 mL) and hexane (2 mL), *p*-anisaldehyde (0.986g, 7.24 mmol) and piperidine (617 mg, 7.24 mmol) were added. The mixture was stirred at rt for 2 days (If not solidified for some substrates, keep it at rt until it solidifies). The solid was separated by filtration and recrystallized from ethanol to give the white crystal **1d** (2.22 g, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ 12.58 (br s, 1H), 7.28 (br s, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.41 (s, 1H), 6.33 (s, 1H), 5.81 (d, *J* = 13.6 Hz, 2H), 4.33 (s, 1H), 3.79 (s, 3H), 1.20-13.10 (br, 10H).

3.5.3 General procedure for the catalytic synthesis of products 3:

To a 10 mL flame-dry Schlenk reaction tube equipped with a magnetic stir bar, chiral NHC pre-catalyst **C1** (0.02 mmol, 20 mol%, 8.4 mg) and NaOAc (0.1 mmol, 100 mol%, 8.2 mg) were added. The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). CH₂Cl₂ (1.0 mL) and aldehyde **2** (0.2 mmol) were then added via syringe. Then the Schlenk reaction tube was put into 40 °C oil bath and diarylmethylamine **1** (0.1 mmol) was added in small portions within 30 minutes under nitrogen atmosphere. After 30 minutes, the reaction mixture was allowed to stir for 24 hours at 40°C. After completion of the reaction, monitored by TLC plate, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography directly using hexane/EtOAc (10:1) as eluent to afford the

desired product **3**.

3.5.4 Stereochemistry determination via X-ray crystallographic analysis:

Good quality crystal of **3q** (colorless needle crystal) was obtained by vaporization of a hexane/ethyl acetate solution of compound **3q**. CCDC 1520379 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3.5.5 Characterization of products:

(7S,8S)-7-benzyl-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3a**):

white foamy solid, 82% yield, 31.8 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.34 (m, 3H), 7.14 (d, $J = 6.4$ Hz, 2H), 6.94 (d, $J = 7.6$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 5.92 (s, 1H), 5.87 (s, 1H), 3.83 (d, $J = 6.0$ Hz, 1H), 3.77 (s, 3H), 3.31-3.37 (m, 2H), 2.45-2.52 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ

170.0, 159.1, 147.4, 145.2, 144.3, 138.5, 130.6, 129.1, 129.0, 128.6, 126.6, 119.8, 114.4, 107.2, 101.6, 99.0, 55.3, 45.9, 43.9, 32.6; IR ν_{max} (film, cm^{-1}): 1764, 1610, 1481, 1252, 1151, 1033, 737; $[\alpha]_D^{21} = 192.7$ ($c = 2.3$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{O}_5\text{H}^+$ 389.1384, found 389.1378; HPLC analysis: 99.8:0.2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: *i*-PrOH/hexane = 10:90; retention times: 30.6 min (major), 32.3 min (minor)].

(7S,8S)-8-(4-methoxyphenyl)-7-(4-methylbenzyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3b): white foamy solid. 78% yield,

31.3 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.13 (d, J =

8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.4

Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.65 (s, 1H), 6.46 (s,

1H), 5.92 (s, 1H), 5.87 (s, 1H), 3.82 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.26-3.34 (m, 2H),

2.43 (dd, J = 8.8, 13.6 Hz, 1H), 2.35 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.1, 159.0,

147.4, 145.2, 144.3, 136.1, 135.4, 130.7, 129.3, 129.1, 128.9, 119.9, 114.4, 107.2, 101.6,

99.0, 55.3, 45.9, 43.8, 32.1, 21.1; **IR** ν_{max} (film, cm^{-1}): 1763, 1512, 1481, 1151, 1035, 736;

$[\alpha]^{21}_{\text{D}}$ = 131.1 (c = 1.4 in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{22}\text{O}_5\text{H}^+$ 403.1540,

found 403.1533; **HPLC analysis**: 99.8:0.2 er, [CHIRALPAK IC column; 0.6 mL/min;

solvent system: i-PrOH/hexane = 10:90; retention times: 35.2 min (major), 31.9 min

(minor)].

(7S,8S)-7-(4-fluorobenzyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3c): white foamy solid. 84% yield,

34.1 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.08-7.12 (m,

2H), 6.93-7.02 (m, 4H), 6.82 (d, J = 6.4 Hz, 2H), 6.65 (s,

1H), 6.48 (s, 1H), 5.92 (s, 1H), 5.88 (s, 1H), 3.82 (d, J =

6.0 Hz, 1H), 3.77 (s, 3H), 3.23-3.33 (m, 2H), 2.48 (dd, J = 4.8, 14.0 Hz, 1H); $^{13}\text{C NMR}$

(100 MHz, CDCl_3) δ 169.8, 159.1, 147.5, 145.2, 144.3, 134.2, 130.5, 130.4, 128.9, 119.6,

115.5, 115.3, 114.5, 107.2, 101.7, 99.1, 55.3, 45.9, 44.1, 31.9; **IR** ν_{max} (film, cm^{-1}): 1761,

1637, 1255, 1151, 736; $[\alpha]^{20}_{\text{D}}$ = 174.2 (c = 1.6 in CHCl_3); **HRMS** (ESI, m/z): calcd. for

$\text{C}_{24}\text{H}_{19}\text{FO}_5\text{H}^+$ 407.1289, found 407.1288; **HPLC analysis**: 99.8:0.2 er, [CHIRALPAK IC

column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 25.1 min

(major), 28.9 min (minor)].

(7S,8S)-7-(4-chlorobenzyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3d): white foamy solid. 83% yield,

34.8 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.28 (d, $J = 6.8$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 6.4$ Hz, 2H), 6.82 (d, $J = 6.8$ Hz, 2H), 6.65 (s, 1H), 6.47 (s, 1H), 5.93 (s, 1H), 5.88 (s, 1H), 3.82 (d, $J = 6.0$ Hz, 1H), 3.77 (s, 3H),

3.23-3.32 (m, 2H), 2.47 (dd, $J = 7.2, 14.4$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.7, 159.1, 147.5, 145.1, 144.4, 137.0, 132.4, 130.4, 130.3, 128.9, 128.7, 119.5, 114.5, 107.2, 101.7, 99.1, 55.3, 45.8, 44.1, 32.2; **IR** ν_{max} (film, cm^{-1}): 1761, 1629, 1512, 1481, 1253, 1151, 736; $[\alpha]_D^{21} = 156.9$ ($c = 2.1$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{ClO}_5\text{H}^+$ 423.0994, found 423.0988; **HPLC analysis**: 99.9:0.1 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 25.2 min (major), 28.1 min (minor)].

(7S,8S)-7-(4-bromobenzyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3e): white foamy solid. 76% yield,

35.5 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.44 (d, $J = 6.4$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 6.4$ Hz, 2H), 6.82 (d, $J = 6.8$ Hz, 2H), 6.65 (s, 1H), 6.47 (s, 1H), 5.92 (s, 1H), 5.88 (s, 1H), 3.81 (d, $J = 6.4$ Hz, 1H), 3.77 (s, 3H), 3.22-3.33 (m, 2H), 2.45 (dd, $J =$

7.2, 14.8 Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.7, 159.1, 147.5, 145.1, 144.4, 137.6, 131.7, 130.8, 130.4, 128.9, 120.4, 119.5, 114.5, 107.2, 101.7, 99.1, 55.2, 45.7, 44.1, 32.3; **IR** ν_{max} (film, cm^{-1}): 1763, 1629, 1481, 1265, 1151, 736; $[\alpha]_D^{21} = 177.5$ ($c = 3.5$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{BrO}_5\text{H}^+$ 467.0489, found 467.0483; **HPLC analysis**: 99.9:0.1 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 26.1 min (major), 30.0 min (minor)].

(7S,8S)-7-(3-chlorobenzyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3f): white foamy solid. 77% yield,

32.1 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.23-7.25 (m,

2H), 7.13 (s, 1H), 7.02 (d, $J = 6.4$ Hz, 1H), 6.94 (d, $J = 6.8$

Hz, 2H), 6.83 (d, $J = 6.4$ Hz, 2H), 6.65 (s, 1H), 6.48 (s,

1H), 5.93 (s, 1H), 5.88 (s, 1H), 3.82 (d, $J = 6.4$ Hz, 1H), 3.78 (s, 3H), 3.25-3.33 (m, 2H),

2.48 (dd, $J = 8.8, 14.4$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.6, 159.1, 147.5,

145.1, 144.4, 140.7, 134.4, 130.4, 129.9, 129.1, 129.0, 127.3, 126.8, 119.5, 114.5, 107.2,

101.7, 99.1, 55.3, 45.7, 44.2, 32.5; **IR** ν_{max} (film, cm^{-1}): 1759, 1635, 1481, 1149, 1034,

736; $[\alpha]_{\text{D}}^{21} = 180.6$ ($c = 1.4$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{ClO}_5\text{H}^+$

423.0994, found 423.0996; **HPLC analysis**: 93.2:6.7 er, [CHIRALPAK IC column; 0.6

mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 24.7 min (major), 26.8

min (minor)].

(7S,8S)-7-(2-bromobenzyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3g): white foamy solid. 71% yield, 33 mg

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.53 (d, $J = 8.4$ Hz, 1H), 7.20-

7.25 (m, 2H), 7.11 (t, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.8$ Hz, 2H),

6.84 (d, $J = 8.8$ Hz, 2H), 6.63 (s, 1H), 6.53 (s, 1H), 5.93 (s, 1H),

5.88 (s, 1H), 3.96 (d, $J = 6.4$ Hz, 1H), 3.78 (s, 3H), 3.48 (q, $J = 6.4$ Hz, 1H), 3.18 (dd, $J =$

6.4, 14.0 Hz, 1H), 2.76 (dd, $J = 6.8, 14.4$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.7,

159.1, 147.4, 145.2, 144.3, 138.2, 132.9, 132.4, 130.9, 128.9, 128.4, 127.3, 124.7, 119.6,

114.5, 107.1, 101.7, 99.1, 55.3, 45.3, 44.2, 34.1; **IR** ν_{max} (film, cm^{-1}): 1761, 1629, 1265,

1151, 735; $[\alpha]_{\text{D}}^{20} = 138.8$ ($c = 1.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for

$\text{C}_{24}\text{H}_{19}\text{BrO}_5\text{H}^+$ 467.0489, found 467.0486; **HPLC analysis**: 99.3:0.7 er, [CHIRALPAK IC

column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 24.2 min

(major), 22.2 min (minor)].

(7S,8S)-8-(4-methoxyphenyl)-7-(naphthalen-1-ylmethyl)-7,8-dihydro-6H-

[1,3]dioxolo[4,5-g]chromen-6-one (3h): white foamy

solid. 92% yield, 40.2 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ

7.85-7.89 (m, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.39-7.48 (m,

3H), 7.25 (d, $J = 6.8$ Hz, 1H), 7.04 (d, $J = 8.8$ Hz, 2H),

6.85 (d, $J = 8.8$ Hz, 2H), 6.61 (s, 1H), 6.41 (s, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 3.78-3.89

(m, 2H), 3.78 (s, 3H), 3.46-3.51 (m, 1H), 2.94 (dd, $J = 7.2, 14.8$ Hz, 1H); $^{13}\text{C NMR}$ (100

MHz, CDCl_3) δ 170.2, 159.1, 147.4, 145.0, 144.3, 134.5, 134.1, 131.7, 131.0, 129.1,

129.0, 127.6, 127.4, 126.3, 125.7, 125.4, 123.4, 119.8, 114.6, 107.2, 101.6, 99.1, 55.3,

44.9, 44.2, 29.6; **IR** ν_{max} (film, cm^{-1}): 1759, 1612, 1514, 1151, 1035, 736; $[\alpha]_{\text{D}}^{21} = 191.3$

($c = 3.9$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{22}\text{O}_5\text{H}^+$ 439.1540, found 439.1537;

HPLC analysis: 99.9:0.1 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-

PrOH/hexane = 10:90; retention times: 28.3 min (major), 25.2 min (minor)].

(7R,8S)-8-(4-methoxyphenyl)-7-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-

6-one (3i): yellowish foamy solid. 64% yield, 23.8 mg; ^1H

NMR (400 MHz, CDCl_3) δ 7.16-7.25 (m, 3H), 6.79 (d, $J = 8.4$

Hz, 2H), 6.75 (s, 1H), 6.62-6.70 (m, 4H), 6.54 (s, 1H), 5.97 (s,

1H), 5.94 (s, 1H), 4.31 (d, $J = 6.4$ Hz, 1H), 4.12 (d, $J = 6.4$ Hz,

1H), 3.74 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 168.0, 159.1, 147.7, 145.7, 144.5,

134.2, 130.1, 129.8, 129.7, 127.9, 127.6, 119.4, 113.9, 107.2, 101.7, 99.1, 55.2, 52.2, 48.9;

IR ν_{max} (film, cm^{-1}): 1767, 1637, 1481, 1251, 1035, 736; $[\alpha]_{\text{D}}^{21} = 270.2$ ($c = 1.6$ in

CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{19}\text{O}_5\text{H}^+$ 375.1227, found 375.1223; **HPLC**

analysis: 99.8:0.2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-

PrOH/hexane = 10:90; retention times: 43.9 min (major), 54.9 min (minor)].

(7S,8S)-7-hexyl-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3j):

one (3j): colorless oil. 83% yield, 31.7 mg; ^1H NMR (400 MHz, CDCl_3) δ 6.98 (d, $J = 6.8$ Hz, 2H), 6.80 (d, $J = 6.4$ Hz, 2H), 6.65 (s, 1H), 6.56 (s, 1H), 5.95 (s, 1H), 5.90 (s, 1H), 4.00 (d, $J = 6.4$ Hz, 1H), 3.75 (s, 3H), 2.89 (q, $J = 6.4$ Hz, 1H), 3.17-3.83 (m, 1H), 1.43-1.47 (m, 2H), 1.23-1.31 (m, 7H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 158.9, 147.4, 145.5, 144.2, 130.7, 128.8, 119.7, 114.3, 107.2, 101.6, 99.0, 55.2, 44.8, 44.6, 31.6, 29.1, 27.2, 26.9, 22.6, 14.0; **IR** ν_{max} (film, cm^{-1}): 1761, 1637, 1481, 1252, 1153, 736; $[\alpha]_{\text{D}}^{21} = 106.1$ ($c = 1.5$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_5\text{H}^+$ 383.1853, found 383.1856; **HPLC analysis**: 99.9:0.1 er, [CHIRALPAK OD-H column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 14.7 min (major), 18.6 min (minor)].

(7S,8S)-7-heptyl-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3k):

one (3k): colorless oil. 86% yield, 34 mg; ^1H NMR (400 MHz, CDCl_3) δ 6.98 (d, $J = 6.8$ Hz, 2H), 6.80 (d, $J = 6.8$ Hz, 2H), 6.65 (s, 1H), 6.56 (s, 1H), 5.95 (s, 1H), 5.90 (s, 1H), 4.00 (d, $J = 6.4$ Hz, 1H), 3.75 (s, 3H), 2.89 (q, $J = 6.4$ Hz, 1H), 1.74-1.81 (m, 1H), 1.40-1.47 (m, 2H), 1.26-1.31 (m, 9H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 158.9, 147.4, 145.5, 144.2, 130.7, 128.8, 119.7, 114.3, 107.2, 101.6, 99.0, 55.2, 44.8, 44.6, 31.8, 29.4, 29.1, 27.3, 26.8, 22.6, 14.1; **IR** ν_{max} (film, cm^{-1}): 1765, 1635, 1512, 1481, 1251, 1151; $[\alpha]_{\text{D}}^{19} = 103.0$ ($c = 1.6$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{H}^+$ 397.2013, found 397.2009; **HPLC analysis**: 99.9:0.1 er, [CHIRALPAK OD-H column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 14.8 min (major), 24.6 min (minor)].

(7S,8S)-7-decyl-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3l):

one (3l): colorless oil. 81% yield, 35.4 mg; ^1H NMR (400 MHz, CDCl_3) δ 6.98 (d, $J =$

6.8 Hz, 2H), 6.80 (d, $J = 6.8$ Hz, 2H), 6.65 (s, 1H), 6.56 (s, 1H), 5.95 (s, 1H), 5.90 (s, 1H),

4.00 (d, $J = 6.4$ Hz, 1H), 3.75 (s, 3H), 2.89 (q, $J = 6.4$ Hz, 1H),
1.73-1.82 (m, 1H), 1.40-1.48 (m, 2H), 1.26-1.29 (m, 15H),
0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ
170.3, 158.9, 147.4, 145.5, 144.2, 130.7, 128.8, 119.7, 114.3,

107.2, 101.6, 99.0, 55.2, 44.8, 44.6, 31.9, 29.6, 29.5, 29.4, 29.3, 27.3, 26.8, 22.6, 14.1; **IR**
 ν_{max} (film, cm^{-1}): 1764, 1627, 1265, 1151, 736; $[\alpha]^{21}_{\text{D}} = 83.7$ ($c = 2.0$ in CHCl_3); **HRMS**
(ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{34}\text{O}_5\text{H}^+$ 439.2479, found 439.2475; **HPLC analysis**: 99.8:0.2 er,
[CHIRALPAK IB column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90;
retention times: 10.9 min (major), 13.9 min (minor)].

(7S,8S)-7-benzyl-8-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3m):

white foamy solid. 67% yield, 23.9 mg; ^1H NMR (400 MHz,
 CDCl_3) δ 7.25-7.33 (m, 6H), 7.13 (d, $J = 7.2$ Hz, 2H), 7.03 (d, $J =$
7.2 Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 5.91 (s, 1H), 5.86 (s, 1H),

3.87 (d, $J = 5.6$ Hz, 1H), 3.31-3.40 (m, 2H), 2.46 (dd, $J = 9.6, 14.0$ Hz, 1H); ^{13}C NMR
(100 MHz, CDCl_3) δ 169.9, 147.5, 145.3, 144.3, 138.7, 138.5, 129.1, 129.0, 128.6, 128.0,
127.8, 126.6, 119.5, 107.3, 101.7, 99.1, 45.7, 44.7, 32.6; **IR** ν_{max} (film, cm^{-1}): 1762, 1637,
1481, 1151, 1031, 698; $[\alpha]^{21}_{\text{D}} = 177.5$ ($c = 2.4$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for
 $\text{C}_{23}\text{H}_{18}\text{O}_4\text{H}^+$ 359.1278, found 359.1271; **HPLC analysis**: 99.4:0.6 er, [CHIRALPAK IC
column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 21.3 min
(major), 24.2 min (minor)].

(7S,8S)-7-benzyl-8-(p-tolyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3n):

white foamy solid. 87% yield, 32.4 mg; ^1H NMR (400 MHz,
 CDCl_3) δ 7.24-7.33 (m, 3H), 7.13 (d, $J = 7.6$ Hz, 2H), 7.09 (d, $J =$
7.6 Hz, 2H), 6.92 (d, $J = 8.0$ Hz, 2H), 6.64 (s, 1H), 6.45 (s, 1H),

5.90 (s, 1H), 5.85 (s, 1H), 3.83 (d, $J = 6.0$ Hz, 1H), 3.30-3.38 (m, 2H), 2.48 (dd, $J = 4.8$, 15.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.0, 147.4, 145.3, 144.3, 138.6, 137.5, 135.7, 129.8, 129.1, 128.6, 127.9, 126.6, 119.7, 107.3, 101.7, 99.1, 45.8, 44.4, 32.6, 21.1; IR ν_{max} (film, cm^{-1}): 1765, 1635, 1481, 1151, 1035, 736; $[\alpha]_{\text{D}}^{21} = 147.5$ ($c = 3.1$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{20}\text{O}_4\text{H}^+$ 373.1434, found 373.1435; HPLC analysis: 99.7:0.3 er, [CHIRALPAK IA column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 17.2 min (major), 31.8 min (minor)].

