7-6-2012

Development of novel organocatalytic cascade reactions and application in organic systheses

Xixi Song

Xixi Song

Candidate

Department of Chemistry and Chemical Biology

Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

Wei Wang , Chairperson

Patrick S. Mariano

Hua Guo

Changjian Feng

DEVELOPMENT OF NOVEL ORGANOCATALYTIC CASCADE METHODOLOGIES AND APPLICATIONS IN ORGANIC SYNTHESES

by

XIXI SONG

B.S., Chemistry, Zhengzhou University, 2003
M.S., Chemistry, North Dakota State University, 2008

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Chemistry

The University of New Mexico
Albuquerque, New Mexico

May, 2012

DEDICATION

This dissertation is dedicated to my beloved parents:

Jianzhi Mao and Shengan Song

ACKNOWLEDGEMENTS

I heartily and deeply acknowledge Professor Wei Wang, my advisor for constantly encourage and support me through the years of research and personal development. His broad knowledge, creativity, guidance, patience and professional style will remain with me as I continue my career.

I also thank my committee members, Professor Patrick S. Mariano, Professor Hua Guo and Professor Changjian Feng for their valuable suggestions pertaining to this study and assistance in my professional development.

I would like to express my full gratitude to all the current and previous members in Professor Wang's research group. Special thanks would deliver to Dr. Hexin Xie, Dr. Liansuo Zu, Dr. Wei Jiang, Dr. Shilei Zhang, Dr. Yinan Zhang, Dr. Zhihong Ke (Professor Guo's research group), Dr. Deawon Cho (Professor Mariano's research group), Xinshuai Zhang, Sihan Zhao, Yanting Cao, Aiguo Song, Weimin Xuan, Xiaobei Chen, Wenhan He.

Sincere thanks also go to Eileen Duesler for her help in crystallography as well as her kindness and patience. Same appreciation goes to Karen Ann Smith for her help in NMR spectroscopy experiments.

Finally, my special thanks go to Professor Gregory Cook, Professor Mukund P. Sibi, Dr. Xiaopeng Li, Dr. Yonghua Yang, Dr. Zhiqiang Ji and Dr. Niu Zhang for their continual support.

DEVELOPMENT OF NOVEL ORGANOCATALYTIC CASCADE REACTIONS AND APPLICATION IN ORGANIC SYNTHESES

By

Xixi Song

B.S., Chemistry, Zhengzhou University, 2003

M.S., Chemistry, North Dakota State University, 2008

Ph.D., Chemistry, University of New Mexico, 2012

ABSTRACT

The development of new catalytic reactions, particularly synthetically efficient cascade processes for the facile preparation of important molecular architectures, which otherwise are difficult to access via traditional methods, is of considerable significance. Toward this end, my Ph.D. work focuses on developing new organocatalytic reactions and their applications in organic syntheses.

A novel direct organocatalytic stereoselective α-arylation methodology has been discovered. The cross-coupling-like products are assembled using simple enals and various brominated aromatic systems, such as *p*-bromophenols, bromonaphthols and 3-bromoindoles. The products have been applied in the concise photo-syntheses of [α]-annulated carbazoles. Moreover, an unexpected reaction has been identified with aliphatic enals, and fully developed into a new [3+3] formal cycloaddition cascade reaction, and serves as a powerful approach to polysubstituted arenes from simple enals in a highly regio- and chemo-selective fashion.

The Diels-Alder reaction of acetylenic aldehydes has been realized for "one-pot" synthesis of polysubstituted salicylaldehyde frameworks that were constructed via an unprecedented aminocatalytic Diels-Alder-retro-Diels-Alder cascade from simple alkynals and 2-pyrones. Furthermore, the use of *N*-protected 3-hydroxy-2-pyridines as dienes leads to catalytic enantioselective Diels-Alder process without subsequent retro-Diels-Alder reaction. A chiral C_2 symmetric organocatalyst is found as an effective promoter for the activation and stereo-control of various substituted alkynals.

Table of Contents

DEDICATION ..... **iii**

ACKNOWLEDGEMENTS ..... **iv**

ABSTRACT ..... **vi**

Table of Contents ..... **vii**

List of Schemes ..... **xii**

List of Figures ..... **xv**

List of Tables ..... **xvii**

List of Abbreviations ..... **xx**

Chapter 1. Introduction **1**

1.1. Cascade Reaction 1

1.2. Organocatalysis 4

1.3. Organocatalytic Cascade Reaction 11

1.4. Summary of Dissertation Research 14

1.5. Reference 15

Chapter 2. Direct Stereoselective α-Arylation of Unmodified Enals with *p*-Bromophenols using an Organocatalytic Cross-Coupling-Like Reaction **18**

2.1. Introduction 18

2.2. Organocatalytic Approaches to Functionalized Enals via a Cross-coupling Like Reaction 19

2.3. Substrate Design 21

2.4. Optimization of Reaction Conditions 22

2.5. Expansion of Substrate Scopes 29

2.6. Investigation of Mechanism 32

2.7. Summary 37

2.8. Experimental Section 38

2.9. Reference 52

Chapter 3. Direct Stereoselective α-Arylation of Simple Enals with Bromonaphthols using an Organocatalytic Cross-Coupling-Like Approach 57

3.1. Introduction to Functionalized Naphthol Frameworks 57

3.2. Substrate Design 58

3.3. Optimization of Reaction Conditions 59

3.4. Expansion of Substrate Scopes 62

3.5. Amine Integrated Three-Component Reaction 65

3.6. Summary 70

3.7. Experimental Section 71

3.8. Reference 92

Chapter 4. Direct Stereoselective α-Arylation of Unmodified Enals with 3-Bromoindoles via an Organocatalytic Cross-Coupling-Like Strategy 95

4.1. Introduction 95

4.2. Optimization of Reaction Conditions 96

4.3. Expansion of Substrate Scopes 101

4.4. Proposed Reaction Mechanism 103

4.5. Photosynthesis of Furocarbazole 105

4.6. Summary 106

4.7. Experimental Section 107

4.8. Reference 120

Chapter 5. Organocatalytic Regio- and Chemo-selective "One-pot" Access to Polysubstituted Arenes from Simple Enals via a Michael-Aldol Condensation-Aromatization Cascade 124

5.1. Introduction 124

5.2. Initial Discoveries 125

5.3. Optimization of Reaction Conditions 126

5.4. Expansion of Substrate Scope 129

5.5. Investigation of Mechanism 132

5.6. Summary 134

5.7. Experimental Section 135

5.8. Reference 146

Chapter 6. Aminocatalytic Diels-Alder-retro-Diels-Alder Cascade Reaction of Alkynals and 2-Pyrones for the One-Pot Construction of Polysubstituted Salicylaldehyde Frameworks 150

6.1. Introduction to Polysubstituted Salicylaldehydes 150

6.2. Diels-Alder-retro-Diels-Alder process 151

6.3. Substrate Design 152

6.4. Optimization of Reaction Conditions 153

6.5. Expansion of Substrate Scopes 155

6.6. Summary 158

6.7. Experimental Section 159

6.8. Reference 168

Chapter 7. Enantioselective Diels-Alder Reaction of Alkynals and 3-Hydroxy-2-Pyridones with a C_2 Symmetric Organocatalyst 172

7.1. Introduction 172

7.2. Substrate Design 173

7.3. Optimization of Reaction Conditions 173

7.4. Expansion of Substrate Scopes 176

7.5. Summary 179

7.6. Experimental Section 180

7.7. Reference 187

List of Schemes

Chapter 1. Introduction..... 1

Scheme 1.1. Robinson's synthesis of tropinone and its proposed mechanism.....2

Scheme 1.2. Catalysis modes of covalent catalysts.....6

Scheme 1.3. Catalysis modes of non-covalent catalysts.....9

Scheme 1.4. Organocatalytic quadruple cascade reaction and its mechanism.....13

Chapter 2. Direct Stereoselective α-Arylation of Unmodified Enals with *p*-Bromophenols using an Organocatalytic Cross-Coupling-Like Reaction..... 18

Scheme 2.1. Approaches to selective (E)-α-arylation of enals and acrylates.....20

Chapter 3. Direct Stereoselective α-Arylation of Simple Enals with Bromonaphthols using an Organocatalytic Cross-Coupling-Like Approach..... 57

Scheme 3.1. Cross-coupling-like strategy for the direct α-arylation of unmodified α, β-unsaturated aldehydes with 4-bromophenols.....59

Scheme 3.2. The α-arylation reaction of trans-p-methoxy-cinnamaldehyde with 1-bromo-2-naphthol.....68

Scheme 3.3. Three-component α-arylation reaction of enals with 2-bromo-1-naphthol and 3-bromo-4-hydroxycoumarine.....69

Scheme 3.4. Conversion from the E-isomer 3a to the three-component Z-isomer **4a** using piperidine 70

Chapter 4. Direct Stereoselective α-Arylation of Unmodified Enals with 3-Bromoindoles via an Organocatalytic Cross-Coupling-Like Strategy 95

Chapter 5. Organocatalytic Regio- and Chemo-selective "One-pot" Access to Polysubstituted Arenes from Simple Enals via a Michael-Aldol Condensation-Aromatization Cascade 124

Scheme 5.1. An unexpected formation of 4-methyl benzaldehyde from the study of cross-coupling-like α-arylation process 126

Scheme 5.2. A proposed reaction mechanism 133

Scheme 5.3. Transformation of two key intermediate analogues **17** and **18** to aromatic compounds in the proposed reaction mechanism involving MBH and aromatization processes 134

Chapter 6. Aminocatalytic Diels-Alder-retro-Diels-Alder Cascade Reaction of Alkynals and 2-Pyrones for the One-Pot Construction of Polysubstituted Salicylaldehyde Frameworks 150