(7S,8S)-7-benzyl-8-(4-fluorophenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3o): white foamy solid. 61% yield, 22.9 mg; ^1H NMR (400

MHz, CDCl_3) δ 7.25-7.33 (m, 3H), 7.13 (d, $J = 7.2$ Hz, 2H), 6.98 (d, $J = 6.8$ Hz, 4H), 6.66 (s, 1H), 6.45 (s, 1H), 5.93 (s, 1H), 5.88 (s, 1H), 3.87 (d, $J = 5.6$ Hz, 1H), 3.32-3.42 (m, 2H), 2.45 (dd, $J = 6.4$, 14.0

Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.7, 162.7 (d, $J = 245.4$ Hz), 147.7, 145.2, 144.4, 138.2, 134.4 (d, $J = 3.4$ Hz), 129.7, 129.6, 128.9, 128.7, 126.6, 119.2, 116.0 (d, $J = 21.3$ Hz), 107.1, 101.7, 99.1, 45.7, 43.8, 32.5; IR ν_{max} (film, cm^{-1}): 1761, 1507, 1215, 1151, 927, 756; $[\alpha]_{\text{D}}^{21} = 155.7$ ($c = 2.2$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{17}\text{FO}_4\text{H}^+$ 377.1184, found 377.1178; HPLC analysis: 99.7:0.3 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 26.3 min (major), 20.9 min (minor)].

(7S,8S)-7-benzyl-8-(4-chlorophenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3p): white foamy solid. 72% yield, 28.1 mg; ^1H NMR (400

MHz, CDCl_3) δ 7.25-7.33 (m, 5H), 7.12 (d, $J = 7.2$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.65 (s, 1H), 6.44 (s, 1H), 5.92 (s, 1H), 5.88 (s, 1H), 3.85 (d, $J = 6.0$ Hz, 1H), 3.32-3.43 (m, 2H), 2.43 (dd, $J = 9.2$, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.6, 147.7, 145.3, 144.5, 138.2, 137.2, 133.7, 129.4, 129.3, 129.0, 128.7, 126.8, 118.9, 107.1, 101.7, 99.2, 45.5, 44.0, 31.6; IR

ν_{max} (film, cm^{-1}): 1761, 1507, 1215, 1151, 927, 756; $[\alpha]_{\text{D}}^{21} = 155.7$ ($c = 2.2$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{17}\text{ClO}_4\text{H}^+$ 377.1034, found 377.1034; HPLC analysis: 99.7:0.3 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 26.3 min (major), 20.9 min (minor)].

$\nu_{\max}$ (film, cm^{-1}): 1763, 1637, 1483, 1265, 1151, 738; $[\alpha]_{\text{D}}^{22} = 177.1$ ($c = 2.8$ in CHCl_3);

HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{17}\text{ClO}_4\text{H}^+$ 393.0888, found 393.0882; **HPLC analysis**:

99.8:0.2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 26.7 min (major), 20.8 min (minor)].

(7S,8S)-7-benzyl-8-(4-bromophenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3q):

one (3q): white foamy solid. 75% yield, 32.7 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.43 (m, 5H), 7.12 (d, $J = 7.2$ Hz, 2H), 6.89 (d, $J = 7.6$ Hz, 2H), 6.65 (s, 1H), 6.44 (s, 1H), 5.93 (s, 1H), 5.88 (s, 1H), 3.83 (d, $J = 5.2$ Hz, 1H), 3.33-3.42 (m, 2H), 2.44 (dd, $J = 9.6$,

14.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.6, 147.7, 145.3, 144.5, 138.1, 137.7, 132.2, 129.7, 128.9, 128.7, 126.8, 121.8, 118.8, 107.1, 101.7, 99.2, 45.4, 44.1, 32.6; **IR**

$\nu_{\max}$ (film, cm^{-1}): 1763, 1637, 1481, 1265, 1151, 736; $[\alpha]_{\text{D}}^{21} = 175.8$ ($c = 1.9$ in CHCl_3);

HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{17}\text{BrO}_4\text{H}^+$ 437.0383, found 437.0381; **HPLC analysis**:

99.8:0.2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 27.8 min (major), 21.5 min (minor)].

(7S,8S)-7-benzyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3r): white foamy solid. 64% yield, 27.3 mg

^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 7.6$ Hz, 2H), 7.26-7.36 (m, 3H), 7.12-7.16 (m, 4H), 6.68 (s, 1H), 6.44 (s, 1H), 5.93 (s, 1H), 5.89 (s, 1H), 3.94 (d, $J = 6.0$ Hz, 1H), 3.35-3.45 (m, 2H), 2.43 (dd, J

= 10.0, 14.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 147.9, 145.4, 144.5, 142.8, 137.9, 128.9, 128.8, 128.4, 126.9, 126.1, 126.0, 118.4, 107.1, 101.8, 99.2, 45.4, 44.4, 32.6;

IR $\nu_{\max}$ (film, cm^{-1}): 1765, 1618, 1483, 1327, 1153, 1128; $[\alpha]_{\text{D}}^{21} = 153.8$ ($c = 2.7$ in

CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{17}\text{F}_3\text{O}_4\text{H}^+$ 427.1152, found 427.1146; **HPLC**

analysis: 98.3:1.7 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 22.5 min (major), 13.8 min (minor)].

(7S,8S)-7-benzyl-8-(4-nitrophenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one

(3c): yellowish foamy solid. 72% yield, 28.8 mg; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, $J = 8.0$ Hz, 2H), 7.03-7.28 (m, 7H), 6.61 (s, 1H), 6.37 (s, 1H), 5.87 (s, 1H), 5.83 (s, 1H), 3.93 (d, $J = 6.0$ Hz, 1H), 3.26-3.42 (m, 2H), 2.33 (dd, $J = 10.0, 14.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.1, 148.1, 147.5, 146.1, 145.4, 144.6, 137.6, 129.0, 128.9, 128.8, 127.0, 124.3, 117.7, 107.1, 101.9, 99.4, 45.2, 44.3, 32.6; **IR** ν_{max} (film, cm^{-1}): 1765, 1637, 1348, 1151, 689; $[\alpha]_D^{21} = 210.3$ ($c = 2.7$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{17}\text{NO}_6\text{H}^+$ 404.1129, found 404.1121; **HPLC analysis**: 99.8:0.2 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 40.6 min (major), 43.4 min (minor)].

(7S,8S)-7-benzyl-8-(4-(dimethylamino)phenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3t): white foamy solid. 63% yield, 25.2 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.15-7.33 (m, 5H), 6.89 (d, $J = 8.0$ Hz, 2H), 6.63 (d, $J = 4.8$ Hz, 3H), 6.45 (s, 1H), 5.89 (s, 1H), 5.85 (s, 1H), 3.77 (d, $J = 6.0$ Hz, 1H), 3.31-3.37 (m, 2H), 2.91 (s, 6H), 2.52 (dd, $J = 10.8, 15.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 149.9, 147.2, 145.2, 144.2, 138.9, 129.1, 128.7, 128.6, 126.5, 126.1, 120.3, 112.8, 107.3, 101.6, 99.0, 46.1, 43.9, 40.5, 32.6; **IR** ν_{max} (film, cm^{-1}): 1764, 1635, 1481, 1361, 1147, 756; $[\alpha]_D^{21} = 206.0$ ($c = 2.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{23}\text{NO}_4\text{H}^+$ 402.1700, found 402.1694; **HPLC analysis**: 99.9:0.1 er, [CHIRALPAK IB column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 20.3 min (major), 14.8 min (minor)].

(7S,8S)-7-benzyl-8-(3-chlorophenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-

one (3u): white foamy solid. 74% yield, 29 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.12-7.35 (m, 5H), 6.99 (s, 1H), 6.91 (d, $J = 6.0$

Hz, 1H), 6.66 (s, 1H), 6.44 (s, 1H), 5.93 (s, 1H), 5.89 (s, 1H), 3.85 (d, $J = 4.2$ Hz, 1H), 3.33-3.42 (m, 2H), 2.45 (dd, $J = 9.2, 13.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.5, 147.8, 145.4, 144.5, 140.6, 138.1, 134.8, 130.4, 128.9, 128.8, 128.4, 128.0, 126.8, 125.9, 118.6, 107.2, 101.8, 99.2, 45.5, 44.3, 32.6; IR ν_{max} (film, cm^{-1}): 1767, 1629, 1481, 1153, 1128, 698; $[\alpha]_{\text{D}}^{21} = 171.5$ ($c = 2.8$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{17}\text{ClO}_4\text{H}^+$ 393.0888, found 393.0886; HPLC analysis: 99.5:0.5 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 19.8 min (major), 21.5 min (minor)].

(7S,8S)-8-(benzo[d][1,3]dioxol-5-yl)-7-benzyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-

g]chromen-6-one (3v): white foamy solid. 60% yield, 24 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.34 (m, 3H), 7.16 (d, $J = 7.2$ Hz, 2H), 6.72 (d, $J = 7.6$ Hz, 1H), 6.65 (s, 1H), 6.45-6.51 (m, 3H), 5.92 (s, 3H), 5.88 (s, 1H), 3.80 (d, $J = 6.0$ Hz, 1H), 3.31-3.37 (m, 2H),

2.51 (dd, $J = 10.8, 15.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.8, 148.3, 147.5, 147.1, 145.2, 144.3, 138.5, 132.3, 129.0, 128.7, 126.6, 121.5, 119.5, 108.5, 108.0, 107.2, 101.7, 101.2, 99.1, 45.8, 44.4, 32.6; IR ν_{max} (film, cm^{-1}): 1765, 1635, 1481, 1153, 1037, 735; $[\alpha]_{\text{D}}^{21} = 179.8$ ($c = 2.2$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{18}\text{O}_6\text{H}^+$ 403.1176, found 403.1171; HPLC analysis: 99.9:0.1 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 37.1 min (major), 33.8 min (minor)].

(7S,8S)-7-benzyl-8-(naphthalen-2-yl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-

one (3w): white foamy solid. 78% yield, 31.8 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.66-7.72 (m, 3H), 7.37 (s, 3H), 7.04-7.25 (m, 6H), 6.61 (s, 1H), 6.41 (s, 1H), 5.83 (s, 1H), 5.77 (s, 1H), 3.96 (d, $J = 6.0$ Hz, 1H), 3.25-3.39 (m, 2H), 2.41 (dd, $J = 6.0, 14.4$ Hz, 1H); ^{13}C

NMR (100 MHz, CDCl_3) δ 169.9, 147.6, 145.4, 144.4, 138.5, 136.1, 133.4, 132.8, 129.1,

129.0, 128.7, 127.9, 127.7, 127.2, 126.7, 126.5, 126.2, 125.5, 119.2, 107.4, 101.7, 99.1, 45.6, 44.8, 32.7; **IR** ν_{max} (film, cm^{-1}): 1763, 1629, 1265, 1153, 735; $[\alpha]_{\text{D}}^{21} = 227.2$ ($c = 3.2$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{20}\text{O}_4\text{H}^+$ 409.1434, found 409.1430; **HPLC analysis**: 99.2:0.8 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 25.2 min (major), 28.5 min (minor)].

(7S,8R)-7-benzyl-8-(thiophen-2-yl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one

(3x): yellowish oil. 91% yield, 33.1 mg; **^1H NMR** (400 MHz, CDCl_3) δ 7.19-7.34 (m, 6H), 6.93 (s, 1H), 6.79 (s, 1H), 6.64 (s, 1H), 6.49 (s, 1H), 5.91 (s, 1H), 5.88 (s, 1H), 4.13 (d, $J = 5.2$ Hz, 1H), 3.29-3.44 (m, 2H), 2.67 (dd, $J = 10.4, 14.4$ Hz, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ 169.5, 147.7, 145.1, 144.3, 141.0, 138.3, 129.2, 128.7, 127.3, 126.8, 125.6, 125.0, 119.7, 107.0, 101.7, 99.3, 46.6, 39.5, 32.6; **IR** ν_{max} (film, cm^{-1}): 1765, 1629, 1481, 1444, 1153, 700; $[\alpha]_{\text{D}}^{21} = 129.6$ ($c = 3.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{21}\text{H}_{16}\text{O}_4\text{SH}^+$ 365.0842, found 365.0836; **HPLC analysis**: 99.8:0.2 er, [CHIRALPAK ID column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 33.3 min (major), 41.4 min (minor)].

(3S,4S)-3-benzyl-7-(dimethylamino)-4-(4-methoxyphenyl)chroman-2-one (3y): white

foamy solid. 66% yield, 25.5 mg; **^1H NMR** (400 MHz, CDCl_3) δ 7.24-7.33 (m, 3H), 7.14 (d, $J = 7.2$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 2H), 6.45 (s, 1H), 6.38 (d, $J = 8.4$ Hz, 1H), 3.88 (d, $J = 6.0$ Hz, 1H), 3.76 (s, 3H), 3.30-3.40 (m, 2H), 2.91 (s, 6H), 2.50 (dd, $J = 9.6, 14.4$ Hz, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ 170.7, 158.8, 151.7, 150.9, 138.8, 131.7, 129.1, 129.0, 128.6, 126.5, 115.0, 114.3, 108.8, 100.4, 55.2, 46.6, 43.2, 40.5, 32.8; **IR** ν_{max} (film, cm^{-1}): 1762, 1628, 1512, 1265, 1031, 735; $[\alpha]_{\text{D}}^{20} = 137.6$ ($c = 2.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{25}\text{NO}_3\text{H}^+$ 388.1907, found 388.1906; **HPLC analysis**: 94.7:5.3 er,

[CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 32.3 min (major), 34.7 min (minor)].

(3S,4S)-3-benzyl-7-(dimethylamino)-4-(naphthalen-2-yl)chroman-2-one (3z):

Colorless oil. 60% yield, 24.5 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.74-7.70 (m, 3H), 7.43-7.46 (m, 3H), 7.12-7.34 (m, 6H), 6.91 (d, J = 8.4 Hz, 1H), 6.50 (s, 1H), 6.38 (d, J = 8.4 Hz, 1H), 4.10 (d, J = 6.4 Hz, 1H), 3.45-3.51 (m, 1H), 3.35 (dd, J = 4.4, 14.4 Hz, 1H), 2.92 (s, 6H), 2.51 (dd, J = 9.6, 14.8 Hz, 1H); ^{13}C NMR

(100 MHz, CDCl_3) δ 170.6, 151.8, 151.0, 138.7, 137.2, 133.4, 132.7, 129.2, 129.1, 128.9, 128.8, 128.6, 127.9, 127.6, 127.1, 126.6, 126.3, 125.9, 125.7, 108.9, 100.5, 46.3, 44.2, 40.5, 32.9; **IR** ν_{max} (film, cm^{-1}): 1764, 1629, 1519, 1361, 1111, 734; $[\alpha]_{\text{D}}^{19}$ = 270.8 (c = 2.3 in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{25}\text{NO}_2\text{H}^+$ 408.1958, found 408.1955;

HPLC analysis: 99.8:0.2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 21.2 min (major), 28.8 min (minor)].

(3S,4S)-4-(benzo[d][1,3]dioxol-5-yl)-3-benzyl-7-(dimethylamino)chroman-2-one (3za):

white foamy solid. 73% yield, 29.2 mg; ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 4.2 Hz, 1H), 7.15 (d, J = 6.8 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.38-6.52 (m, 4H), 5.89 (s, 2H), 3.86 (d, J = 5.6 Hz, 1H), 3.32-3.39 (m, 2H), 2.92 (s, 6H), 2.53 (dd, J = 11.2, 16.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 151.7, 150.9, 148.1, 146.9, 138.8, 133.4, 129.1, 128.6, 128.5, 128.3, 126.5, 121.4, 108.8, 108.4, 108.1, 101.1, 100.4, 46.5, 43.7, 40.5, 32.8; **IR** ν_{max} (film, cm^{-1}): 1764, 1627, 1444, 1242, 1111, 736; $[\alpha]_{\text{D}}^{20}$ = 155.7 (c = 2.9 in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{23}\text{NO}_4\text{H}^+$ 402.1700, found 402.1703; **HPLC analysis:** 99.9:0.1 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 37.2 min (major), 40.2 min (minor)].

(3S,4S)-3-benzyl-7-methoxy-4-(4-methoxyphenyl)chroman-2-one (3zb): Colorless oil.

36% yield, 13.5 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.27-7.34 (m, 3H), 7.15 (d, $J = 6.8$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 3H), 6.81 (d, $J = 6.8$ Hz, 2H), 6.68 (d, $J = 2.8$ Hz, 1H), 6.59 (dd, $J = 2.8, 8.4$ Hz, 1H), 3.93 (d, $J = 6.0$ Hz, 1H), 3.78 (s, 6H), 3.31-3.41 (m, 2H), 2.51 (dd, $J = 9.2, 14.0$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.1, 159.8, 158.9, 151.6, 138.6, 131.1, 129.1, 129.0, 128.9, 128.6, 126.6, 119.6, 114.4, 110.8, 102.4, 55.6, 55.2, 46.3, 43.3, 32.6; **IR** ν_{max} (film, cm^{-1}): 1761, 1625, 1508, 1253, 1122, 700; $[\alpha]_{\text{D}}^{21} = 188.7$ ($c = 1.9$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{24}\text{H}_{22}\text{NO}_4\text{H}^+$ 375.1591, found 375.1591; **HPLC analysis**: 99.7:0.3 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 20.3 min (major), 23.1 min (minor)].

(3S,4S)-3-benzyl-6,7-dimethoxy-4-(4-methoxyphenyl)chroman-2-one (3zc): Colorless

oil. 55% yield, 22 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.32 (t, $J = 7.6$ Hz, 2H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.16 (d, $J = 7.2$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.69 (s, 1H), 6.50 (s, 1H), 3.87 (s, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 3.32-3.41 (m, 2H), 2.48 (dd, $J = 9.2, 14.4$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.2, 159.0, 149.0, 145.8, 144.5, 138.7, 130.8, 129.1, 129.0, 128.6, 126.6, 118.5, 114.4, 110.3, 101.1, 56.2, 55.3, 46.3, 43.4, 32.7, 32.6; **IR** ν_{max} (film, cm^{-1}): 1759, 1622, 1512, 1228, 1122, 700; $[\alpha]_{\text{D}}^{21} = 217.1$ ($c = 1.4$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{24}\text{O}_5\text{H}^+$ 405.1697, found 405.1696; **HPLC analysis**: 99.9:0.1 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: i-PrOH/hexane = 10:80; retention times: 38.8 min (major), 41.1 min (minor)].

(3S,4S)-3-benzyl-4-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[h]chromen-2-one (3zd):

white foamy solid. 57% yield, 22.5 mg; ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 8.4$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.49-7.57 (m, 3H), 7.17-7.35 (m, 5H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 2H), 4.08 (d, $J = 6.4$ Hz, 1H), 3.75 (s, 3H), 3.51-3.53 (m, 1H), 3.42 (dd, $J = 4.8, 14.8$ Hz, 1H),

2.58 (dd, $J = 9.6, 14.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 159.1, 145.7, 138.6, 133.6, 130.3, 129.3, 129.1, 128.7, 127.6, 126.8, 126.7, 126.6, 125.5, 124.3, 123.8, 122.2, 121.4, 114.4, 55.3, 46.1, 43.4, 32.6; IR ν_{max} (film, cm^{-1}): 1768, 1512, 1377, 1251, 1124, 700; $[\alpha]_{\text{D}}^{21} = 454.4$ ($c = 2.0$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{27}\text{H}_{22}\text{O}_3\text{H}^+$ 395.1642, found 395.1640; HPLC analysis: 99.9:0.1 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 17.1 min (major), 13.5 min (minor)].