Scheme 6.1. The competition between Diels-Alder reaction and O-Michael addition 158

Chapter 7. Enantioselective Diels-Alder Reaction of Alkynals and 3-Hydroxy-2-Pyridones with a C_2 Symmetric Organocatalyst 172

Scheme 7.1. Diels-Alder process of acetylenic aldehydes 173

Scheme 7.2. The competition between the oxo-Michael addition pathway and the Diels-Alder pathway using alkynal **1j**.....179

List of Figures

Chapter 1. Introduction..... 1

Chapter 2. Direct Stereoselective α-Arylation of Unmodified Enals with *p*-Bromophenols using an Organocatalytic Cross-Coupling-Like Reaction..... 18

Figure 2.1. Single X-ray crystal structure of **3a** at probability ellipsoids of 20%.....24

Figure 2.2. A proposed reaction mechanism for α-arylation reactions of enals with 4-bromophenol.....33

Figure 2.3. Preparation of the stable p-acetoxy quinol **9** and catalyst I catalyzed retro-Michael addition reaction of **9** 35

Figure 2.4. Monitoring quinol formation by ^{1}H NMR 37

Chapter 3. Direct Stereoselective α-Arylation of Simple Enals with Bromonaphthols using an Organocatalytic Cross-Coupling-Like Approach..... 57

Figure 3.1. Single X-ray crystal structure of **3a** at probability ellipsoids of 20%.....62

Chapter 4. Direct Stereoselective α-Arylation of Unmodified Enals with 3-Bromoindoles via an Organocatalytic Cross-Coupling-Like Strategy 95

Figure 4.1. Single X-ray crystal structure of **3a** at probability ellipsoids of 20%.....97

Figure 4.2. A proposed reaction mechanism for α-arylation reactions of enals with 3-bromoindole 104

Figure 4.3. Synthesis of furocarbazoles **5** via photoelectronic cycliszation-photoinduced decarboxylation cascade process 106

Chapter 5. Organocatalytic Regio- and Chemo-selective "One-pot" Access to Polysubstituted Arenes from Simple Enals via a Michael-Aldol Condensation-Aromatization Cascade 124

Chapter 6. Aminocatalytic Diels-Alder-retro-Diels-Alder Cascade Reaction of Alkynals and 2-Pyrones for the One-Pot Construction of Polysubstituted Salicylaldehyde Frameworks 150

Chapter 7. Enantioselective Diels-Alder Reaction of Alkynals and 3-Hydroxy-2-Pyridones with a C_2 Symmetric Organocatalyst 172

Figure 7.1. Single X-ray crystal structure of **3h** at probability ellipsoids of 20% 178

List of Tables

Chapter 1. Introduction..... 1

Chapter 2. Direct Stereoselective α-Arylation of Unmodified Enals with *p*-Bromophenols using an Organocatalytic Cross-Coupling-Like Reaction..... 18

Table 2.1. Catalyst screening for amine-catalysed direct α-arylation reaction of trans-p-nitro-cinnamaldehyde **2a** with p-bromophenol **1a** 23

Table 2.2. Solvent screening for amine-catalysed direct α-arylation reaction of trans-p-nitro-cinnamaldehyde **2a** with p-bromophenol **1a** 25

Table 2.3. Optimization of experimental procedure for amine-catalysed direct α-arylation reaction of trans-p-nitro-cinnamaldehyde **2a** with p-bromophenol **1a** 28

Table 2.4. Scope of amine-catalysed direct α-arylation reaction of p-bromophenols with enals.....30

Table 2.5. The effects of leaving groups **X** on the fate of the arylation reactions.....34

Chapter 3. Direct Stereoselective α-Arylation of Simple Enals with Bromonaphthols using an Organocatalytic Cross-Coupling-Like Approach..... 57

Table 3.1. Reaction conditions optimization of amine-catalyzed direct α-arylation reaction of trans-p-nitrocinnamaldehyde with 1-bromo-2-naphthol 60

Table 3.2. Substrates scope of amine-catalyzed direct α-arylation reactions of 1-bromo-2-naphthols with enals 64

Table 3.3. Three component reactions of 1-bromo-2-naphthols and enals with stoichiometric amount of amines 66

Chapter 4. Direct Stereoselective α-Arylation of Unmodified Enals with 3-Bromoindoles via an Organocatalytic Cross-Coupling-Like Strategy 95

Table 4.1. Screening of catalysts for the cascade reactions using enal **1a** and 3-bromoindole **4a** 98

Table 4.2. Effect of additives and solvents on the synthesis of (E)-α-indolyl-β-arylacrylaldehyde **3a** 100

Table 4.3. Scope of amine-catalysed direct α-arylation reactions of 3-bromoindoles with enals.....102

Chapter 5. Organocatalytic Regio- and Chemo-selective "One-pot" Access to Polysubstituted Arenes from Simple Enals via a Michael-Aldol Condensation-Aromatization Cascade 124