(3S,4S)-3-benzyl-6-methoxy-4-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[h]chromen-2-one (3ze):

white foamy solid. 62% yield, 26 mg; ^1H NMR (400 MHz, CDCl_3) δ 8.25 (d, $J = 8.4$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.58 (t, $J = 8.4$ Hz, 1H), 7.50 (t, $J = 8.4$ Hz, 1H), 7.18-7.36 (m, 5H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.38 (s, 1H), 4.01 (d, $J = 6.4$ Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.51-3.54 (m, 1H), 3.41 (dd, $J = 8.4, 14.8$ Hz, 1H), 2.55 (dd, $J = 9.2, 14.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 159.1, 152.2, 139.6, 138.8, 130.2, 129.4, 129.1, 128.7, 128.3, 127.3, 126.6, 126.1, 125.4, 124.7, 122.1, 121.9, 121.1, 102.7, 55.6, 55.2, 46.3, 44.8, 32.6; IR ν_{max} (film, cm^{-1}): 1759, 1639, 1512, 1382, 1251, 1132, 700; $[\alpha]_{\text{D}}^{21} = 427.3$ ($c = 2.2$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{24}\text{O}_4\text{H}^+$ 425.1747, found 425.1741; HPLC analysis: 100:0 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 22.7 min (major), 14.8 min (minor)].

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Chapter 4

A New Mode of Carbene-Catalyzed Aryl Aldehyde

Activation and Induced Phenol O-H Bond

Functionalization

4.1 Introduction

Aromatic moieties are among the most common functional groups in natural products, bioactive molecules, and polymeric materials. Thus, selective functionalization of aromatic molecules and their derivatives has received continuous attention in organic synthesis. Currently, the field of aromatic molecule functionalization, such as aromatic $\text{sp}^2\text{-CH}$ activation and benzylic $\text{sp}^3\text{-CH}$ activation, is dominated by transition metal catalysis¹⁻³. Organic catalyst-enabled activation of aromatic or benzylic carbon as the reactive center has been much less developed. Representative examples in this direction include photoredox/organocatalytic radical reactions from MacMillan⁴ and Melchiorre⁵, and amine-mediated reactions via enamine or iminium intermediate from Melchiorre⁶, Jørgensen⁷, Chen⁸ and Xu⁹. In the area of *N*-heterocyclic carbene (abbreviated as NHC or carbene in this manuscript) organocatalysis^{10, 11}, aldehydes¹²⁻¹⁶, esters¹⁷⁻¹⁹, and ketenes^{20, 21} have been widely employed as substrates. However, nearly all these reactions were focused on using carbon atoms in non-aromatic (and acyclic) molecules as the reactive sites (Fig. 4.1a). For example, the α , and β -carbons of acyclic α,β -unsaturated aldehydes²² have been widely explored with a large set of asymmetric reactions. In contrast, aromatic aldehydes are only used in benzoin-type reactions. It still remains a challenge for the stereo-electronic power of the carbene catalyst to go across the conjugated bonds of the aromatic frameworks to induce activation and selective reactions (Fig. 4.1b). In 2013, we disclosed that the benzylic $\text{sp}^3\text{-CH}$ of indole-type heteroaryl aldehyde²³ could be activated via an analogous vinyl enolate intermediate (NHC-bound *o*-QDMs, Fig. 4.1b). However, the activation of simple aromatic aldehydes (such as benzaldehyde) without the heteroatom incorporated in the aromatic rings remains difficult.

Figure 4.1 Activation modes in carbene organic catalysis

4.2 Our Proposal.

Here we demonstrate that the simple aryl aldehyde could be activated by a carbene catalyst (Fig. 4.2). Addition of the carbene catalyst to the aldehyde moiety of 2-hydroxyl benzaldehyde (salicylaldehyde, **1a**) eventually leads to the acyl azolium intermediate **I** under an oxidative condition. The electron-withdrawing effect from the acyl azolium moiety, in combination with the electron-donating ability of the OH group, enables a dearomatization²⁴ process that forms the azolium-bound *ortho*-quinone methide intermediate **II** (*o*-QM). *Ortho*-quinone methide is a reactive intermediate broadly used in the synthesis of sophisticated natural products and other functional molecules^{25, 26}. The oxygen atom in intermediate **II** behaves as an active site to react with ketone substrate **2a** to afford chiral ketal-like **3a** as the product. The overall process is a carbene-catalyzed functionalization of the phenol OH group via a new type of NHC-bound *o*-QMs intermediate (**II**). Notably, in nearly all of the reported reactions, only carbon atoms of the NHC-bound intermediates (Fig. 4.1a) were explored as the reactive centers^{27, 28}. The exceptions are NHC-mediated polymerization of lactone²⁹ and Breslow intermediate-induced ring expansion³⁰⁻³². Our present work involves oxygen atom activation, in which the reactivity of the oxygen atom is modulated by the covalently-bound NHC catalyst in intermediate **II**. The azolium-bound *ortho*-quinone methides intermediate (**II**) constitutes a new mode for NHC catalysis. Additionally, we discovered an urea/NHC cooperative

catalytic process³³ (**III**, Fig. 4.2), in which an achiral urea co-catalyst significantly and consistently improves the enantioselectivity of the reaction.

Figure 4.2 Simple aryl aldehyde activation and O-H bond functionalization.

4.3 Results and Discussions

Salicylaldehyde (**1a**) and trifluoroacetophenone (**2a**) were chosen as the model substrates to form 1,3-dioxin-4-one (**3a**). Quinone (**DQ**), first explored by Studer in NHC catalysis³⁴, is an effective oxidant. Firstly, by the bases screening, several bases could produce the desired product in such reactions (Table 4.1). Here, we chose stable DABCO as base for the next screening. Notably, in the absence of NHC catalyst, product **3a** was not formed. The two starting materials (**1a** and **2a**) remained unreacted and could be recovered (Table 4.1, entry 1). Then, we used DABCO as base to screen other solvents. Studies on the solvent effects found that CH₂Cl₂ is the optimal choice. The search for NHC catalysts found that aminoindanol-derived triazolium precatalyst **C1** with a *N*-mesityl substituent (first explored by Bode)³⁵ could mediate the formation of **3a** with 72% yield and 63:37 e.r. (Table 4-2, entry 1). The reaction yield could be dramatically

Table 4.1. Screening of different bases ^a

entry	NHC	solvent	Base	yield (%) ^b	er ^c
1	—	THF	DABCO	—	—
2	C	THF	DABCO	90	—
3	C1	THF	CS ₂ CO ₃	56	52:48
4	C1	THF	TEA	28	52:48
5	C1	THF	DMAP	19	52:48
6	C1	THF	DABCO	77	52:48
7	C1	THF	K ₃ PO ₄	80	52:48
8	C1	THF	K ₂ CO ₃	76	52:48
9	C1	CH ₂ Cl ₂	DABCO	72	63:37
10	C1	Toluene	DABCO	95	60:40
11	C1	MeCN	DABCO	30	50:50
12	C1	Ethyl Acetate	DABCO	22	50:50
13	C1	Hexane	DABCO	45	64:36
14	C1	DCE	DABCO	56	60:40

^a Reaction conditions: **1a** (0.11 mmol), **2a** (0.1 mmol), base (0.1 mmol), solvent (1 mL), rt, 24 h. ^b Yield determined by NMR analysis with an internal standard. ^c Enantiomeric ratio of **3a**, determined *via* chiral phase HPLC analysis.

increased to 97% when precatalyst **C2** with an *N*-trichlorophenyl substituent (first explored by Rovis)³⁶ was used (Table 4.2, entry 2). Using **C2** (as it was the best catalyst) along with a solvent mixture of CH₂Cl₂/hexane slightly improved the e.r. value (Table 4.2, entry 10). Decreasing the reaction temperature from room temperature to -10 °C led to a small but consistent improvement in e.r. value without affecting the reaction yield (Table 4.2, entry 11). Further decrease in the reaction temperature, however, slowed down the reaction without enhancing the enantioselectivity. We then moved to identify conditions that could improve the reaction enantioselectivity. In our studies on the solvent effects, we found that solvents could impact the reaction enantioselectivity. For example, when THF was used as the solvent, the e.r. value of **3a** decreased from 73:27 to 52:48.

Table 4.2 Screening of chiral carbene catalysts^a

entry	NHC	Additive	yield (%) ^b	er ^c
1	C1	—	72	63:37
2	C2	—	98	68:32
3	C3	—	34	61:39
4	C4	—	94	53:47
5	C5	—	23	60:40
6	C6	—	27	52:48
7	C7	—	22	54:46
8	C8	—	97	55:45
9	C9	—	trace	—
10 ^d	C2	—	99	70:30
11 ^{d,e}	C2	—	99	73:27
12 ^{d,f}	C2	—	92	73:27

^a Reaction conditions: **1a** (0.11 mmol), **2a** (0.1 mmol), CH₂Cl₂ (1 mL), rt, 24 h. ^b Yield determined by NMR analysis

with an internal standard. ^c Enantiomeric ratio of **3a**, determined *via* chiral phase HPLC analysis. ^d CH₂Cl₂/Hexane = 1:1

(2 mL). ^e -10 °C. ^f -40 °C, 48 h.

These results suggest that non-covalent interaction is likely to play an important role in enantioselectivity control in our reactions. Thus we moved to examine non-covalent organic catalysts and found that using achiral thiourea³⁷⁻⁴¹ **A1** as a co-catalyst could improve the e.r. values of **3a** from 73:27 to 85:15 (Table 4.3, entry 3). Increasing the amount of **A1** led to a lower yield of **3a** with little benefit to the enantioselectivity. Further studies found that both thiourea and urea⁴² co-catalysts can improve the enantioselectivity. We finally found that using asymmetric urea **A3** could lead to **3a** with 99% yield and 94:6 e.r. (Table 4.3, entry 5). The loading of the NHC catalyst (**C2**) could be decreased to 5 mol%, without affecting the reaction yield and e.r. (Table 4.3, entry 12).

The urea co-catalyst most likely forms hydrogen-bonding interactions with the ketone substrate (e.g., **2a**) and/or intermediate **II** (Fig. 4.2), which improves the reaction enantioselectivity. The hydrogen-bonding interactions are sensitive to solvents.

Table 4.3 Screening of chiral bases and additives ^a

entry	Base (100 mol%)	Additive (20 mol%)	yield (%) ^b	er ^c
1	Quinine	—	99	72:28
2	Quinidine	—	99	71:29
3	DABCO	A1	90	85:15
4	DABCO	A2	99	92:8
5	DABCO	A3	99(99)	94:6
6	DABCO	A4	95	92:8
7	DABCO	A5	99	93:7
8	DABCO	A6	99	86:14
9	DABCO	A7	89	87:13
10	DABCO	A8	99	89:11
11	DABCO	A9	99	87:13
12 ^d	DABCO	A3	99	94:6

^a Reaction conditions: **1a** (0.11 mmol), **2a** (0.1 mmol), DCM/Hexane = 1:1 (2 mL), -10 °C, 24 h. ^b Yield determined by NMR analysis with an internal standard. Isolated yield in parentheses based on **2a**. ^c Enantiomeric ratio of **3a**, determined *via* chiral phase HPLC analysis. ^d 5 mol% **C2**.

With an acceptable reaction conditions in hand (Table 4.3, entry 12), the generality of the reaction was then explored. Firstly, we studied the scope of 2-hydroxyl aryl aldehydes (Table 4.4). With trifluoroacetophenone **2a** as a model electrophile, different substituents and substitution patterns on the phenyl ring were examined. Electron-releasing substituents such as alkyl (**3b**, **3d** and **3k**) and alkoxy (**3c**, **3g** and **3j**) units on the phenyl

ring of the aldehyde substrates were well tolerated. Electron-withdrawing groups such as halogen atoms (**3e**, **3f**, and **3h**) and a carboxylic ester unit (**3i**) could also be placed on the phenyl ring of the aldehyde substrates. It's worth noting that the steric effect of substituents in different positions on the phenyl ring did not affect the results, including 3- and 6- substituents on the 2-hydroxyl aryl aldehydes, as both gave good yields and e.r. (**3j**, **3k** and **3l**). Product **3m** bearing a sesamol moiety (3,4-methylenedioxyphenol) could also be made by our method. The benzene ring of **1a** could be extended to other aromatic frameworks, such as naphthyl units (**3n-3p**). Additionally, steric influence has little effect on the reaction outcomes for all the three naphthaldehyde substrates (**3n-3p**). Notably, in all cases, the reactions were highly efficient and the products were obtained with excellent yields. The two starting materials were used with nearly 1:1 ratio.

Table 4.4 Examples of 2-hydroxyl aryl aldehyde substrates^a.

 3a : 99%, 94:6 e.r.	 3b : 99%, 96:4 e.r.	 3c : 98%, 96:4 e.r.	 3d : 95%, 96:4 e.r.
 3e : 93%, 91:9 e.r.	 3f : 83%, 92:8 e.r.	 3g : 98%, 94:6 e.r.	 3h : 87%, 91:9 e.r.
 3i : 93%, 90:10 e.r.	 3j : 87%, 97:3 e.r.	 3k : 86%, 93:7 e.r.	 3l : 84%, 98:2 e.r.
 3m : 91%, 97:3 e.r.	 3n : 92%, 98:2 e.r.	 3o : 94%, 95:5 e.r.	 3p : 87%, 94:6 e.r.

^a Conditions as Table 4.1, entry 11. Yields are isolated yield after SiO₂ column chromatography. The e.r. was determined via chiral phase HPLC analysis. Supplementary crystallographic data for **3h** can be found in CCDC 1486140.

We next moved to examine the trifluoromethyl ketone substrates **2** with our standard conditions (Table 4.5). Here we chose 5-methylsalicylaldehyde (**1b**) as a model aldehyde substrate because it is easier to handle than **1a**, as **1b** is a solid at room temperature and stable towards air-oxidation. Different substituents and substitution patterns on the phenyl ring of the ketone substrates were all tolerated (**3b** & **3q-3x**). Electron-donating groups such as methyl (**3q**), methoxy (**3r**) and *N,N*-dimethyl amino group (**3s**) on the phenyl *para*-position were all tolerated, giving the corresponding products with excellent yields and e.r. values. Electron-withdrawing substituents on the phenyl *meta*- or *para*- position (**3t**, **3x**) had little effect on the yields and selectivities. The phenyl substituent of ketone **2a** could be replaced by a heteroaryl substituent (**3y**). Alkyl substituted trifluoromethyl ketones are typically challenging substrates when used as electrophiles because of the ketone/enol isomerization. These substrates were used in our reactions as well (**3z**, **3za**), albeit with a small to moderate drop in the yields and e.r. values.

Table 4.5 Scope of trifluoromethyl ketones^a.

^a Conditions as Table 4.1, entry 11. Yields are isolated yield after SiO₂ column chromatography. The e.r. was determined via chiral phase HPLC analysis. *Replacing 20 mol% **A3** to 20 mol% **A1**.

Our reaction is amenable for large-scale synthesis (Fig. 4.3a). Notably, in the gram scale synthesis, the use of 1 mol% NHC pre-catalyst was sufficient to produce **3b** (1.5 gram) with 98% yield and 96:4 e.r.. Additionally, the organic oxidant (**DQ**) could be used in catalytic amount by using inexpensive MnO_2 as a terminal oxidant⁴³ (Fig. 4.3b).

Fig. 4.3 Scalable and practical synthesis.

Our catalytic reaction product contains a benzo[1,3]dioxin scaffold. This chiral benzo[1,3]dioxin unit itself, and its closely related structures are widely found in natural products and bioactive synthetic molecules. Examples of such molecules include natural product, Epicocconigrone A with anticancer activities⁴⁴, and Efavirenz, which is commercially used as a HIV reverse transcriptase inhibitor⁴⁵. Our laboratory group is interested in the antiviral and antibacterial activities of these compounds for agricultural use⁴⁶⁻⁴⁸. We then evaluated the *in vitro* bioactivities of our products against several types of bacteria and fungi that can cause plant infections (Table 4.6). The commercially available and commonly applied bactericide Kresoxim-methyl was used as the positive control, and dimethyl sulfoxide (DMSO) was used as the negative control. Preliminary studies found that a range of our compounds showed significant activities against eggplant verticillium, phytophthora infestans and fusarium oxysporum. For example, compound **3l** showed 25-38% inhibition rate against the above three fungi at a concentration of 50 $\mu\text{g/mL}$.

Table 4.6 The antifungal activity of our products.

Sample	Inhibition rate (%)		
	Eggplant verticillium	Phytophthora infestans	Fusarium oxysporum
3c	26.10±0.64	26.47±2.45	26.71±2.18
3b	34.98±2.92	16.98±6.26	11.50±2.75
3i	3.60±1.61	10.49±0.93	4.71±1.06
3l	32.91±1.36	38.58±0.59	25.65±0.61
Positive control	100	84.00±3.59	69.61±2.54
Negative control	0	0	0

Inhibitory effects of compounds at a concentration of 50 µg/mL. Each data is the average of three replicates. Kresoxim-methyl was used as the positive control, DMSO was used as negative control.

4.4 Summary.

In short, we have developed a new mode of carbene-catalyzed activation of aryl aldehydes. Addition of carbene catalyst to the aldehyde moiety eventually leads to remote phenol OH activation and dearomatization. The catalytic reaction involves a new NHC-bound intermediate (*o*-QMs) with the oxygen atom as the reactive center. Hydrogen-bond donating co-catalyst (urea or thiourea) works cooperatively with the NHC catalyst, resulting in significant and consistent enhancement of the reaction enantioselectivity. Our method is amenable for large-scale enantioselective synthesis with relatively low loading of the NHC catalyst. Preliminary studies on the bioactivities of our compounds identified a few leads with antifungal activities. We expect our study to encourage further exploration on new reaction modes and alternative intermediates with NHC organic catalysis. Our findings of NHC/urea cooperative catalysis shall provide new possibilities in controlling challenging stereoselectivities, for example, in remote group functionalizations.

4.5 Experimental Section

4.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were

used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), tt (triplet of triplets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

4.5.2 General Procedures.

General procedure for the catalytic synthesis of products 3:

Chiral NHC pre-catalyst **C2** (0.005 mmol, 5 mol%, 2.4 mg), urea **A3** (0.02 mmol, 20 mol%, 8.76 mg), DABCO (0.1 mmol, 100 mol%, 11.2 mg), oxidant **DQ** (0.11 mmol, 110 mol%, 45 mg), aldehyde (0.11 mmol) and 4 Å molecular sieves were added to a 10 mL flame-dry Schlenk reaction tube equipped with a magnetic stir bar. The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). Solvent

(CH₂Cl₂/Hexane =1:1, 2.0 mL) and trifluoromethyl ketone **2** (0.1 mmol) were then added via syringe. The reaction mixture was allowed to stir for 24 hours at -10 °C. After completion of the reaction, monitored by TLC plate, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography or TLC plate directly using hexane/EtOAc as eluent to afford the desired product **3**.

Procedure for scale-up synthesis of 3b with 1 mol% carbene catalyst:

Chiral NHC pre-catalyst **C2** (0.05 mmol, 1 mol%, 24 mg), urea **A3** (1.0 mmol, 20 mol%, 438 mg), DABCO (5.0 mmol, 100 mol%, 560 mg), oxidant **DQ** (5.1 mmol, 102 mol%, 2.08 mg), aldehyde (5.1 mmol, 694mg) and 4 Å molecular sieves were added to a 250 mL flame-dry two-neck round bottom flask (RBF) equipped with a magnetic stir bar. The RBF was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). Solvent (CH₂Cl₂/Hexane =1:1, 100 mL) and trifluoromethyl ketone **2** (5.0 mmol, 870 mg) were then added via syringe. The reaction mixture was allowed to stir for 24 hours at -10 °C. After completion of the reaction, monitored by TLC plate, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography directly using hexane/EtOAc (20/1) as eluent to afford the desired product **3b** 1.5g in 98% yield and 96:4 er.

Procedure for using MnO₂ as terminal oxidant:

Chiral NHC pre-catalyst **C2** (0.005 mmol, 5 mol%, 2.4 mg), urea **A3** (0.02 mmol, 20 mol%, 8.76 mg), DABCO (0.1 mmol, 100 mol%, 11.2 mg), oxidant **DQ** (0.01 mmol, 10 mol%, 4.1 mg), MnO₂ (0.5 mmol, 500 mol%, 43 mg), aldehyde (0.11 mmol) and 4 Å molecular sieves were added to a 10 mL flame-dry Schlenk reaction tube equipped with a magnetic stir bar, was added. The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). Solvent (CH₂Cl₂/Hexane =1:1, 2.0 mL) and trifluoromethyl ketone **2** (0.1 mmol) were then added via syringe. The reaction mixture was allowed to stir for 24 hours at -10°C. After completion of the reaction, monitored by TLC plate, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography directly using hexane/EtOAc as eluent to afford the desired product **3b** with 95% yield and 95:5 er.

Note: Racemic samples for the chiral phase HPLC analysis were prepared using C as the NHC pre-catalyst.

4.5.3 Stereochemistry Determination via X-Ray Crystallographic Analysis.

Good quality crystal of **3h** (colorless needle crystal) was obtained by vaporization of a hexane/ethyl acetate solution of compound **3c** (~500mg). CCDC 1486140 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.5.4 Computational method for mechanism study

We performed density functional theory (DFT) calculations using Gaussian 09 software. For geometry optimization calculations, the B3LYP functional was used in combination with the 6-311G(d) basis set. Single-point calculations on the optimized structures were performed using the dispersion-corrected B3LYP (B3LYP-D3) functional and the 6-311+G(d,p) basis set, with Grimme's D3 correction combined with Becke-Johnson (BJ) damping. The solvent effect of DCM was taken into account using the IEF-PCM method in single-point calculations. Although a mixed solvent (CH_2Cl_2 /hexane = 1:1) was used in the optimized experimental condition, for the sake of simplicity, we examined the effect of CH_2Cl_2 because a similar e.r. was observed experimentally with this solvent. Vibrational frequency calculations were performed to confirm that each optimized structure resides at a stationary point on the potential energy surface. Free energy corrections were also obtained from frequency calculations. All relative energies are free energy at $-10\text{ }^\circ\text{C}$ (263.15 K) and 1 atm. Mulliken atomic charges were calculated at the B3LYP/6-311G(d) level.

Conformation of triazolium salt precursor **C2**

Triazolium salt precursor **C2** has two conformers (A and B in Fig. 4.4) that differ in the geometry of the oxygen-containing ring. Conformer A is more stable than conformer B by 1.3 kcal/mol. Therefore, in the following calculations, conformer A was used for **C2**.

Figure 4.4 Optimized structures of triazolium salt precursor **C2**. Relative free energies are shown in kcal/mol and are with respect to conformer A.

Optimized structures of conformers of intermediate II:

DFT calculations were used to assess the nature of *o*-QM in intermediate II. Six conformers of II were obtained from DFT calculations, and II-1 was the most stable one. A weak CH $\cdots$ O hydrogen bond between the phenolate oxygen and hydrogen atom of the indane moiety from the NHC catalyst was formed in II-1 but not in II-2, which makes the intermediate II-1 more stable by 0.9 kcal/mol. II-3 and II-4 are even less stable, probably because the phenolate oxygen points away from the NHC group, leading to weaker electrostatic stabilization. II-5 and II-6 (Fig. 4.5), in which a carbon atom of the azolium ring forms a covalent bond with the phenolate oxygen atom, are less stable than II-1. The covalent bond in II-5 and II-6 prevents the azolium ring from gaining resonance stabilization that II-1 can have, and this explains the difference in stability of these intermediates. Key Mulliken atomic charges for II-2 are given in Table 4.7. The charge distribution in II-2 is similar to that in II-1.

Figure 4.5 Optimized structures of the six conformers of intermediate II. Relative free energies are shown in kcal/mol and are with respect to II-1. Key interatomic distances are indicated in Å.

Table 4.7 Key Mulliken atomic charges for II-2.

Group	Mulliken Charge
+NHC	0.51
C1	0.20
O1	-0.35
O2	-0.45

Mechanisms of [4+2] annulation without urea

The calculations excluding urea suggest that NHC-bound intermediate II can react with ketone substrate **2a** in a [4+2] mechanism (Fig. 1c) to afford a ketal-like product, without having a barrier too high. Our calculations also suggest that the reaction should consist of two steps: (1) a ring-annulation step and (2) an NHC dissociation step (see Fig. 4.6). The four conformers (II-1, II-2, II-3, and II-4) in Fig 4.5 can react with **2a**, giving rise to several possible reaction pathways (16 pathways in total). Nevertheless, here we focus on low-energy pathways. When the resultant product does not have the predominant stereochemical pattern observed in the experiment, “minor” is attached to the labels. The *o*-QM moiety has two distinct faces on which **2a** can possibly attack, and thus reaction pathways may be classified into Paths A and B; Path A features the attack of **2a** on II from the “indane side” depicted in Fig. 4.7, whereas Path B involves the attack from the “PhCl₃ side” in Fig. 4.7. For example, Path 1-A corresponds to the attack of **2a** on II-1 from the indane side. Each of Paths A and B can also have two pathways that differ in the orientation of substrate **2a**.

Figure 4.6 Reaction mechanism obtained from DFT calculations

Figure 4.7 The indane and PhCl_3 sides of **II-1**

[4+2] annulation pathways without urea for intermediates **II-1** or **II-2**:

Our DFT calculations on the reactions of **II-1** and **II-2** with **2a** without urea showed that this reaction consists of two steps: (1) a ring-annulation step and (2) an NHC dissociation step. It should be noted that Path 1-A proceeds in a concerted fashion and the optimized structure of **TS2_{1-A}** is similar to those of several other **TS2s** for the NHC dissociation step. After the formation of the product (the minor enantiomeric product), the NHC catalyst is recovered and may abstract a proton from H^+ -DABCO (protonated base) to regenerate the triazolium salt precursor. The regeneration of the triazolium salt precursor is exothermic by 8.2 kcal/mol (Fig. 4.8).

Table 4.8 Relative free energies of different species formed in four [4+2] annulation pathways for II-1

	RC	TS1	Int1	TS2	PC
Path 1-A	0.0	-	-	16.8	5.7
Path 1-A-minor	1.1	13.4	13.0	18.3	5.6
Path 1-B	2.1	13.9	13.7	19.5	1.3
Path 1-B-minor	1.9	12.8	12.3	18.4	4.5

*Relative free energies are shown in kcal/mol and are with respect to RC_{1-A}

Table 4.9 Relative free energies of different species formed in four [4+2] annulation pathways for II-2

	RC	TS1	Int1	TS2	PC
Path 2-A	5.1	13.2	12.3	17.7	8.7
Path 2-A-minor	3.3	10.4	10.0	17.4	6.3
Path 2-B	2.3	17.0	14.9	19.5	6.8
Path 2-B-minor	1.3	18.9	14.6	19.9	7.7

*Relative free energies are shown in kcal/mol and are with respect to RC_{1-A}

Table 4.10 Relative free energies of key species in Path 1-A-minor at B3LYP-D3/6-311+G(d,p) or M06-2X/6-311+G(d,p) (ref. 14).

	RC	TS1	Int1	TS2
B3LYP-D3	0.0	12.3	11.9	17.2
M06-2X ¹	0.0	4.5	4.2	4.2

¹Dispersion corrections were calculated using Grimme's D3 correction combined with zero-damping.

*Relative free energies are shown in kcal/mol and are with respect to RC_{1-A-minor}.

*Geometry optimization was performed at the B3LYP/6-311G(d) level.

Figure 4.8 Regeneration of the triazolium salt precursor from the NHC catalyst.

[4+2] annulation pathways without urea for intermediates II-3 or II-4:

We also examined the reactions of conformers II-3 and II-4 with **2a**, and in these conformers, the phenolate oxygen points away from the NHC group. The reaction on Path 3-A can take place via a 6-membered ring intermediate (Int1_{3-A}), which should be structurally equivalent to Int1_{2-B}, as illustrated in Fig. 4.9. In a similar fashion, Paths 3-B, 4-A, and 4-B also involve 6-membered ring intermediates, which should be structurally equivalent to Int1_{2-A}, Int1_{1-B}, and Int1_{1-A}, respectively. However, as shown in Tables 4.11 and 4.12, Int1's on Paths 3-A, 3-B, 4-A, and 4-B are not as stable as Int1's on Paths 2-B, 2-A, 1-B, and 1-A, respectively. It should be noted that these energy differences are small, which therefore suggests that Int1's on Paths 3-A, 3-B, 4-A, and 4-B may be readily converted into the corresponding Int1's (Int1's in Tables 4.11 and 4.12) before the NHC dissociation process. Thus, we assumed that TS2's and PC's on Paths 3-A, 3-B, 4-A, and 4-B are equivalent to those on Paths 2-B, 2-A, 1-B, and 1-A, respectively.

Figure 4.9 The first step of the [4+2] annulation in Paths 3-A and 2-B

Table 4.11 Relative free energies of different species formed in four [4+2] annulation pathways for II-3

	RC	TS1	Int1	Int1'	TS2	PC
Path 3-A	7.9	12.7	11.7	14.9 (Int1 _{2-B})	19.5 (TS2 _{2-B})	6.8 (PC _{2-B})
Path 3-A-minor	10.0	14.4	14.2	14.6 (Int1 _{2-B-minor})	19.9 (TS2 _{2-B-minor})	7.7 (PC _{2-B-minor})
Path 3-B	7.4	19.1	12.9	12.3 (Int1 _{2-A})	17.7 (TS2 _{2-A})	8.7 (PC _{2-A})
Path 3-B-minor	7.3	16.6	14.4	10.0 (Int1 _{2-A-minor})	17.4 (TS2 _{2-A-minor})	6.3 (PC _{2-A-minor})

*Relative free energies are shown in kcal/mol and are with respect to RC_{1-A}.

Table 4.12 Relative free energies of different species formed in four [4+2] annulation pathways for II-4

	RC	TS1	Int1	Int1'	TS2	PC
Path 4-A	8.2	15.3	14.7	13.7 (Int1 _{1-B})	19.5 (TS2 _{1-B})	1.3 (PC _{1-B})
Path 4-A-minor	6.4	12.9	12.3	12.3 (Int1 _{1-B-minor})	18.4 (TS2 _{1-B-minor})	4.5 (PC _{1-B-minor})
Path 4-B	8.7	19.0	15.6	-	16.8 (TS2 _{1-A})	5.7 (PC _{1-A})
Path 4-B-minor	8.3	21.6	21.9	13.0 (Int1 _{1-A-minor})	18.3 (TS2 _{1-A-minor})	5.6 (PC _{1-A-minor})

*Relative free energies are shown in kcal/mol and are with respect to RC_{1-A}

Reaction mechanisms with urea co-catalyst:

Our DFT calculations without urea showed that step 2 is more important than step 1. We calculated the reaction mechanism in Path 1-A with thiourea **A1** and obtained three transition states, namely A1-TS1_{1-A}, A1-TS1'_{1-A}, and A1-TS2_{1-A}, as shown in Fig. 4.10.

For the reaction without urea, the NHC dissociation step has the highest energy. Overall, the reaction looks endothermic, but after the formation of PC, NHC can be further stabilized by forming a triazolium salt precursor. Note that **A1** is attached on the label when **A1** is added in the system. Thiourea A1 interacts with ketone through a hydrogen bond that should make ketone more reactive, and therefore the activation energy for the ring-annulation step should be lowered. In the calculations with **A1**, we examined several binding modes of **A1** to find the most stable TS1_{1-A} and TS2_{1-A}. We obtained one binding mode for A1-TS1_{1-A} (Fig. 4.10) and two binding mode for A1-TS2_{1-A} (Fig. 4.11). A1-TS2_{1-A}, in which **A1** forms hydrogen bonds with the carbonyl oxygen of *o*-QM, is more stable than A1-TS2_{1-A'}, where **A1** forms hydrogen bonds with the CF₃ group of ketone. It should be noted that A3-TS2's, which are involved in the reaction with urea **A3**, should be the rate-determining step because the urea moiety of both **A1** and **A3** should interact with the same atom(s) through hydrogen bond(s) in each key species, and therefore A1-TS1's and A3-TS1's should be stabilized by the same hydrogen bond(s).

Figure 4.10 Energy diagram of the reaction with urea **A1** and structures of key species. Relative free energies are shown in kcal/mol and are with respect to A1-RC_{1-A}.

Figure 4.11 Schematic drawing of A1-TS2_{1-A} and A1-TS2_{1-A'}. Relative free energies are shown in kcal/mol and are with respect to A1-TS2_{1-A}.

Table 4.13 Relative free energies of transition states in Path 1-A with urea **A1** at the B3LYP-D3/6-311+G(d,p) and M06-2X/6-311+G(d,p) levels.

	A1-TS1 _{1-A}	A1-TS1' _{1-A}	A1-TS2 _{1-A}
B3LYP-D3	0.0	0.0	7.7
M06-2X ¹	0.0	0.0	5.8

¹Dispersion corrections were calculated using Grimme's D3 correction combined with zero-damping.

*Relative free energies are shown in kcal/mol and are with respect to TS1.

*Geometry optimization was performed at the B3LYP/6-311G(d) level.

Energy differences of A3-TS2's:

We further investigated each A3-TS2's to identify the key factors that control the enantioselectivity (Table 4.14). A3-TS2_{1-A}, which is the lowest-energy in A3-TS2, was found to have attractive π - π stacking between the pentafluorophenyl group of urea **A3** and the indane moiety of the catalyst. Such π - π stacking was also observed in A3-TS2_{1-A-minor}, but was not found in other A3-TS2's. Therefore, A3-TS2_{1-A} and A3-TS2_{1-A-minor} are more stable than the other A3-TS2's. Note that we examined several binding modes between TS2 and urea **A3** in each pathway to obtain the lowest-energy A3-TS2 (Table 4.15).

Table 4.14 Relative free energies of TS2 with urea A3 calculated at the B3LYP-D3/6-311+G(d,p) and M06-2X/6-311+G(d,p) levels.

	A3-TS2 _{1-A}	A3-TS2 _{1-A-minor}	A3-TS2 _{1-B}	A3-TS2 _{1-B-minor}	A3-TS2 _{2-A}	A3-TS2 _{2-A-minor}
B3LYP-D3	0.0	2.8	4.1	3.9	4.2	4.3
M06-2X ¹	0.0	2.7	5.8	3.6	4.3	4.0

	A3-TS2 _{2-B}	A3-TS2 _{2-B-minor}
B3LYP-D3	4.4	4.7
M06-2X ¹	3.9	5.8

¹Dispersion corrections were calculated using Grimme's D3 correction combined with zero damping.

*Relative free energies are shown in kcal/mol and are with respect to TS2_{1-A}.

*Geometry optimization was performed at the B3LYP/6-311G(d) level.

Table 4.15 Free energy differences of optimized structures of A3-TS2's

	A3-TS2 _{1-A}	A3-TS2 _{1-A-minor}	A3-TS2 _{1-B}	A3-TS2 _{1-B-minor}	A3-TS2 _{2-A}	A3-TS2 _{2-A-minor}
1	0.0	2.8	4.1	3.9	4.2	4.3
2	2.9	4.3	4.4	4.2	5.0	5.5
3	3.5	6.5	4.8	-	-	6.1
4	-	-	5.1	-	-	6.6

	A3-TS2 _{2-B}	A3-TS2 _{2-B-minor}
B		
1	4.4	4.7
2	6.5	5.1
3	-	-
4	-	-

*Relative free energies are shown in kcal/mol and are with respect to A3-TS2_{1-A}

4.5.5 Characterization of products.

(S)-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3a): colorless oil, 99%

yield, 29.2 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.08 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 1.6$ Hz, 1H), 7.19-7.41 (m, 3H), 7.58 (t, $J = 8.8$ Hz, 1H), 7.64 (t, $J = 6.4$ Hz, 2H), 7.83 (dd, $J = 1.6, 7.6$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 101.5 (q, $J = 34.5$ Hz), 113.9, 117.4, 120.3 (q, $J = 283$ Hz), 124.0, 128.1, 128.8, 130.1, 131.1, 131.4, 137.2, 154.6, 157.9; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1762, 1467, 1300, 1265, 1124, 738; $[\alpha]_{\text{D}}^{23} = 69.5$ ($c = 1.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_9\text{F}_3\text{O}_3\text{H}^+$ 295.0577, found 295.0574; **HPLC analysis**: 94:6 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 7.8 min (major), 7.5 min (minor)].

(S)-6-methyl-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3b):

colorless oil. 99% yield, 30.6 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.26 (s, 3H), 7.07 (d, $J = 8.4$ Hz, 1H), 7.35-7.41 (m, 4H), 7.61-7.65 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 20.4, 101.4 (q, $J = 34.3$ Hz), 113.6, 117.1, 120.3 (q, $J = 282.7$ Hz), 128.2, 128.8, 129.9, 130.0, 131.6, 133.8, 138.1, 152.6, 158.1; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1764, 1494, 1265, 1203, 742; $[\alpha]_{\text{D}}^{22} = 66.8$ ($c = 2.6$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{O}_3\text{H}^+$ 309.0733, found 309.0728; **HPLC analysis**: 96:4 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 8.2 min (major), 7.6 min (minor)].

(S)-6-methoxy-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3c): light

yellow oil. 98% yield, 31.7 mg; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.73 (s, 3H), 7.09-7.16 (m, 2H), 7.25 (d, $J = 4.8$ Hz, 1H), 7.37-7.41 (m, 3H), 7.62 (d, $J = 7.2$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 55.8, 101.5 (q, $J = 35.0$ Hz), 111.3, 114.1, 118.6, 120.3 (q, $J = 282.6$ Hz), 125.5,

128.2, 128.8, 131.0, 131.5, 148.7, 155.6, 158.1; ^{19}F NMR (376 MHz, CDCl_3) δ -83.1; **IR** ν_{max} (film, cm^{-1}): 1766, 1494, 1265, 1232, 1201, 738; $[\alpha]_{\text{D}}^{23} = 44.5$ ($c = 2.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{O}_4\text{H}^+$ 325.0682, found 325.0676; **HPLC analysis**: 96:4 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 12.3 min (major), 10.9 min (minor)].