Table 5.1. Optimization of reaction conditions 127

Table 5.2. Substrate scope of self-dimerization 129

Table 5.3. Substrate scope of cross-over dimerization.....130

Chapter 6. Aminocatalytic Diels-Alder-retro-Diels-Alder Cascade Reaction of Alkynals and 2-Pyrones for the One-Pot Construction of Polysubstituted Salicylaldehyde Frameworks 150

Table 6.1. Optimization of secondary amine catalyzed Diels-Alder-retro-Diels-Alder cascade process 154

Table 6.2. Substrates scope expansion of Diels-Alder-retro-Diels-Alder cascade reaction 156

Chapter 7. Enantioselective Diels-Alder Reaction of Alkynals and 3-Hydroxy-2-Pyridones with a C_2 Symmetric Organocatalyst 172

Table 7.2. Reaction Condition Optimization of Enantioselective Diels-Alder reaction of Alkynal **1a**.....175

Table 7.2. Substrate Scope Expansion of Enantioselective Diels-Alder reaction of Alkynal **1** 177

List of Abbreviations

Ac	acetyl
Ar	aryl
BINOL	1, 1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalyst
$CDCl_3$	deuterated chloroform
δ	chemical shift
DA	Diels-Alder
DABCO	1, 4-diazabicyclo[2.2.2]octane
DCE	dichloroethane
DDQ	2, 3-dichloro-5, 6-dicyanobenzoquinone
DMAP	4-dimethylaminopyridine
DMF	*N, N*-dimethylformamide
DMSO	dimethyl sulfoxide

DOS	diversity oriented synthesis
d.r.	diastereomeric ratio
ESI	electro-spray ionization
e.e.	enantiomeric excess
Elect.	electrophile
equiv.	equivalent
exp.	experiment
EWG	electronic withdrawing group
EDG	electronic donation group
g	gram(s)
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
Hz	hertz
J	coupling constant
λ	wavelength

LUMO	lowest unoccupied molecular orbital
M	molar
m	meta
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nuc.	nucleophile
p	para
PG	protecting group
Ph	phenyl
PTC	phase transfer catalysis
r.t.	room temperature
SOMO	singly occupied molecular orbital

TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEA	triethylamine
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
μL	microliter
UV	ultra-violet