(S)-6-ethyl-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3d):

3d: 95%, 96:4 er

yellowish oil. 95% yield, 30.4 mg; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (t, $J = 7.6$ Hz, 3H), 2.56 (q, $J = 7.6$ Hz, 2H), 7.09 (d, $J = 7.6$ Hz, 1H), 7.35-7.42 (m, 4H), 7.64 (d, $J = 3.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 15.0, 27.8, 101.4 (q, $J = 34.4$ Hz), 113.6, 117.2, 120.3 (q, $J = 282.9$ Hz), 128.2, 128.7, 128.8, 131.0, 131.6, 137.1, 140.1, 152.7, 158.2; ^{19}F NMR (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1766, 1496, 1265, 1234, 1203, 738; $[\alpha]_{\text{D}}^{22} = 52.6$ ($c = 3.0$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_3\text{H}^+$ 323.0890, found 323.0885; **HPLC analysis**: 96:4 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 9.6 min (major), 8.6 min (minor)].

(S)-6-chloro-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3e):

3e: 93%, 91:9 er

colorless oil. 31.4 mg, 93% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.08 (d, $J = 7.6$ Hz, 1H), 7.23 (s, 1H), 7.38-7.44 (m, 3H), 7.63 (d, $J = 6.8$ Hz, 2H), 7.77 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 101.8 (q, $J = 34.5$ Hz), 112.4, 117.8, 120.1 (q, $J = 282.8$ Hz), 124.8, 128.0, 129.0, 131.0, 131.2, 131.3, 143.4, 155.0, 157.1; ^{19}F NMR (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1766, 1608, 1423, 1265, 1203, 750; $[\alpha]_{\text{D}}^{22} = 153.8$ ($c = 2.9$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_8\text{ClF}_3\text{O}_3\text{H}^+$ 329.0187, found 329.0186; **HPLC analysis**: 91:9 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 8.3 min (major), 7.5 min (minor)].

(S)-6-bromo-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3f): light

3f: 83%, 92:8 er

yellow oil. 31 mg, 83% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.09

(d, $J = 8.8$ Hz, 1H), 7.38-7.44 (m, 3H), 7.61 (d, $J = 7.6$ Hz, 2H),

6.66 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.95 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR

(100 MHz, CDCl_3) δ 101.7 (q, $J = 34.8$ Hz), 115.4, 116.5, 119.2, 120.1 (q, $J = 282.9$ Hz),

128.1, 129.0, 131.0, 131.3, 132.5, 140.1, 153.6, 156.6; ^{19}F NMR (376 MHz, CDCl_3) δ -

83.1; **IR** ν_{max} (film, cm^{-1}): 1774, 1473, 1265, 1236, 1203, 738; $[\alpha]_{\text{D}}^{21} = 44.1$ ($c = 2.9$ in

CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_8\text{BrF}_3\text{O}_3\text{H}^+$ 372.9682, found 372.8684; **HPLC**

analysis: 92:8 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane

= 1:99; retention times: 8.8 min (major), 7.9 min (minor)].

(S)-7-methoxy-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3g):

3g: 98%, 94:6 er

colorless oil. 31.7 mg, 98% yield; ^1H NMR (400 MHz, CDCl_3) δ

3.86 (s, 1H), 6.60-6.64 (m, 2H), 7.38-7.41 (m, 3H), 7.64 (d, $J =$

8.0 Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz,

CDCl_3) δ 55.9, 101.4, 101.5 (q, $J = 34.0$ Hz), 106.5, 111.5, 120.3 (q, $J = 282.6$ Hz), 128.0,

128.8, 131.0, 131.6, 131.7, 156.5, 157.7, 166.9; ^{19}F NMR (376 MHz, CDCl_3) δ -83.2;

IR ν_{max} (film, cm^{-1}): 1759, 1620, 1444, 1265, 1207, 1126, 742; $[\alpha]_{\text{D}}^{23} = 183.5$ ($c = 2.4$ in

CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{O}_4\text{H}^+$ 325.0682, found 325.0680; **HPLC**

analysis: 94:6 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane

= 5:95; retention times: 13.4 min (major), 9.5 min (minor)].

(S)-7-bromo-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3h): white

3h: 87%, 91:9 er

powder 32.3 mg, 87% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.24

(dd, $J = 1.6, 8.4$ Hz, 1H), 7.40-7.44 (m, 4H), 7.62 (d, $J = 8.0$ Hz,

2H), 7.69 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 101.8

(q, $J = 34.7$ Hz), 112.8, 120.6 (q, $J = 282.9$ Hz), 120.8, 127.7, 128.0, 129.0, 131.0, 131.1,

131.3, 131.8, 154.9, 157.2; ^{19}F NMR (376 MHz, CDCl_3) δ -83.1; **IR** ν_{max} (film, cm^{-1})

¹): 1766, 1602, 1423, 1265, 1203, 1080, 738; $[\alpha]^{23}_{\text{D}} = 173.5$ ($c = 3.0$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{15}\text{H}_8\text{BrF}_3\text{O}_3\text{H}^+$ 372.9682, found 372.9681; **HPLC analysis**: 91:9 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 9.3 min (major), 8.1 min (minor)].

Methyl (S)-4-oxo-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxine-7-carboxy-

-late (3i): yellowish oil. 32.7 mg, 93% yield; ¹H NMR (400 MHz, CDCl_3) δ 3.95 (s, 3H), 7.37-7.43 (m, 3H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.86 (s, 1H), 7.91 (d, $J =$

8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl_3) δ 52.9, 101.8 (q, $J = 34.6$ Hz), 117.2, 118.7, 120.6 (q, $J = 282.6$ Hz), 124.5, 128.2, 129.0, 130.3, 130.9, 131.3, 138.1, 154.5, 157.2, 164.9; ¹⁹F NMR (376 MHz, CDCl_3) δ -83.1; **IR** ν_{max} (film, cm^{-1}): 1768, 1730, 1429, 1265, 1203, 738; $[\alpha]^{22}_{\text{D}} = 155.1$ ($c = 2.1$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{11}\text{F}_3\text{O}_5\text{H}^+$ 353.0631, found 353.0628; **HPLC analysis**: 90:10 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 10:90; retention times: 12.0 min (major), 8.9 min (minor)].

(S)-8-ethoxy-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3j):

yellowish oil. 29.4 mg, 87% yield; ¹H NMR (400 MHz, CDCl_3) δ 1.52 (t, $J = 7.6$ Hz, 3H), 4.18 (q, $J = 7.6$ Hz, 2H), 6.98 (t, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 1H), 7.34-7.40 (m, 4H), 7.66 (d, $J = 6.8$ Hz, 2H);

¹³C NMR (100 MHz, CDCl_3) δ 14.7, 65.2, 101.8 (q, $J = 34.4$ Hz), 115.0, 120.0, 120.3 (q, $J = 282.7$ Hz), 120.7, 123.7, 127.9, 128.8, 131.1, 131.5, 144.8, 147.7, 158.0; ¹⁹F NMR (376 MHz, CDCl_3) δ -83.1; **IR** ν_{max} (film, cm^{-1}): 1755, 1593, 1475, 1230, 1136, 746; $[\alpha]^{23}_{\text{D}} = 204.8$ ($c = 2.9$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_4\text{H}^+$ 339.0839, found 339.0833; **HPLC analysis**: 97:3 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 5:95; retention times: 8.9 min (major), 8.3 min (minor)].

(S)-8-methyl-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3k): **3k:** 86%, 93:7 er

yellowish oil. 26.5 mg, 86% yield; ^1H NMR (400 MHz, CDCl_3) δ 2.43 (s, 3H), 6.98 (t, $J = 7.6$ Hz, 1H), 7.35-7.42 (m, 4H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.9, 101.5 (q, $J = 34.1$ Hz), 113.7, 120.8 (q, $J = 282.7$ Hz), 123.4, 126.6, 127.6, 127.7, 128.9, 131.1, 131.6, 138.2, 152.8, 158.2; ^{19}F NMR (376 MHz, CDCl_3) δ -83.1; IR ν_{max} (film, cm^{-1}): 1759, 1483, 1185, 1201, 1132, 750; $[\alpha]_{\text{D}}^{21} = 94.4$ ($c = 2.5$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{O}_3\text{H}^+$ 309.0733, found 309.0732; HPLC analysis: 93:7 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 10.0 min (major), 8.6 min (minor)].

(S)-5,7-dimethyl-2-phenyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3l): **3l:** 84%, 98:2 er

yellowish oil. 26.9 mg, 84% yield; ^1H NMR (400 MHz, CDCl_3) δ 2.31 (s, 3H), 2.50 (s, 3H), 6.69 (s, 1H), 6.83 (s, 1H), 7.37 (m, 3H), 7.62 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 21.8, 100.6 (q, $J = 33.9$ Hz), 109.9, 115.5, 120.4 (q, $J = 282.9$ Hz), 128.1, 128.7, 130.8, 131.8, 144.0, 147.7, 155.5, 157.4; ^{19}F NMR (376 MHz, CDCl_3) δ -83.3; IR ν_{max} (film, cm^{-1}): 1759, 1484, 1185, 1203, 1132, 750; $[\alpha]_{\text{D}}^{21} = 92.7$ ($c = 2.5$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_3\text{H}^+$ 323.0890, found 323.0888; HPLC analysis: 98:2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 5:95; retention times: 8.3 min (major), 7.7 min (minor)].

(S)-6-phenyl-6-(trifluoromethyl)-8H-[1,3]dioxolo[4',5':4,5]benzo[1,2-d][1,3]dioxin-8-one (3m): **3m:** 91%, 97:3 er

yellowish oil. 30.7 mg, 91% yield; ^1H NMR (400 MHz, CDCl_3) δ 5.97 (s, 1H), 6.02 (s, 1H), 6.63 (s, 1H), 7.12 (s, 1H), 7.37-7.42 (m, 3H), 7.62 (d, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 98.4, 101.4 (q, $J = 37.0$ Hz), 102.7, 106.5, 107.0, 120.7 (q, $J = 286.1$ Hz), 128.0, 128.8, 131.0, 131.4, 144.4, 152.1, 155.1, 157.6; ^{19}F NMR (376

MHz, CDCl_3) δ -83.1; **IR** ν_{max} (film, cm^{-1}): 1751, 1463, 1265, 1207, 738; $[\alpha]_{\text{D}}^{23} = 120.6$ ($c = 2.3$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_9\text{F}_3\text{O}_5\text{H}^+$ 339.0475, found 339.0475; **HPLC analysis**: 97:3 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 5:95; retention times: 16.6 min (major), 12.2 min (minor)].

(S)-3-phenyl-3-(trifluoromethyl)-1H-naphtho[2,1-d][1,3]dioxin-1-one (3n): yellowish

3n: 92%, 98:2 er

oil. 31.6 mg, 92% yield; **^1H NMR** (400 MHz, CDCl_3) δ 7.30-7.37 (m, 4H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.61-7.78 (m, 4H), 8.06 (d, $J = 8.8$ Hz, 1H), 9.05 (d, $J = 8.4$ Hz, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ 101.0 (q, $J = 33.6$ Hz), 106.4, 116.7, 120.3 (q, $J = 283.9$ Hz), 125.6, 126.0, 128.0, 128.8, 130.1, 131.1, 131.3, 131.4, 139.0, 156.3, 157.2; **^{19}F NMR** (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1751, 1517, 1265, 1203, 1130, 734; $[\alpha]_{\text{D}}^{21} = -54.4$ ($c = 1.5$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{11}\text{F}_3\text{O}_3\text{H}^+$ 345.0733, found 345.0731; **HPLC analysis**: 98:2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 5:95; retention times: 8.7 min (major), 8.3 min (minor)].

(S)-2-phenyl-2-(trifluoromethyl)-4H-naphtho[1,2-d][1,3]dioxin-4-one (3o): white

3o: 94%, 95:5 er

powder. 32.2 mg, 94% yield; **^1H NMR** (400 MHz, CDCl_3) δ 7.29-7.37 (m, 3H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.69-7.73 (m, 5H), 8.82 (d, $J = 7.6$ Hz, 1H), 8.44 (d, $J = 6.4$ Hz, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ 101.9 (q, $J = 34.5$ Hz), 108.6, 120.4 (q, $J = 282.7$ Hz), 122.5, 123.1, 123.2, 124.7, 127.5, 127.6, 128.3, 128.9, 130.5, 131.2, 131.4, 137.7, 152.9, 158.1; **^{19}F NMR** (376 MHz, CDCl_3) δ -83.0; **IR** ν_{max} (film, cm^{-1}): 1759, 1635, 1388, 1265, 1064, 738; $[\alpha]_{\text{D}}^{23} = 338.3$ ($c = 2.0$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{19}\text{H}_{11}\text{F}_3\text{O}_3\text{H}^+$ 345.0733, found 345.0730; **HPLC analysis**: 95:5 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 5:95; retention times: 9.7 min (major), 8.3 min (minor)].

(S)-2-phenyl-2-(trifluoromethyl)-4H-naphtho[2,3-*d*][1,3]dioxin-4-one (3p): colorless

3p: 87%, 94:6 er

oil. 29.9 mg, 87% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.38

(m, 3H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.56-7.81 (m, 6H), 8.47 (s, 1H);

^{13}C NMR (100 MHz, CDCl_3) δ 101.5 (q, $J = 34.4$ Hz), 113.6,

113.8, 120.9 (q, $J = 282.7$ Hz), 126.2, 127.1, 128.4, 128.9, 129.4, 129.8, 130.2, 131.0,

131.7, 133.1, 137.7, 149.6, 158.5; ^{19}F NMR (376 MHz, CDCl_3) δ -83.1; **IR** ν_{max} (film,

cm^{-1}): 1766, 1639, 1265, 1207, 732; $[\alpha]^{23}_{\text{D}} = 258.2$ ($c = 2.0$ in CHCl_3); **HRMS** (ESI, m/z):

calcd. for $\text{C}_{19}\text{H}_{11}\text{F}_3\text{O}_3\text{H}^+$ 345.0733, found 345.0733; **HPLC analysis:** 94:6 er,

[CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 20.2 min (major), 12.3 min (minor)].

(S)-6-methyl-2-(p-tolyl)-2-(trifluoromethyl)-4H-benzo[*d*][1,3]dioxin-4-one (3q):

3q: 99%, 98:2 er

colorless oil. 99% yield, 31.7 mg; ^1H NMR (400 MHz,

CDCl_3) δ 2.25 (s, 3H), 2.30 (s, 3H), 7.05 (d, $J = 8.4$ Hz,

1H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.36 (dd, $J = 2.0, 8.4$ Hz, 1H),

7.50 (d, $J = 8.0$ Hz, 2H), 7.61 (s, 1H); ^{13}C NMR (100 MHz,

CDCl_3) δ 20.5, 21.2, 101.5 (q, $J = 34.3$ Hz), 113.7, 117.1, 120.3 (q, $J = 282.5$ Hz), 128.1,

128.5, 129.5, 129.8, 133.7, 138.0, 141.3, 152.6, 158.3; ^{19}F NMR (376 MHz, CDCl_3) δ -

83.3; **IR** ν_{max} (film, cm^{-1}): 1762, 1494, 1265, 1184, 736; $[\alpha]^{23}_{\text{D}} = 63.8$ ($c = 2.7$ in CHCl_3);

HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_3\text{H}^+$ 323.0890, found 323.0888; **HPLC analysis:**

98:2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99;

retention times: 9.8 min (major), 9.1 min (minor)].

(S)-2-(4-methoxyphenyl)-6-methyl-2-(trifluoromethyl)-4H-benzo[*d*][1,3]dioxin-4-one

3r: 99%, 98:2 er

(3r): yellowish oil. 99% yield, 33.5 mg; ^1H NMR (400

MHz, CDCl_3) δ 2.26 (s, 3H), 3.76 (s, 3H), 6.85 (d, $J =$

6.8 Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 1H), 7.36 (dd, $J = 2.0,$

8.4 Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.61 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.4, 55.3, 101.5 (q, $J = 34.2$ Hz), 113.7, 114.2, 117.1, 120.3 (q, $J = 282.5$ Hz), 123.2, 129.7, 129.8, 133.7, 138.0, 152.6, 158.3, 161.5; ^{19}F NMR (376 MHz, CDCl_3) δ -83.5; IR ν_{max} (film, cm^{-1}): 1762, 1494, 1265, 1203, 1087, 740; $[\alpha]_{\text{D}}^{21} = 62.8$ ($c = 1.7$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_4\text{H}^+$ 339.0839, found 339.0834; HPLC analysis: 98:2 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 5:95; retention times: 10.3 min (major), 9.6 min (minor)].

(S)-2-(4-(dimethylamino)phenyl)-6-methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]

dioxin-4-one (3s): yellowish oil. 96% yield, 33.6 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.25 (s, 3H), 2.93 (s, 6H), 6.59 (d, $J = 8.8$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.62 (s, 1H); ^{13}C

NMR (100 MHz, CDCl_3) δ 20.5, 39.9, 102.1 (q, $J = 32.3$ Hz), 111.4, 113.9, 117.1, 117.4, 120.5 (q, $J = 281.3$ Hz), 129.2, 129.8, 133.4, 137.8, 151.6, 152.8, 158.8; ^{19}F NMR (376 MHz, CDCl_3) δ 83.6; IR ν_{max} (film, cm^{-1}): 1762, 1612, 1265, 1184, 894, 738; $[\alpha]_{\text{D}}^{22} = 60.1$ ($c = 1.3$ in CHCl_3); HRMS (ESI, m/z): calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{NO}_3\text{H}^+$ 352.1155, found 352.1154; HPLC analysis: 98:2 er, [CHIRALPAK ID column; 0.5 mL/min; solvent system: i-PrOH/hexane = 0.5:99.5; retention times: 21.8 min (major), 22.8 min (minor)].

(S)-6-methyl-2-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-4H-benzo[d][1,3]

dioxin-4-one (3t): colorless oil. 98% yield, 36.8 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (s, 3H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 3H), 7.79 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ

20.4, 100.7 (q, $J = 34.6$ Hz), 113.3, 117.0, 120.1 (q, $J = 283.2$ Hz), 123.3 (q, $J = 271.1$ Hz), 125.8, 128.7, 130.0, 133.2 (q, $J = 32.8$ Hz), 134.3, 135.6, 138.4, 152.3, 157.5; ^{19}F NMR (376 MHz, CDCl_3) δ -63.2, -82.9; IR ν_{max} (film, cm^{-1}): 1766, 1327, 1265, 1136, 740;

$[\alpha]^{22}_{\text{D}} = 52.8$ ($c = 3.2$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{10}\text{F}_6\text{O}_3\text{H}^+$ 377.0607, found 377.0601; **HPLC analysis**: 97:3 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 9.2 min (major), 8.6 min (minor)].

(S)-2-(4-chlorophenyl)-6-methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one

(3u): colorless oil. 99% yield, 33.7 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (s, 3H), 7.06 (d, $J = 8.4$ Hz, 1H), 7.34-7.41 (m, 3H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 100.7 (q, $J = 37.9$ Hz), 113.4, 117.1, 120.1 (q, $J = 283.8$ Hz), 129.2, 129.6, 129.9, 130.2, 134.1, 137.5, 138.3, 152.3, 157.8; ^{19}F NMR (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1766, 1494, 1265, 1199, 1087, 819; $[\alpha]^{23}_{\text{D}} = 54.2$ ($c = 2.6$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{10}\text{ClF}_3\text{O}_3\text{H}^+$ 343.0343, found 343.0340; **HPLC analysis**: 96:4 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 9.1 min (major), 8.4 min (minor)].