Chapter 1

Introduction

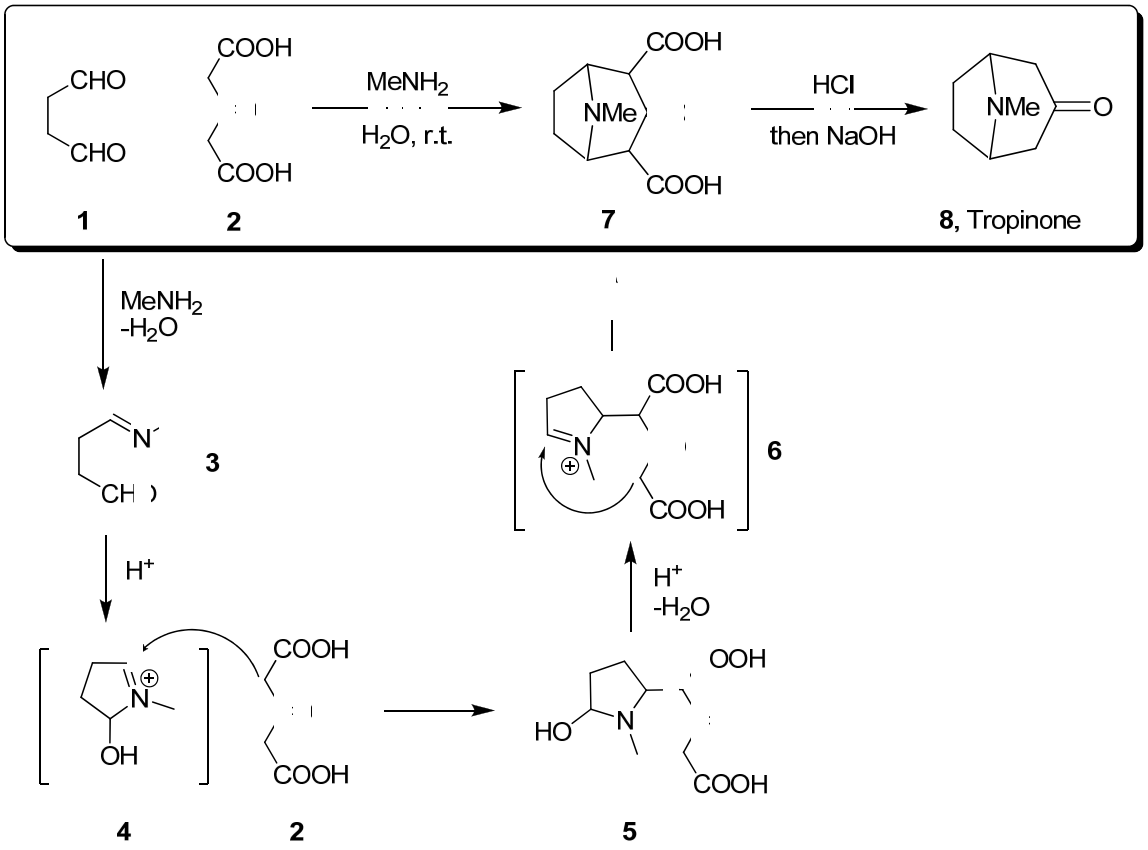
1.1. Cascade Reaction

Chemical knowledge and technology have advanced to the stage that, given a sufficient amount of time, money, manpower and chemical resource, it is possible to synthesize almost any desired organic substance. Among the main challenges that remain to be addressed in modern organic synthesis are the improvement of synthetic efficiency, the avoidance of toxic reagents, and the reduction of waste and hazardous byproducts. General solutions to these problems will become increasingly important as chemists and society strive to develop effective and responsible synthetic methodologies that can contribute to sustaining our precious and limited resources. One effective way to surmount these challenges is to uncover and utilize novel cascade strategies.[1, 2]

Cascade (or domino, or tandem) reaction is a sequence of chemical transformations, in which several bond forming steps take place in a single operation. In the process, only a single reaction solvent, workup procedure, and purification step is required to produce a product that would otherwise be derived from a tedious multi-step synthetic sequence. The starting materials are rationally designed to, or serendipitously happened to undergo an initial reaction step, which produce a reactive intermediate that becomes the substrate for the consecutive step, whose product again acts as the substrate for the successive step, and so on, until a product stable enough to the reaction conditions is received. The overall sequential transformations occur under the same reaction

conditions, without introducing additional reagents or catalysts. Besides those obvious advantages in elevation of synthetic efficiency, the methodology of cascade also significantly broadens our spectra of organic reactions and strategies by granting the utilization of synthetically reactive intermediates that would be difficult to construct and not feasible to isolate.[1, 2, 3]

Scheme 1.1. Robinson's synthesis of tropinone and its proposed mechanism



Historically, cascade strategies have already been used by organic chemists since the inception of total synthesis. Robinson's one-pot synthesis of tropinone (Scheme 1.1)

back as early as 1917 is considered as the seminal work in the realm of cascade reaction.[4] Tropinone is produced after the decarboxylation of compound **7**, which is synthesized using succinaldehyde **1**, methylamine, and acetonedicarboxylic acid **2** in water at room temperature. Such a cascade process is initiated from the condensation of methylamine and succinaldehyde to form a Schiff base **3**. The reactive intermediate species **4** is generated via intramolecular addition of imine moiety to aldehyde moiety. The following intermolecular Mannich reaction between **4** and starting material **2** yields compound **5**. After condensation, the second reactive intermediate species **6** is formed, and it spontaneously transforms to bicyclic product **7** via intramolecular Mannich reaction. Using simple compounds as starting materials, under mild and green one-pot reaction conditions, the cascade reaction demonstrates a great synthetic efficiency with the overall yield of more than 90% after optimization of reaction conditions.

Because of their unique features, cascade processes often serve as the basis for highly efficient synthetic strategies for the construction of complex molecular architectures from simple starting materials. Consequently, these reactions have been the subject of intense research in recent years, as evidenced by the number of reviews that have appeared.[5, 6, 7] However, the current status of cascade reactions is limited, particularly catalytic asymmetric versions. Therefore, it is clear that new investigations in this field are required in order to develop more atom-economic, cost effective catalytic enantioselective versions of cascade reactions.[8, 9]

In biological aspects, small molecule modulation of protein gene products (chemical genetics) is an extremely powerful tool for studying biological systems and drug discovery. In order to find a selective small molecule modulator of any protein

function, a structurally diverse compound collection is required. Historically, nature has provided many of these pharmaceutically active small molecules. Unfortunately, there are disadvantages with screening natural product extracts; for example, the need for active component(s) identification, limited supply, and formidable analog synthesis. As a result, the quick and successful identification of new and highly specific small-molecule probes remains an important challenge in the fields of chemical biology and medicinal chemistry. The bottleneck is the lack of efficient synthetic strategies to quickly construct structurally diverse small molecules and explore chemical space. The number of drug-like molecules possible in chemical space has been estimated to be 10^{30}-10^{200}. Therefore, clearly it is impossible to synthesize every drug-like molecule and chemists must be selective. These problems have led to an alternative strategy of synthesizing structurally diverse small molecules directly and efficiently, which is known as diversity oriented synthesis (DOS). A significant approach of DOS is to develop new powerful cascade reactions to assemble compound libraries of biologically significant frameworks. [10, 11, 12]

1.2. Organocatalysis

In modern organic chemistry, atom economy and selectivity (chemo-, regio-, stereo-) are the two major criteria for the discovery and development of a practical synthetic methodology.[13, 14] Catalysis is undoubtedly the main vehicle for such exploration, since the use of catalyst could significantly reduce reaction time, decrease reaction temperature, improve selectivity, optimize reaction route or increase product yield.[15] Although it has been discovered and utilized since the infancy of organic