(S)-2-(4-bromophenyl)-6-methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one

(3v): colorless oil. 99% yield, 38.1 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (s, 3H), 7.06 (d, $J = 8.4$ Hz, 1H), 7.39 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.49-7.53 (m, 4H), 7.63 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 101.1 (q, $J = 34.5$ Hz), 113.4, 117.1, 120.1 (q, $J = 282.8$ Hz), 125.9, 129.7, 129.9, 130.7, 132.2, 134.1, 138.3, 152.3, 157.7; ^{19}F NMR (376 MHz, CDCl_3) δ -83.2; **IR** ν_{max} (film, cm^{-1}): 1766, 1622, 1496, 1288, 1203, 704; $[\alpha]^{22}_{\text{D}} = 45.6$ ($c = 3.2$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{10}\text{BrF}_3\text{O}_3\text{H}^+$ 386.9838, found 386.9838; **HPLC analysis**: 95:5 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 2:98; retention times: 8.1 min (major), 7.7 min (minor)].

(S)-2-(3-bromophenyl)-6-methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one **3w**: 96%, 93:7 er

(3w): colorless oil. 96% yield, 37.1 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (s, 3H), 7.08 (d, J = 8.4 Hz, 1H), 7.26 (t, J = 8.4 Hz, 1H), 7.40 (dd, J = 2.0, 8.4 Hz, 1H), 7.53-7.76 (m, 2H), 7.64 (s, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 100.5 (q, J = 34.5 Hz), 113.3, 117.1, 120.1 (q, J = 283.3 Hz), 123.1, 126.9, 130.0, 130.3, 131.1, 133.9, 134.2, 134.3, 138.4, 152.3, 157.6; ^{19}F NMR (376 MHz, CDCl_3) δ -83.0; **IR** ν_{max} (film, cm^{-1}): 1766, 1265, 1203, 738; $[\alpha]_{\text{D}}^{23}$ = 53.8 (c = 2.4 in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{16}\text{H}_{10}\text{BrF}_3\text{O}_3\text{H}^+$ 386.9838, found 386.9836; **HPLC analysis**: 93:7 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 2:98; retention times: 8.3 min (major), 7.7 min (minor)].

(S)-6-methyl-2-(trifluoromethyl)-2-(3-(trifluoromethyl)phenyl)-4H-benzo[d][1,3]dioxin-4-one (3x) **3x**: 94%, 96:4 er

dioxin-4-one (3x): white powder. 94% yield, 35.5 mg;

^1H NMR (400 MHz, CDCl_3) δ 2.29 (s, 3H), 7.11 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 1.6, 8.4 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.4, 100.7 (q, J = 34.4 Hz), 113.2, 117.0, 120.1 (q, J = 283.3 Hz), 123.4 (q, J = 270.7 Hz), 127.9, 128.0, 129.6, 130.0, 131.4, 131.5 (q, J = 32.8 Hz), 133.0, 134.3, 138.5, 152.2, 157.4; ^{19}F NMR (376 MHz, CDCl_3) δ -62.9, -83.0; **IR** ν_{max} (film, cm^{-1}): 1766, 1494, 1265, 1203, 738; $[\alpha]_{\text{D}}^{23}$ = 42.2 (c = 2.2 in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{10}\text{F}_6\text{O}_3\text{H}^+$ 377.0607, found 377.0601; **HPLC analysis**: 96:4 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 7.7 min (major), 7.1 min (minor)].

(R)-6-methyl-2-(thiophen-2-yl)-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3y)

(3y): yellowish oil. 75% yield, 23.5 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.31 (s, 3H), 6.98 (dd, J = 3.6, 4.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.38-7.41 (m, 3H), 7.67 (d, J = 1.6 Hz,

1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 100.3 (q, $J = 35.6$ Hz), 113.2, 117.2, 120.1 (q,

3y: 75%y, 89:11 er

$J = 283.3$ Hz), 127.4, 129.8, 129.9, 131.4, 133.8, 134.1, 138.4, 152.5, 157.7; ^{19}F NMR (376 MHz, CDCl_3) δ -83.5; **IR** ν_{max} (film, cm^{-1}): 1766, 1494, 1265, 1108, 734; $[\alpha]_{\text{D}}^{23} = 46.7$ ($c = 1.7$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{14}\text{H}_9\text{F}_3\text{O}_3\text{SH}^+$

315.0297, found 315.0296; **HPLC analysis**: 89:11 er, [CHIRALPAK IC column; 0.6 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 11.8 min (major), 10.0 min (minor)].

(S)-2-benzyl-6-methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3z):

3z: 64%, 90:10 er

yellowish oil. 64% yield, 20.6 mg; ^1H NMR (400 MHz, CDCl_3) δ 2.27 (s, 3H), 3.38 (d, $J = 3.2$ Hz, 2H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.23-7.33 (m, 6H), 7.58 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.4, 39.5, 101.8 (q, $J = 31.9$ Hz), 111.1, 115.9, 121.8 (q, $J = 284.3$ Hz), 127.7, 128.3, 129.2, 130.8, 131.2, 133.1, 137.7, 153.1, 157.6; ^{19}F NMR (376 MHz, CDCl_3) δ -81.0; **IR** ν_{max} (film, cm^{-1}): 1766, 1496, 1265, 1172, 746; $[\alpha]_{\text{D}}^{22} = 9.2$ ($c = 1.4$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_3\text{H}^+$ 323.0890, found 323.0886; **HPLC analysis**: 90:10 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 12.4 min (major), 21.5 min (minor)].

(S)-2-ethyl-6-methyl-2-(trifluoromethyl)-4H-benzo[d][1,3]dioxin-4-one (3za):

3za: 81%, 82:18 er

colorless oil. 81% yield, 21.1 mg; ^1H NMR (400 MHz, CDCl_3) δ 1.14 (t, $J = 7.6$ Hz, 3H), 2.14 (q, $J = 7.6$ Hz, 2H), 2.35 (s, 3H), 6.94 (d, $J = 8.4$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.74 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 5.8, 20.5, 26.8, 102.7 (q, $J = 32.2$ Hz), 111.5, 116.0, 121.9 (q, $J = 288.9$ Hz), 129.4, 133.3, 137.8, 153.3, 158.2; ^{19}F NMR (376 MHz, CDCl_3) δ -80.8; **IR** ν_{max} (film, cm^{-1}): 1761, 1496, 1265, 1188, 738; $[\alpha]_{\text{D}}^{23} = -5.3$ ($c = 2.2$ in CHCl_3); **HRMS** (ESI, m/z): calcd. for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_3\text{H}^+$ 261.0733, found

261.0730; **HPLC analysis:** 82:18 er, [CHIRALPAK OD-H column; 0.5 mL/min; solvent system: i-PrOH/hexane = 1:99; retention times: 9.6 min (major), 9.0 min (minor)].

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Chapter 5

Carbene-Catalyzed Dynamic Kinetic Resolution of Carboxylic Esters

5.1 Introduction

The acyl moiety represents one of the most important functional groups in organic chemistry, playing a paramount role in biology and biochemistry and serving both as key intermediate or protecting group in organic transformations.¹ Thus, the synthesis of optically active carboxylic esters/acids is a very important topic. The transesterification of an ester by exchange of an alkoxy moiety represents a mild and efficient alternative to esterification reactions. Recently, *N*-heterocyclic carbene (NHC) has emerged as a promising organocatalyst for enantioselective chemical transformations due to its unique umpolung ability.² Indeed, early in 1994, Smith group reported a *N*-heterocyclic carbene promoted esterification reaction with stoichiometric amount of imidazolium salts.³ Ten years later, Nolan and Hedrick group almost simultaneously reported the first carbene promoted transesterification that only required catalytic amounts of carbene catalyst.⁴ Suzuki group first developed a chiral *N*-heterocyclic carbene catalyzed enantioselective acylation of racemic secondary alcohols *via* kinetic resolution, although the selectivities were not satisfactory.⁵ Since then, many *N*-heterocyclic carbene catalyzed enantioselective acylations of racemic secondary alcohols were achieved.⁶ However, kinetic resolution of racemic secondary alcohols just gets a maximum fifty percent yield of acyl protected chiral alcohol product. *N*-heterocyclic carbene catalyzed dynamic kinetic resolution is still rarely reported.⁷ Dynamic kinetic resolution is a more superior method than the kinetic resolution due to the theoretical quantitative yield. We have been engaged in exploring new activation modes and/or selective formation of functional molecules with *N*-heterocyclic carbene organocatalysis. Enantioselective activation of α carbons, β carbons and γ carbons of stable carboxylic esters with NHC has recently been demonstrated by our laboratory.⁸ On the basis of the same intermediate, we envisioned that our ester substrates could undergo a transesterification reaction with NHC catalysis.

Optically active α -arylpropanoics and their derivatives represent important classes of chiral chemicals that have found widespread use in pharmaceutical and synthetic applications. For example, α -arylpropanoic acids such as Naproxen and Ibuprofen are well known non-steroid anti-inflammatory drugs.⁹ Transition metal catalyzed asymmetric hydrogenation of unsaturated acids and enzymatic kinetic resolution of racemic acids\esters have been the most used methods in previous years.¹⁰ Here the first dynamic kinetic asymmetric transesterification reaction of α -disubstituted esters by NHC catalyst, is reported. (Figure 5.1)

Figure 5.1. Representative α -disubstituted acid\ester drugs and our synthetic strategy.

5.2 Results and discussion

Key results of our initial reaction optimization are summarized in Table 5.1. We started the evaluation of our hypothesis by combining ester substrate **1a** with achiral alcohol **2** and Cs_2CO_3 as the base in THF for 24h at room temperature (entry 1). To our delight, without NHC catalyst the reaction almost had no product formation (<5% conversion). When achiral triazolium NHC pre-catalyst **A** was used, the reaction proceeded smoothly and afforded the desired product **3a** in quantitative yield. Encouraged by this result, we next focused on a chiral NHC catalyst and found that amino alcohol derived chiral NHC catalyst **B** could mediate this reaction with complete conversion and 67:33 er (entry 3).

Using the chiral NHC precatalyst **B**, other common solvents were tested (entries 4-10). The results indicate that almost all the solvents were suitable for this transformation with a high yield except for 1,4-dioxane. CHCl_3 is the best solvent as it consistently formed the product with 80:20 er. With the goal of improving the enantioselectivity, several commonly used chiral NHC catalysts were screened. The bulky N-mesityl substituent

Table 5.1. Condition Optimization^a

entry	NHC	solvent	yield (%) ^b	er ^c
1	--	THF	<5	--
2	A	THF	99	--
3	B	THF	99	67:33
4	B	ether	99	68:32
5	B	CHCl_3	99	80:20
6	B	CH_2Cl_2	99	75:25
7	B	EA	99	63:37
8	B	1,4-dioxane	45	64:36
9	B	toluene	99	70:30
10	B	hexane	99	67:33
11	C	CHCl_3	80	88:12
12	D	CHCl_3	99	85:15
13	E	CHCl_3	99(96)	96:4
14	F	CHCl_3	70	91:9

^aReaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), solvent (1 mL), rt, 24 h. ^bYield determined by NMR analysis with an internal standard. Isolated yield in parentheses based on **1a**. ^cEnantiomeric ratio of **3a**, determined *via* chiral phase HPLC analysis. **F**.

catalyst worked better than the N-phenyl substituent catalyst (entries 11 vs 5, 13 vs 12). Amino acid derived NHC catalyst **E** which was developed by Rovis is much more efficient than indanol-derived NHC **F**, affording a high yield and high enantioselectivity (96% yield, 96:4 er).

With the optimal reaction conditions in hand (Table 5.1, entry 13), we turned our attention to examining the scope of esters. As indicated in Table 5.2, a board variety of

substituted α -arylalkanoic carboxylic esters, bearing electron-neutral (**3a**) or electron-deficient (**3b**, **3c**) substituents on the aromatic ring, were reacted with alcohol **2** to produce the products with excellent yields and enantioselectivity. Esters with electron-donating substituents (-Me and -OMe) on the aromatic ring led to the corresponding transesterification products **3d-3g** in good yields and high enantioselectivities, whereas the esters with para- substituents resulted in decreased enantioselectivities (**3d**, **3f**). Esters with sterically demanding substituents such as 1-naphthyl reacted effectively as well (**3h**). Heteroaryl substituted esters can be readily accommodated, achieving the corresponding 3-furyl, 3-indolyl substituted products **3i** and **3j** in good yields and high enantioselectivities. Pleasingly, 1,3-disubstituent ester also worked well to give the non-meso product **3k** in good yield and stereoselectivity. Next, when R² group was changed from Methyl to the Ethyl or Benzyl group, dynamic kinetic resolution of these substrates were also tolerated (**3l**, **3n**). Although the ee of **3l** was moderate, it could be enhanced with a bulky alcohol substrate (**3m**). When cyanomethyl substituted ester was used in our optimal reaction conditions, the corresponding transesterification products (**3o**) could be obtained in quantitative yield but with zero percent ee, switching the ratio of two substrates and with 40 mol% Cs₂CO₃, product (**3o**) could be achieved in good result. In my opinion, one major reason for this phenomenon is product **3o** can be easily racemized at basic conditions. Racemization was suppressed in the presence of a small amount of base and big amount of acidic substrate condition. Containing a TBS protecting group substrate was also tolerated in this reaction (**3p**).

Optically active α -arylpropanoic and their derivatives are widely found in pharmaceutical and natural product synthesis.¹¹ Except for enzymatic catalysis and transition-metal-catalyzed asymmetric hydrogenation, catalytic asymmetric synthesis of optically active α -arylpropanoic derivatives with organocatalysis is still very attractive.^{12,13}

Recently, List group described an efficient asymmetric protonation reaction with silyl ketene imines substrates; α -alkyl- α -arylnitriles products could be easily transformed to α -arylpropanoic.¹⁴ We next performed the DKR of a variety of 2-arylpropanoic acids which

Table 5.2. Scope of Reactions^a

^aReaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), CHCl₃ (1 mL). ^b 40 °C. ^c **1** (0.21 mmol), **2** (0.1 mmol), 40 °C.

Table 5.3 Scope of Reactions^a

^aReaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), CHCl₃ (1 mL).

are used as nonsteroidal anti-inflammatory drugs (NSAIDs) under the optimized reaction conditions to assess the general applicability of this novel method (Table 5.3). All the reactions provided very good results, and the desired carboxylic esters (**3q-3v**) were obtained in excellent yields and enantioselectivities.

To illustrate the practical utility of our reaction, a preparative scale experiment was performed. Accordingly, 3 mmol of naproxen ester was added to our catalytic asymmetric transesterification protocol and formed 1.1 g of corresponding product **3q** in 94% yield and 96:4 er. (Scheme 5.1)

Scheme 5.1 Concise Enantioselective Synthesis of (*R*)-Naproxen.

5.3 Mechanistic Study.

Scheme 5.2 Postulated Catalytic Cycles:

A postulated reaction pathway is briefly illustrated in Scheme 5.2. The addition of chiral carbene catalyst **E** to racemic ester substrate **1a** gave intermediate (*R*)-**I** and (*S*)-**I**, which are diastereomers of each other. Intermediate (*R*)-**I** preferentially reacts with alcohol substrate **2** to give **3a** with high enantiomeric ratio. Intermediate (*S*)-**I** reacts with alcohol substrate **2** slower than Intermediate (*R*)-**I** does. At base conditions, Intermediate (*R*)-**I** and (*S*)-**I** could be interchanged to one another *via* enolate intermediate.

To further understand the reaction mechanism, we performed the reaction using enantiomerically pure (*S*)-**1v** (>99:1 er) as the substrate in the absence of carbene catalyst (in the presence or absence of alcohol **2**). Neither background trans-esterification reaction nor racemization of (*S*)-**1v** was observed, suggesting that the carbene catalyst is required for the racemization of the ester substrate (isomerization between (*R*)-**I** and (*S*)-**I**) and the transesterification reaction (**1v** to **3v**). (Figure 5.2)

Figure 5.2

Although asymmetric protonation may have contributed to the observed reaction efficiency product ee; this contribution would have been very minor in our reactions. The dynamic kinetic process proposed in our manuscript is likely to play the dominated roles (i.e., the two enantiomers of the ester substrate can isomerize to one another (as the acylazolium ester intermediate forms), and the final step of transesterification will be selective). Our experimental evidence and rational are detailed below:

- 1) We added chiral ester substrate *R*-**1v** (>99:1 er) and *S*-**1v** (>99:1 er) into one equivalent of free chiral NHC **E** (de-protonation by NaH) respectively. After one hour, we found that 50% of both the two ester enantiomers had transformed to the acylazolium intermediate. This was determined by NMR spectrum. (see Figure 5.3a) Therefore, in the first step (Figure 5.3b, step A), there is no difference in which ester substrate (*R*-**1v** and *S*-**1v**) the NHC catalyst is reacted with. Then we added two equivalents of benzhydrol **2** to the acylazolium intermediate. After 24h, we found that ester isomer *R*-**1v** had transformed the most to product **3v**, however, *S*-**1v** isomer formed almost no product. This indicated that the transesterification is an asymmetric

step.(Figure5.3b)

Figure 5.3a

Figure 5.3b

2) Our experiments found that added 4-nitrophenol (as an “alcohol”) could undergo transesterification with the ester substrate *R*-**1v** under the catalysis of NHC, leading to a product with a significantly dropped er (er dropped from 99:1 to 66:34, Figure 5.4a). When racemic ester **1v** was used with 4-nitrophenol as an alcohol (to replace the optimal alcohol substrate **2**) under NHC catalysis, the product was found to be nearly racemic (Figure 5.4b). If the asymmetric protonation was a major contributor and the ee came from the “selective delivery of a proton by the alcohol to

the enolate intermediate”, 4-nitrophenol should be a poor proton source based on the experimental observations in Figure 3a and 3b. For example, G. C. Fu had found that using a different proton source could affect the asymmetric protonation of the enolate generated from a ketene (ref. 5a of manuscript). However, the addition of 4-nitrophenol to our standard reaction condition (to compete with alcohol **2** in the enolate protonation step) did not affect the reaction enantioselectivity at all (Figure 5.4c). This result (Figure 5.4c) suggests that protonation of the enolate intermediate is unlikely to be a key step that leads to the product enantioselectivity. (Figure 5.4)

Computational Study :

All calculations were performed with the program package Gaussian 09.⁶ All structures were optimized and subjected to frequency analysis with the B3LYP/6-31G* method in the gas phase.

Computational Results and Discussions

Table 5.4 Energetic information of transition states in the final step

TS	Energy+ZPE (a.u.)	Relative Energy (kcal/mol)
R	-2490.2680	0.00
S	-2490.2600	5.02

The key step of alcohol addition to the acylazolium ester intermediate was evaluated via DFT calculation (TS-R and TS-S are the lowest energy transition states in which the reaction occurs; other transition states such as benzyhl alcohol approaches from the more hindered bottom face where the benzyl group side on the catalyst were not considered here, due to the high steric hindrance effect). The calculation revealed that the energy of the addition of alcohol **2** to intermediate (*S*)-**I** is 5.02 kcal/mol higher than that of adding alcohol **2** to the intermediate (*R*)-**I**. This is consistent with our experimental observations. The steric benzhydrol **2** has a rigid structure, with the optimized transition state, in this transition state (TS-S), the steric repulsion effect between the benzhydrol and phenyl group (from the ester substrate) severely increased compared with the methyl group in TS-R. Therefore, NHC-mediated dynamic kinetic resolution of a racemic ester has been proceeded with the high enantioselectivity.

Activation energy for the addition of alcohol **2** to azolium ester intermediates

5.4 Summary

In summary, we have developed an efficient dynamic kinetic asymmetric transesterification reaction *via* *N*-heterocyclic carbene catalysis. This is the first carbene-catalyzed dynamic kinetic resolution of α,α -disubstituted carboxylic esters with up to 99:1 er and 99% yield. The reaction conditions were mild and various functional groups could be tolerated. Our method could be a very effective way to prepare many bioactive molecules and medicines at a gram scale. In addition, enantiomerically enriched α,α -disubstituted carboxylic ester products cannot effectively be accessed by using aldehyde substrates. This study clearly illustrates the unique power of carboxylic ester substrates in carbene-catalyzed reactions. Further exploration of ester activation by carbene catalysis is under progress in our laboratory.

5.5 Experimental Section

5.5.1 General Information

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a

Bruker BBFO (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker BBFO (100 MHz) spectrometer. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer as neat thin films between NaCl plates. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *er* was performed *via* chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]_D^{rt}$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp. Ester substrates were prepared following the literatures procedures.¹⁵

5.5.2 General procedure for the catalytic synthesis of products 3:

Chiral NHC pre-catalyst **E** (0.02 mmol), 4-nitrophenyl esters **1** (0.1 mmol), benzhydrol **2** (0.2 mmol), Cs_2CO_3 (0.15 mmol) and 4 Å molecular sieves were added to a 10 mL flame-dry Schlenk reaction tube equipped with a magnetic stir bar. The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). CHCl_3 (1.0 mL) was then added and the reaction mixture was allowed to stir for 24 hours at room temperature

(noted: RT = 24-26 °C, reaction occurred slowly at low temperatures < 20 °C). After completion of the reaction, monitored by TLC plate, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography directly using hexane/EtOAc (most use 10/1) as eluent to afford the desired product **3**.

Synthesis of Naproxen ester (**3v**) in gram scale and transformation of **3v** to **4**¹⁶:

Chiral NHC pre-catalyst **E** (0.6 mmol, 0.24g), 4-nitrophenyl esters **1v** (3.0 mmol, 1.05g), benzhydrol **2** (6.0 mmol, 1.1g), Cs_2CO_3 (4.5 mmol, 1.46g) and 4 Å molecular sieves, were added to a 50 mL dry Schlenk reaction tube equipped with a magnetic stir bar. The Schlenk tube was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). CHCl_3 (30.0 mL) was then added and the reaction mixture was allowed to stir for 24 hours at room temperature. After completion of the reaction, monitored by TLC plate, the reaction mixture was filtered through a short plug of SiO_2 and washed with DCM. The solution was concentrated under reduced pressure and the residue was subjected to column chromatography (hexane:EtOAc = 10:1) to afford the desired product **3v** (1.1g, 93% yield).

To a 100 mL dry round bottom flask equipped with a magnetic stir bar, was added the Naproxen ester **3v** (1.12g, 2.8 mmol), wet 10% Pd/C (110 mg), and EtOH-THF (1:1, 30 mL), were added to a 100 mL dry round bottom flask equipped with a magnetic stir bar. The reactor was filled with H_2 with a balloon and stirred at room temperature for 24 hours. The reaction mixture was then passed through a short pad of celite, and then washed with MeOH extensively. The filtrate was concentrated under reduced pressure and the residual

was purified by a short flash column chromatography on silica gel (PE/EA = 3/1) to afford the acid **4** with 96% yield and 96:4 er.

Note: Racemic samples for the chiral phase HPLC analysis were prepared using **A** as the NHC pre-catalyst. Absolute configuration of the products were assigned *via* optical rotation comparisons [e.g., **3l**: $[\alpha]_D^{21} = -18.7$ ($c = 1.2$ in CHCl_3); literature value: $[\alpha]_D^{20} = -18.0$ ($c = 1.0$ in CHCl_3)] with the literature.¹⁷

Computational Study:

All calculations were performed with the program package Gaussian 09.²⁰ All structures were optimized and subjected to frequency analysis with the B3LYP/6-31G* method in the gas phase.

TS-R

C	-1.074234	0.888279	0.895936
C	0.000630	1.613158	1.691810
H	0.912200	1.676878	1.092476
O	-1.987554	0.274580	1.438058
C	0.475695	2.733058	-1.484590
C	1.770796	2.280157	-1.770391
C	2.798485	3.230171	-1.740106
C	2.550897	4.583296	-1.498402
C	1.227105	4.994614	-1.294822
C	0.164431	4.090450	-1.291358
H	1.013246	6.049223	-1.137358
H	3.815391	2.897161	-1.930431
O	0.344406	-0.950217	0.111450
C	-0.320681	-2.117874	0.523754
C	-0.823242	-2.933973	-0.673865

C	-1.810368	-3.913978	-0.487520
C	-2.281118	-4.672146	-1.559342
C	-1.766656	-4.466696	-2.843623
C	-0.784459	-3.494552	-3.040193
C	-0.322575	-2.729762	-1.963982
H	0.432576	-1.966137	-2.115143
H	-0.370875	-3.332452	-4.033015
H	-2.124944	-5.062806	-3.678916
H	-1.218599	-1.813125	1.093660
H	1.443948	-0.742274	0.547917
O	2.473236	-0.275078	1.012130
C	-3.219606	0.093114	-3.397060
C	-3.757129	-0.959932	-2.384977
C	0.493602	-2.988241	1.488903
C	1.973027	-4.545894	3.304962
C	1.526550	-3.821197	1.039977
C	0.203716	-2.960957	2.858561
C	0.936744	-3.732004	3.762812
C	2.265173	-4.588411	1.939777
H	1.747861	-3.878632	-0.021413
H	3.068848	-5.221839	1.573976
H	2.548227	-5.145801	4.005258
H	-3.045193	-5.427354	-1.392704
H	-2.202849	-4.091465	0.511882
H	-0.602069	-2.325161	3.218637
H	0.697335	-3.696112	4.822636
C	3.655461	-0.678681	0.623597
C	4.813096	-0.160125	1.271087
C	3.861265	-1.607188	-0.436856
C	6.084798	-0.538485	0.887766
H	4.662685	0.543859	2.084055
C	5.135128	-1.987522	-0.821260
H	2.995382	-2.016143	-0.947017
C	6.249746	-1.454096	-0.162389
H	6.964440	-0.143577	1.382403
H	5.292159	-2.693266	-1.628676
N	7.578303	-1.846699	-0.570680
O	7.692158	-2.659595	-1.499151
O	8.546023	-1.351446	0.023620
N	-0.621635	1.790135	-1.560394
C	-1.262433	1.079617	-0.605074
H	-3.231122	-1.906492	-2.530925
H	-4.826932	-1.145131	-2.501361
H	-2.811226	-0.359742	-4.303682
H	-3.985377	0.815760	-3.702978
C	-3.440765	-0.412686	-0.964341
H	-3.127823	-1.201931	-0.285999

N	-2.266193	0.454317	-1.262616
C	-2.164198	0.770290	-2.585036
N	-1.175932	1.592343	-2.810502
C	-4.578515	0.419210	-0.332800
H	-4.161471	0.966244	0.517025
H	-4.933714	1.158695	-1.062167
C	-5.726327	-0.452616	0.131841
C	-5.586671	-1.236622	1.286848
C	-6.934456	-0.504523	-0.573856
C	-6.628281	-2.056364	1.719118
H	-4.658071	-1.193024	1.851687
C	-7.980169	-1.323333	-0.141752
H	-7.063971	0.110164	-1.462415
C	-7.828262	-2.103025	1.004821
H	-6.505859	-2.654913	2.617769
H	-8.912714	-1.347513	-0.699169
H	-8.640838	-2.739603	1.343926
C	3.675988	5.591111	-1.494578
H	3.613200	6.255887	-2.365514
H	3.640025	6.226513	-0.602086
H	4.652930	5.100019	-1.520452
C	2.048455	0.857130	-2.175443
H	1.491696	0.139830	-1.568994
H	1.759889	0.707586	-3.224646
H	3.111581	0.626326	-2.081817
C	-1.257566	4.569187	-1.128400
H	-1.879366	4.251195	-1.973862
H	-1.716239	4.188077	-0.209677
H	-1.288696	5.660723	-1.081505
C	-0.466729	3.026832	2.057364
C	-1.770655	3.285794	2.506207
C	0.459740	4.078433	2.052661
C	-2.140309	4.566068	2.924789
H	-2.496332	2.478381	2.545863
C	0.094099	5.355278	2.479397
H	1.475815	3.890808	1.716536
C	-1.209746	5.605833	2.911829
H	-3.155449	4.746652	3.268873
H	0.829803	6.155395	2.473568
H	-1.495520	6.600829	3.242264
C	0.321804	0.836988	2.985171
H	0.742614	-0.140953	2.753336
H	1.063976	1.399413	3.558810
H	-0.576202	0.720078	3.597997

TS-S

C	-1.235638	1.010175	1.129449
C	-0.220306	1.536641	2.142275
H	0.736761	1.676543	1.632486
O	-2.163832	0.276319	1.440659
C	0.267608	3.494367	-0.664144
C	1.622504	3.230182	-0.904910
C	2.537913	4.230403	-0.557448
C	2.131983	5.463878	-0.042376
C	0.759637	5.713987	0.085354
C	-0.198315	4.751396	-0.236773
H	0.424822	6.688733	0.432162
H	3.596129	4.037407	-0.714008
O	0.299708	-0.518865	-0.016315
C	-0.332310	-1.775439	0.019147
C	-0.746523	-2.248652	-1.380760
C	-1.653036	-3.310868	-1.521431
C	-2.037326	-3.765166	-2.782809
C	-1.515370	-3.166481	-3.934498
C	-0.615778	-2.107110	-3.806721
C	-0.243114	-1.646940	-2.538932
H	0.447839	-0.817213	-2.436003
H	-0.195425	-1.640043	-4.694547
H	-1.803718	-3.527610	-4.918275
H	-1.266725	-1.658415	0.599671
H	1.438574	-0.466508	0.361811
O	2.545761	-0.186601	0.796538
C	-3.138153	1.162853	-3.347483
C	-3.690584	-0.099712	-2.625144
C	0.472188	-2.849864	0.763422
C	1.930660	-4.782841	2.193927
C	1.432908	-3.640953	0.120063
C	0.247426	-3.048039	2.131151
C	0.970326	-4.006012	2.843153
C	2.160427	-4.596579	0.829589

H	1.608635	-3.518935	-0.944256
H	2.905759	-5.196993	0.314574
H	2.495517	-5.529973	2.745693
C	-0.705187	2.905859	2.690704
H	0.010844	3.255351	3.440089
H	-1.680297	2.809228	3.178222
H	-0.771841	3.669082	1.915378
C	-0.019081	0.584105	3.320860
C	0.439163	-0.995229	5.606015
C	1.264287	0.108951	3.614420
C	-1.073635	0.253705	4.187709
C	-0.847068	-0.533955	5.316252
C	1.490862	-0.673125	4.749340
H	2.076845	0.313291	2.925491
H	-2.079330	0.602424	3.979606
H	-1.677034	-0.781775	5.973419
H	2.493856	-1.037913	4.953809
H	0.616261	-1.602589	6.490101
H	-2.737940	-4.592032	-2.868740
H	-2.046862	-3.795847	-0.630517
H	-0.492155	-2.439159	2.644515
H	0.782822	-4.140357	3.905213
C	3.634838	-0.529640	0.155746
C	4.903185	-0.256026	0.742297
C	3.628281	-1.149369	-1.126507
C	6.081502	-0.576633	0.096436
H	4.918434	0.213531	1.721494
C	4.808201	-1.469865	-1.774457
H	2.675818	-1.367574	-1.597140
C	6.037020	-1.184570	-1.166666
H	7.045707	-0.368717	0.545252
H	4.803256	-1.938997	-2.751437
N	7.267301	-1.513049	-1.848982
O	7.196089	-2.046947	-2.964862
O	8.339215	-1.243980	-1.289347
N	-0.720704	2.501153	-1.030880
C	-1.352994	1.551788	-0.300291
H	-3.135601	-0.980194	-2.955757
H	-4.749546	-0.269439	-2.830147
H	-2.660584	0.927445	-4.301693
H	-3.911054	1.916172	-3.540648
C	-3.452479	0.116481	-1.104921
H	-3.149691	-0.798980	-0.604487
N	-2.292899	1.053736	-1.138684
C	-2.155600	1.674276	-2.344877
N	-1.211076	2.574271	-2.320826
C	-4.643381	0.765373	-0.364403
H	-4.285511	1.113130	0.608283
H	-4.983907	1.643298	-0.928472
C	-5.786418	-0.209331	-0.171322
C	-5.676521	-1.236798	0.777568
C	-6.959374	-0.117601	-0.930317

C	-6.713088	-2.151788	0.956752
H	-4.775565	-1.310357	1.382622
C	-7.999996	-1.031868	-0.751258
H	-7.065979	0.683310	-1.659360
C	-7.877982	-2.052524	0.191614
H	-6.613870	-2.940139	1.698004
H	-8.905215	-0.942708	-1.345880
H	-8.686648	-2.764119	0.333725
C	3.146729	6.506320	0.360844
H	4.068794	6.413883	-0.221485
H	2.756221	7.520426	0.226693
H	3.417611	6.397779	1.419246
C	2.077118	1.975800	-1.600635
H	1.547900	1.090274	-1.247069
H	1.894501	2.069708	-2.679679
H	3.146075	1.811495	-1.454451
C	-1.671092	5.088563	-0.193877
H	-2.093573	5.098139	-1.205933
H	-2.255883	4.372459	0.394296
H	-1.825425	6.078538	0.243573

5.5.6 Characterization of substrates and products.

(R)-Benzhydryl 2-phenylpropanoate (3a)¹⁷: 30.1 mg, 96% yield, pale yellow oil. ¹H

NMR (400 MHz, CDCl₃) δ 1.52 (d, *J* = 7.2 Hz, 3H), 3.83 (q, *J* = 7.2 Hz, 1H), 6.82 (s, 1H), 7.05-7.07 (m, 2H), 7.18-7.31 (m, 13H);

¹³C NMR (100 MHz, CDCl₃) δ 18.2, 45.7, 77.1, 126.6, 127.1, 127.2,

127.6, 127.7, 127.9, 128.3, 128.5, 128.6, 140.1, 140.2, 140.3, 173.3; IR *v*_{max} (film, cm⁻¹):

3030, 1732, 1494, 1454, 1163, 969, 696; [α]_D²¹ = -21.0 (*c* = 1.9 in CHCl₃); HPLC

analysis: 96:4 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane

= 5:95; retention times: 14.3 min (major), 15.1 min (minor)].

(R)-Benzhydryl 2-(4-chlorophenyl)propanoate (3b): 32.5 mg, 93% yield, pale yellow

oil. ¹H NMR (400 MHz, CDCl₃) δ 1.50 (d, *J* = 7.2 Hz, 3H),

3.81 (q, *J* = 7.2 Hz, 1H), 6.82 (s, 1H), 7.07-7.09 (m, 2H), 7.18-

7.32 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 18.1, 45.1, 77.1,

126.7, 127.1, 127.8, 128.0, 128.4, 128.5, 128.7, 129.0, 133.0, 138.7, 139.8, 140.0, 172.9;

IR *v*_{max} (film, cm⁻¹): 2962, 1732, 1454, 1261, 1016, 800; HRMS (ESI, *m/z*): calcd. for

C₂₂H₁₉ClO₂H⁺ 351.1146, found 351.1141. [α]_D²¹ = -4.8 (*c* = 1.7 in CHCl₃); HPLC

analysis: 96:4 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane

= 2:98; retention times: 16.7 min (major), 16.1 min (minor)].

(R)-Benzhydryl 2-(2-chlorophenyl)propanoate (3c): 31.8 mg, 91% yield, colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 1.51 (d, *J* = 6.8 Hz, 3H), 4.36 (q, *J*

= 7.2 Hz, 1H), 6.85 (s, 1H), 7.10-7.12 (m, 2H), 7.18-7.40 (m,

12H); ¹³C NMR (100 MHz, CDCl₃) δ 17.2, 42.2, 77.3, 126.8,

127.0, 127.1, 127.2, 127.7, 127.9, 128.3, 128.5, 128.6, 129.6, 133.7, 138.2, 140.0, 140.1,

172.8; IR *v*_{max} (film, cm⁻¹): 2926, 1737, 1545, 1168, 1080, 744, 698; HRMS (ESI, *m/z*):

calcd. for C₂₂H₁₉ClO₂H⁺ 351.1146, found 351.1144. [α]_D²¹ = -27.1 (*c* = 1.6 in CHCl₃);

HPLC analysis: 93:7 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 16.1 min (minor), 15.4 min (major)].

(*R*)-Benzhydryl 2-(*p*-tolyl)propanoate (3d): 26.1 mg, 79% yield, white powder. ¹H

NMR (400 MHz, CDCl₃) δ 1.50 (d, *J* = 7.2 Hz, 3H), 2.33 (s, 3H), 3.80 (q, *J* = 7.2 Hz, 1H), 6.81 (s, 1H), 7.07-7.30 (m, 14H); ¹³C NMR (100 MHz, CDCl₃) δ 18.2, 21.1, 45.3, 77.3, 126.7, 127.2, 127.5, 127.6, 127.9, 128.3, 128.5, 129.3, 136.7, 137.3, 140.2, 140.3, 173.5; IR ν_{max} (film, cm⁻¹): 2964, 1737, 1454, 1155, 1083, 698; HRMS (ESI, *m/z*): calcd. for C₂₃H₂₂O₂H⁺ 331.1693, found 331.1690. [α]_D²¹ = -18.6 (*c* = 1.3 in CHCl₃); HPLC analysis: 95:5 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 11.6 min (major), 12.6 min (minor)].

(*R*)-Benzhydryl 2-(*o*-tolyl)propanoate (3e): 26.4 mg, 80% yield, colorless oil. ¹H NMR

(400 MHz, CDCl₃) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.35 (s, 3H), 4.07 (q, *J* = 7.2 Hz, 1H), 6.82 (s, 1H), 7.02-7.04 (m, 2H), 7.14-7.29 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 17.5, 19.7, 41.5, 77.1, 126.4, 126.6, 126.7, 127.0, 127.2, 127.6, 127.9, 128.3, 128.5, 130.5, 135.8, 138.8, 140.1, 140.3, 173.6; IR ν_{max} (film, cm⁻¹): 2962, 1736, 1492, 1454, 1161, 697; HRMS (ESI, *m/z*): calcd. for C₂₃H₂₂O₂H⁺ 331.1693, found 331.1691. [α]_D²¹ = -35.6 (*c* = 1.8 in CHCl₃); HPLC analysis: 98:2 er, [CHIRALPAK AS-H column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 1:99; retention times: 10.7 min (minor), 11.3 min (major)].

(*R*)-Benzhydryl 2-(4-methoxyphenyl)propanoate (3f)¹⁸: 29.1 mg, 84% yield, colorless

oil. ¹H NMR (400 MHz, CDCl₃) δ 1.49 (d, *J* = 7.2 Hz, 3H), 3.78 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 4.8 Hz, 2H), 6.85 (s, 1H), 7.07-7.28 (m, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 18.3, 44.9, 55.3, 77.1, 114.0, 126.7, 127.2, 127.7, 127.9, 128.3, 128.5, 128.7,

132.4, 140.2, 140.3, 158.8, 173.6; IR $\nu_{\max}$ (film, cm^{-1}): 2962, 1732, 1512, 1454, 1246, 1157, 698; $[\alpha]_{\text{D}}^{21} = -16.0$ ($c = 3.1$ in CHCl_3); HPLC analysis: 91:9 er, [CHIRALPAK IB column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 13.6 min (minor), 13.0 min (major)].