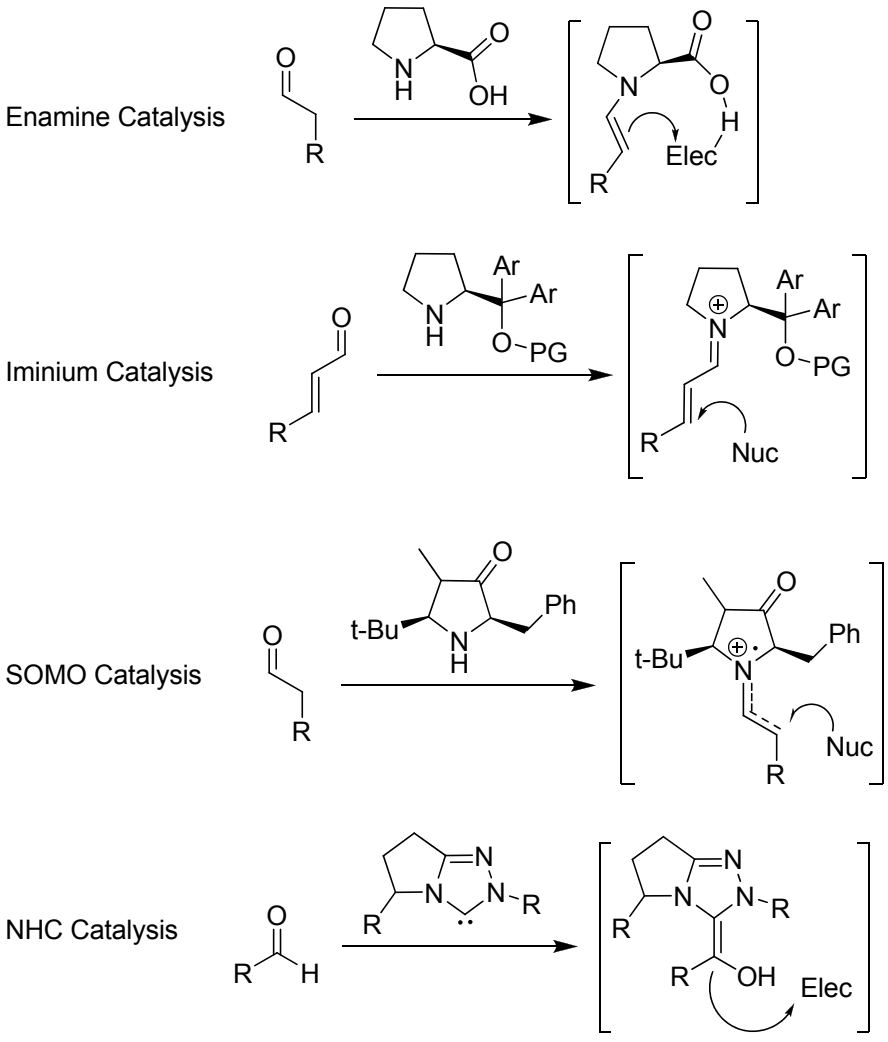
chemistry, the concept of organocatalysis was just brought up at the beginning of the 21st century. The catalysis using small organic molecules exclusively, in which an inorganic element is not participated in the catalytic cycle, is generally considered as organocatalysis. Together with biocatalysis and metal catalysis, organocatalysis becomes a dynamic research area of modern asymmetric catalysis.[16] Compared with metal catalysts and biomolecule based catalysts, typical organocatalysts, such as proline derivatives and thioureas, have tremendous advantages such as stable in air and water, readily available from biological materials, easy to prepare from inexpensive chemicals, simple to apply in various synthetic methodologies, accessible of both enantiomers, and non-toxic.[17]

The organocatalysts can be classified into two categories based on the way it interacts with substrate. The covalent catalyst forms covalent bond with substrate, while the non-covalent catalyst does not form such tight interaction.[17, 18] Each category contains various catalysis modes. Some modes render the substrate more electronic deficient, which is labile for the attacking of nucleophile. And other modes make the substrate more electronic rich, which is labile for electrophilic attacking.

One of the covalent catalysts is enamine catalyst. In this catalysis mode, the electrophilic substitution reactions of the α-position of carbonyl compounds are catalyzed by primary or secondary amine via enamine intermediate. *L*-Proline is a representative catalyst for enamine catalysis. After the secondary amine is associated with aldehyde substrate, α-proton of the aldehyde is extracted to form nucleophilic enamine species. Meanwhile, a reactant electrophile is delivered by the carboxylic moiety of *L*-proline, and is aligned for electrophilic attacking (Scheme 1.2). Enamine catalysis is a fruitful field of

research and becomes a powerful methodology for asymmetric synthesis. Under the catalysis of an increasing amount of aminocatalysts, almost all types of ketones and aldehydes can be used as nucleophiles together various electrophiles with a broad spectra.[19]

Scheme 1.2. Catalysis modes of covalent catalysts



Although the earliest recorded example of an iminium catalyzed reaction is the Knoevenagel condensation mediated by primary or secondary amines in 1894, the concept of LUMO-lowering iminium organocatalysis is not brought up until the turn of the century. MacMillan and co-workers were the first to introduce the iminium catalysis concept to describe the catalytic strategy similar to metal cation Lewis acids.[20] Generally speaking, α, β-unsaturated aldehyde or ketone is activated by secondary or primary amine via iminium intermediate for further nucleophilic attacking or cycloaddition processes, and McMillan's imidazolidinone catalyst family and protected diarylprolinol catalyst series are typical iminium activation promoters (Scheme 1.2).[21]

The concept of SOMO catalysis was introduced by McMillan and coworkers in 2007.[22, 23] The singly occupied molecular orbital (SOMO) is a reactive radical cation species with three π-electrons, which is generated from one-electron oxidation of an electron-rich enamine intermediate. The electrophilicity of the SOMO intermediate makes it vulnerable to the attack of weakly nucleophilic carbon-based nucleophiles, which also has a nick name of "SOMOphiles" (Scheme 1.2). Although SOMO catalysis has just come into being, this novel aminocatalysis mode has already produced several applicable examples in asymmetric synthesis.[24, 25]

N-Heterocyclic carbenes (NHCs) have been extensively used as excellent ligands in metal catalysis, and impressively demonstrated in organic synthesis. In last decades, NHC catalysis has gradually became a hot research area in organocatalysis. Based on Breslow's mechanism, stable NHC or *in situ* generated NHC associates with aldehyde substrate to form an electrophilic intermediate species, which is known as Breslow intermediate.[26] The nucleophilic carbonyl carbon is changed to an electrophilic carbon

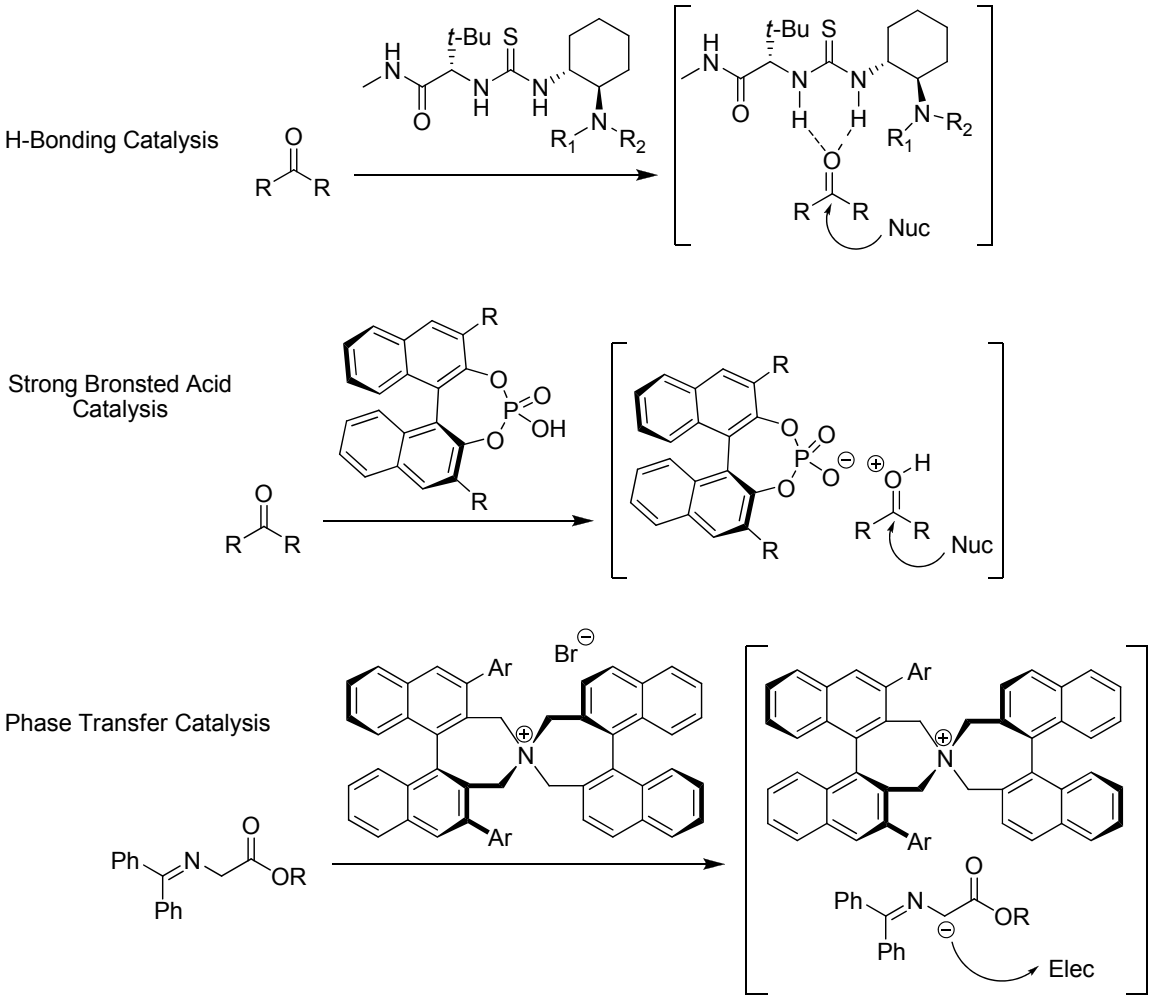
with the help of NHC catalyst, and such a reversion of electronic property is usually named as umpolung, and the NHC catalysis is usually considered as umpolung catalysis.[27]