(R)-Benzhydryl 2-(2-methoxyphenyl)propanoate (3g): 30.1 mg, 87% yield, colorless

oil. ^1H NMR (400 MHz, CDCl_3) δ 1.49 (d, $J = 7.2$ Hz, 3H), 3.58 (s, 3H), 4.10 (q, $J = 7.2$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.88 (s, 1H), 6.91 (d, $J = 7.2$ Hz, 1H), 7.13-7.29 (m, 12H); ^{13}C NMR (100

MHz, CDCl_3) δ 16.7, 40.0, 55.1, 76.6, 110.4, 120.6, 127.0, 127.2, 127.5, 127.7, 128.1, 128.2, 128.3, 128.4, 129.2, 140.5, 140.6, 156.8, 173.9; IR $\nu_{\max}$ (film, cm^{-1}): 2924, 1738, 1494, 1456, 1246, 1029, 752, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{22}\text{O}_3\text{H}^+$ 347.1642, found 347.1642. $[\alpha]_{\text{D}}^{21} = -22.8$ ($c = 2.0$ in CHCl_3); HPLC analysis: 97:3 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 17.4 min (major), 18.7 min (minor)].

(R)-Benzhydryl 2-(naphthalen-1-yl)propanoate (3h): 36.2 mg, 99% yield, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 1.67 (d, $J = 6.8$ Hz, 3H), 4.61 (q, $J = 7.2$ Hz, 1H), 6.85 (s, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 7.12-7.47 (m, 13H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 6.8$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.8, 41.6, 77.2, 123.3, 124.7,

125.5, 126.3, 126.8, 127.1, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 128.9, 131.4, 134.0, 136.5, 139.9, 140.1, 173.7; IR $\nu_{\max}$ (film, cm^{-1}): 2929, 1732, 1454, 1178, 1087, 700; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{22}\text{O}_2\text{H}^+$ 367.1693, found 367.1690. $[\alpha]_{\text{D}}^{21} = -67.8$ ($c = 1.9$ in CHCl_3); HPLC analysis: 99:1 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 3:97; retention times: 18.8 min (major), 17.5 min (minor)].

(R)-Benzhydryl 2-(1-methyl-1H-indol-3-yl)propanoate (3i): 30.3 mg, 83% yield,

colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 1.61 (d, $J = 7.2$ Hz, 3H), 3.70 (s, 3H), 4.14 (q, $J = 7.2$ Hz, 1H), 6.85 (s, 1H), 6.87 (s, 1H), 7.06-7.29 (m, 13H), 7.61 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9, 32.7, 37.0, 77.1, 109.2, 113.8, 119.1, 119.3, 121.8, 126.3, 126.9(3), 126.9(7), 127.2, 127.6, 127.8, 128.2, 128.4, 136.9, 140.2, 140.3, 174.1; IR ν_{max} (film, cm^{-1}): 3431, 2927, 1735, 1450, 1151, 738, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{25}\text{H}_{23}\text{NO}_2\text{H}^+$ 370.1802, found 370.1800. $[\alpha]_D^{21} = -33.6$ ($c = 1.4$ in CHCl_3); HPLC analysis: 98:2 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 10:90; retention times: 26.7 min (major), 18.7 min (minor)].

(R)-Benzhydryl 2-(thiophen-3-yl)propanoate (3j): 28.3 mg, 88% yield, pale yellow

powder. ^1H NMR (400 MHz, CDCl_3) δ 1.60 (d, $J = 7.2$ Hz, 3H), 4.11 (q, $J = 7.2$ Hz, 1H), 6.84 (s, 1H), 6.93 (s, 2H), 7.18-7.31 (m, 11H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2, 41.2, 77.5, 124.4, 125.0, 126.7, 126.8, 127.1, 127.8, 127.9, 128.4, 128.5, 140.0, 140.1, 142.6, 172.3; IR ν_{max} (film, cm^{-1}): 2926, 1737, 1454, 1265, 738, 704; HRMS (ESI, m/z): calcd. for $\text{C}_{20}\text{H}_{18}\text{SO}_2\text{H}^+$ 323.1100, found 323.1103. $[\alpha]_D^{21} = +2.2$ ($c = 1.2$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 1:99; retention times: 21.0 min (minor), 20.1 min (major)].

(2R,2'R)-Dibenzhydryl 2,2'-(1,3-phenylene)dipropionate (3k): 48.2 mg, 78% yield,

colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 1.47 (d, $J = 7.2$ Hz, 6H), 3.79 (q, $J = 7.2$ Hz, 2H), 6.82 (s, 2H), 7.07-7.09 (m, 4H), 7.06-7.28 (m, 20H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.3, 45.7, 77.1, 126.5, 126.7, 127.0, 127.2, 127.7, 127.9, 128.3, 128.5, 128.8, 140.1, 140.2, 140.7, 173.2; IR ν_{max} (film, cm^{-1}): 2927, 1738, 1494, 1454, 1170, 698;

HRMS (ESI, m/z): calcd. for $C_{38}H_{34}O_4H^+$ 555.2530, found 555.2527. $[\alpha]_D^{21} = -22.5$ ($c = 1.8$ in $CHCl_3$); HPLC analysis: 90:10 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 25.7 min (major), 27.9 min (minor)].

(R)-Benzhydryl 2-phenylbutanoate (3l)¹⁹: 28.6 mg, 87% yield, colorless oil. ¹H NMR

(400 MHz, $CDCl_3$) δ 0.86 (t, $J = 7.6$ Hz, 3H), 1.79-1.88 (m, 1H), 2.07-2.16 (m, 1H), 3.57 (t, $J = 8.4$ Hz, 1H), 6.82 (s, 1H), 7.07-7.09 (m, 2H), 7.19-7.29 (m, 13H); ¹³C NMR (100 MHz, $CDCl_3$) δ 12.1,

26.3, 53.6, 77.0, 126.7, 127.1, 127.2, 127.6, 127.9, 128.1, 128.3, 128.5, 128.6, 138.8, 140.1, 140.3, 172.9; $[\alpha]_D^{21} = -18.7$ ($c = 1.2$ in $CHCl_3$); HPLC analysis: 85:15 er, [CHIRALPAK IC column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 9.2 min (major), 9.7 min (minor)].

(R)-Di(naphthalen-1-yl)methyl 2-phenylbutanoate (3m): 33.9 mg, 79% yield, white

powder. ¹H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.6$ Hz, 3H), 1.78-1.85 (m, 1H), 2.13-2.20 (m, 1H), 3.59 (t, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 7.2$ Hz, 1H), 7.12-7.39 (m, 9H), 7.35-7.52 (m, 3H),

7.67 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.89 (d, $J = 7.2$ Hz, 1H), 8.02 (d, $J = 7.6$ Hz, 1H), 8.36 (s, 1H); ¹³C NMR (100 MHz, $CDCl_3$) δ 12.2, 26.2, 53.6, 71.1, 123.4, 123.5, 125.1, 125.2, 125.3, 125.7, 125.9, 126.3, 126.4, 126.7, 127.3, 128.3, 128.6(0), 128.6(8), 128.8, 128.9, 129.2, 130.9, 131.3, 133.7, 133.9, 134.6, 134.9, 138.6, 173.1; $[\alpha]_D^{21} = -46.5$ ($c = 1.1$ in $CHCl_3$); HPLC analysis: 92:8 er, [CHIRALPAK OD-H column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 1:99; retention times: 15.2 min (major), 16.8 min (minor)].

(R)-Benzhydryl 2,3-diphenylpropanoate (3n): 34.1 mg, 87% yield, white powder. ^1H

NMR (400 MHz, CDCl_3) δ 3.04 (dd, $J = 6.4, 13.6$ Hz, 1H), 3.43 (dd, $J = 8.8, 13.6$ Hz, 1H), 4.00 (dd, $J = 6.4, 8.8$ Hz, 1H), 6.76 (s, 1H), 7.03-7.09 (m, 6H), 7.16-7.28 (m, 14H); ^{13}C NMR (100 MHz, CDCl_3) δ 39.4, 53.8, 77.4, 126.4, 126.9, 127.1, 127.4, 127.7, 127.8, 128.1, 128.3, 128.4(1), 128.4(4), 128.7, 129.0, 138.5, 138.9, 139.9, 140.0, 172.3; IR ν_{max} (film, cm^{-1}): 3050, 1734, 1265, 1149, 984, 738; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{24}\text{O}_2\text{H}^+$ 393.1849, found 393.1846. $[\alpha]_{\text{D}}^{21} = -37.0$ ($c = 1.5$ in CHCl_3); HPLC analysis: 95:5 er, [CHIRALPAK IB column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 1:99; retention times: 11.6 min (major), 12.7 min (minor)].

(R)-Benzhydryl 3-cyano-2-phenylpropanoate (3o): 30.6 mg, 90% yield, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 2.81 (dd, $J = 8.0, 17.2$ Hz, 1H), 3.01 (dd, $J = 7.2, 16.8$ Hz, 1H), 4.05 (t, $J = 7.2$ Hz, 1H), 6.85 (s, 1H), 6.97 (d, $J = 6.0$ Hz, 2H), 7.16-7.35 (m, 13H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 47.8, 78.4, 117.5, 126.6, 127.3, 127.8, 127.9, 128.3, 128.4, 128.5(8), 128.6, 129.2, 135.5, 139.3, 139.4, 170.0; IR ν_{max} (film, cm^{-1}): 2920, 1735, 1494, 1454, 1165, 696; HRMS (ESI, m/z): calcd. for $\text{C}_{23}\text{H}_{19}\text{NO}_2\text{H}^+$ 342.1489, found 342.1485. $[\alpha]_{\text{D}}^{21} = -30.4$ ($c = 1.7$ in CHCl_3); HPLC analysis: 90:10 er, [CHIRALPAK IA column; 0.6 mL/min; solvent system: *i*-PrOH/hexane = 20:80; retention times: 11.1 min (major), 11.7 min (minor)].

(S)-Benzhydryl 3-((tert-butyldimethylsilyl)oxy)-2-phenylpropanoate (3p): 34.7 mg,

84% yield, white powder. ^1H NMR (400 MHz, CDCl_3) δ -0.04 (s, 6H), 0.80 (s, 9H), 3.81 (dd, $J = 5.6, 9.6$ Hz, 1H), 3.93 (dd, $J = 5.6, 7.2$ Hz, 1H), 4.22 (t, $J = 7.2$ Hz, 1H), 6.88 (s, 1H), 7.15-7.30 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3) δ 1.1, 18.2, 25.8, 54.9, 65.4, 77.1, 126.9, 127.3, 127.7,

127.9, 128.3, 128.3(7), 128.3(9), 128.4, 128.6, 135.8, 140.0, 140.2, 171.5; IR $\nu_{\max}$ (film, cm^{-1}): 3394, 2927, 1738, 1454, 1259, 837, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{34}\text{SiO}_3\text{H}^+$ 447.2350, found 447.2348. $[\alpha]_{\text{D}}^{21} = -0.7$ ($c = 2.9$ in CHCl_3); HPLC analysis: 90:10 er, [CHIRALPAK IA column; 0.6 mL/min; solvent system: *i*-PrOH/hexane = 1:99; retention times: 18.4 min (major), 16.9 min (minor)].

(R)-Benzhydryl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate (3q): 40.5 mg, 99% yield,

white powder. ^1H NMR (400 MHz, CDCl_3) δ 1.55 (d, $J = 7.2$ Hz, 3H), 3.86 (q, $J = 7.2$ Hz, 1H), 6.86 (s, 1H), 7.05-7.55 (m, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.1, 45.3, 77.4, 115.4

($J = 2.3$ Hz), 123.8 ($J = 3.4$ Hz), 126.8, 127.2, 127.7, 127.8(4), 127.8(7), 127.9, 128.1, 128.4, 128.5(4), 128.5(8), 128.9, 130.8 ($J = 3.9$ Hz), 135.6, 140.0 ($J = 10.5$ Hz), 141.6 ($J = 7.6$ Hz), 159.7 ($J = 247.1$ Hz), 172.8; IR $\nu_{\max}$ (film, cm^{-1}): 3380, 2829, 1734, 1265, 1172, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{23}\text{FO}_2\text{H}^+$ 411.1755, found 411.1753. $[\alpha]_{\text{D}}^{21} = -6.7$ ($c = 4.7$ in CHCl_3); HPLC analysis: 96:4 er, [CHIRALPAK ODH column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 14.1 min (major), 15.3 min (minor)].

(R)-Benzhydryl 2-(4-isobutylphenyl)propanoate (3r): 27.8 mg, 75% yield, pale yellow

oil. ^1H NMR (400 MHz, CDCl_3) δ 0.91 (d, $J = 6.4$ Hz, 6H), 1.51 (d, $J = 7.2$ Hz, 3H), 1.82-1.89 (m, 1H), 2.46 (d, $J = 7.2$ Hz, 2H), 3.80 (q, $J = 7.2$ Hz, 1H), 6.81 (s, 1H), 7.06-7.09 (m,

4H), 7.17-7.19 (m, 5H), 7.24-7.29 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0, 22.4, 30.3, 45.0, 45.3, 76.9, 126.6, 126.5, 127.2, 127.4, 127.6, 127.9, 128.3, 128.5, 129.3, 137.5, 140.2, 140.3, 140.6, 173.5; IR $\nu_{\max}$ (film, cm^{-1}): 2953, 1742, 1494, 1454, 1161, 698; HRMS (ESI, m/z): calcd. for $\text{C}_{26}\text{H}_{28}\text{O}_2\text{H}^+$ 373.2162, found 373.2162. $[\alpha]_{\text{D}}^{21} = -21.6$ ($c = 1.2$ in CHCl_3); HPLC analysis: 98:2 er, [CHIRALPAK ODH column; 0.5 mL/min;

solvent system: *i*-PrOH/hexane = 1:99; retention times: 10.5 min (major), 10.0 min (minor)].

(R)-Benzhydryl 2-(3-phenoxyphenyl)propanoate (3s): 37.8 mg, 93% yield, colorless

oil. ^1H NMR (400 MHz, CDCl_3) δ 1.50 (d, $J = 7.2$ Hz, 3H), 3.80 (q, $J = 7.2$ Hz, 1H), 6.82 (s, 1H), 6.89-7.11 (m, 8H), 7.21-7.31 (m, 11H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.0, 45.6, 77.1, 117.6, 118.4, 118.8, 122.6, 123.2, 126.7, 127.2, 127.7, 128.0, 128.4, 128.5, 129.7, 129.8, 140.0, 140.1, 142.2, 157.2, 157.4, 172.9; IR ν_{max} (film, cm^{-1}): 3032, 2824, 17308, 1583, 1487, 1242, 752, 696; HRMS (ESI, m/z): calcd. for $\text{C}_{28}\text{H}_{24}\text{O}_3\text{H}^+$ 409.1798, found 409.1800. $[\alpha]_{\text{D}}^{21} = -20.4$ ($c = 1.8$ in CHCl_3); HPLC analysis: 97:3 er, [CHIRALPAK IB column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 2:98; retention times: 13.3 min (major), 11.8 min (minor)].

(R)-Benzhydryl 2-(4-(1-oxoisindolin-2-yl)phenyl)propanoate (3t): 40.0 mg, 85%

yield, yellow powder. ^1H NMR (400 MHz, CDCl_3) δ 1.53 (d, $J = 7.2$ Hz, 3H), 3.85 (q, $J = 7.2$ Hz, 1H), 4.81 (s, 2H), 6.84 (s, 1H), 7.11-7.34 (m, 12H), 7.47-7.59 (m, 3H), 7.80 (d, $J = 6.8$ Hz, 2H), 7.91 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.3, 45.2, 50.7, 77.2, 119.6, 122.7, 124.1, 126.7, 127.2, 127.7, 128.0, 128.3(8), 128.4, 128.5, 132.1, 133.2, 136.3, 138.6, 140.0, 140.1, 140.2, 167.5, 173.3; IR ν_{max} (film, cm^{-1}): 2845, 1717, 1687, 1456, 1145, 735; HRMS (ESI, m/z): calcd. for $\text{C}_{30}\text{H}_{25}\text{NO}_3\text{H}^+$ 448.1907, found 448.1903. $[\alpha]_{\text{D}}^{21} = -10.9$ ($c = 1.8$ in CHCl_3); HPLC analysis: 96:4 er, [CHIRALPAK IB column; 0.7 mL/min; solvent system: *i*-PrOH/hexane = 20:80; retention times: 42.2 min (major), 45.5 min (minor)].

(R)-Benzhydryl 2-(3-benzoylphenyl)propanoate (3u): 39.9 mg, 95% yield, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 1.55 (d, $J = 7.2$ Hz, 3H), 3.91 (q, $J = 7.2$ Hz, 1H), 6.84 (s, 1H), 7.09-7.11 (m, 2H), 7.19-7.73 (m, 19H); ^{13}C NMR (100 MHz, CDCl_3)

δ 18.1, 45.6, 77.3, 126.7, 127.1, 127.8, 128.0, 128.3, 128.4, 128.5, 128.6, 129.0, 129.4, 130.1, 131.6, 132.5, 137.5, 137.9, 139.9, 140.0, 140.5, 172.8, 196.4; IR ν_{max} (film, cm^{-1}): 3447, 3062, 1732, 1660, 1454, 690; HRMS (ESI, m/z): calcd. for $\text{C}_{29}\text{H}_{24}\text{O}_3\text{H}^+$ 421.1798, found 421.1794. $[\alpha]_{\text{D}}^{21} = -22.1$ ($c = 1.9$ in CHCl_3); HPLC analysis: 97:3 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 25.2 min (major), 24.0 min (minor)].

(R)-Benzhydryl 2-(6-methoxynaphthalen-2-yl)propanoate (3v): 34.0 mg, 86% yield,

white powder. ^1H NMR (400 MHz, CDCl_3) δ 1.58 (d, $J = 7.2$ Hz, 3H), 3.88 (s, 3H), 3.96 (q, $J = 7.2$ Hz, 1H), 6.84 (s, 1H), 7.04-7.37 (m, 13H), 7.59-7.68 (m, 3H);

^{13}C NMR (100 MHz, CDCl_3) δ 18.4, 45.7, 55.3, 77.2, 105.6, 118.9, 126.1, 126.5, 126.7, 127.1, 127.2, 127.7, 127.9, 128.3, 128.5, 128.9, 129.4, 133.8, 135.5, 140.1, 140.2, 157.7, 173.5; $[\alpha]_{\text{D}}^{21} = -17.2$ ($c = 3.2$ in CHCl_3); HPLC analysis: 97:3 er, [CHIRALPAK IA column; 0.5 mL/min; solvent system: *i*-PrOH/hexane = 5:95; retention times: 23.6 min (major), 21.6 min (minor)].

(R)-2-(6-Methoxynaphthalen-2-yl)propanoic acid (4): ^1H NMR (400 MHz, CDCl_3) δ

1.57 (d, $J = 7.2$ Hz, 3H), 3.85 (q, $J = 7.2$ Hz, 1H), 3.89 (s, 3H), 7.09-7.14 (m, 2H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.68 (d, $J = 9.6$ Hz, 3H); $[\alpha]_{\text{D}}^{21} = -61.0$ ($c = 1.0$ in CHCl_3); { (R)-(-)-6-

Methoxy- α -methyl-2-naphthaleneacetic acid, 98%, $[\alpha]_{\text{D}}^{20} = -66$, $c = 1.0$ in CHCl_3 , Sigma-Aldrich}; HPLC analysis: 97:3 er, [CHIRALPAK IC column; 0.5 mL/min; solvent

system: EtOH/hexane = 1:10, with 0.1% TFA; retention times: 12.7 min (major), 13.4 min (minor)].

5.6 References

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Appendix: pK_a values of commonly used triazolium *N*-Heterocyclic carbenespK_a values determined in H₂O Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.*, **2015**, *115*, 9307.