Although, conceptually as well as practically, covalent catalysis has brought deep and revolutionary impact in the realm of organic chemistry, without non-covalent catalysis, it still cannot depict the big picture of the organocatalysis. As in non-covalent catalysis, only non-bonding weak interactions take place between catalyst and substrate during the catalytic process.

Small-molecule chiral hydrogen-bond donors have been used as non-covalent catalysts in the frontier research field of enantioselective synthesis. Inspired by the function of enzymes in biocatalysis, organic chemists have found that small organic molecules bearing hydrogen-bond donor moiety and complementary functional frameworks were able to catalyze C-C and C-heteroatom bond formation reaction with extensive substrate scope. Chiral thioureas and cinchona alkaloids are typical H-bonding catalysts. In the case of thioureas, two hydrogen bond donating sites are able to pinch the carbonyl oxygen tightly, and the activated substrate is readily available for the nucleophilic attack (Scheme 1.3). Since the proton on the catalyst is not deprotonated, the H-bonding catalyst is usually considered as neutral Brønsted acid catalyst.

Strong Brønsted acid is the other branch of Brønsted acid catalyst besides neutral one, and spectacular achievement has been made in this area. As we known, the proton is the smallest Lewis acid. The general strategy for strong Brønsted acid catalysis is to mimic the process of metal-based Lewis acid catalysis. Since Lewis-acids have already

Scheme 1.3. Catalysis modes of non-covalent catalysts



been widely used as catalysts for C-C bond-forming reactions, strong Brønsted acids are also capable of such employment. Furthermore, in contrast to the Lewis acids, strong Brønsted acids possess various merits of organocatalysts, such as stable in oxygen and environmental friendliness. As a benchmark reaction, BINOL derived chiral phosphoric acid, a typical strong Brønsted acid, is able to activate carbonyl compound for nucleophilic attack (Scheme 1.3). The deprotonated phosphate anion and protonated

carbonyl oxonium cation forms a contact ion pair, which is a crucial intermediate stage for activation and asymmetric control. The phosphate will be re-protonated after the catalytic cycle.[29]

Phase transfer catalysis (PTC), a class of highly useful and active catalysts based on quaternary ammonium salts, belongs to Lewis acid organocatalysis. Different from strong Brønsted acid catalyst, the activation and stereo-control species of PTC is the chiral quaternary ammonium cation. The deprotonated substrate anion and the catalyst cation also generate a contact ion pair, and the activated substrate is ready for electrophilic bombardment.[30]

Besides abovementioned classification method based on catalytic activation modes, there is another method. Benjamin List firstly described that most but not all the organocatalysts could be classified as Lewis bases and acids, and Brønsted bases and acids.[31] Generally speaking, in the Lewis model, a Lewis acid is an electron acceptor, and Lewis base is an electron donor. And in the Lowry-Brønsted model, a Brønsted acid is a proton donor, and a Brønsted base is a proton acceptor or abstractor. The two acid-base theories can be reconciled by recognizing that the proton is a unique and the smallest Lewis acid that is also the agent responsible for the Brønsted acidity. As for organocatalysis, both enamine catalysis and iminium catalysis fall into the category of Lewis base catalysis. Since only one electron transfers from a nucleophilic radical to an electrophilic radical species in the process of SOMO catalysis, the SOMO catalysis is generally considered as a special kind of Lewis base catalysis. Similarly, the *N*-heterocyclic carbene catalysis also belongs to Lewis base catalysis. And the phase

transfer catalysis is a kind of Lewis acid catalysis. Both hydrogen-bonding catalysis and strong Brønsted acid catalysis are Brønsted acid catalysis.[31]

Furthermore, based on the advance of organocatalysis, bifunctional or multifunctional organocatalysts are rationally designed and applied in synthetic chemistry. Multiple catalytic moieties possessing different catalysis modes are integrated in one single catalyst. And such multifunctional catalysts are also considered as cooperative catalysts mimicking enzyme's cooperative catalysis.[32] However, in most of the cases, multifunctional organocatalysts are designed to cope with special scaffolds or functional groups of substrates, and they usually lacks the generality and the ability of catalyzing wide range of one-pot cascade reaction sequences.

1.3. Organocatalytic Cascade Reaction

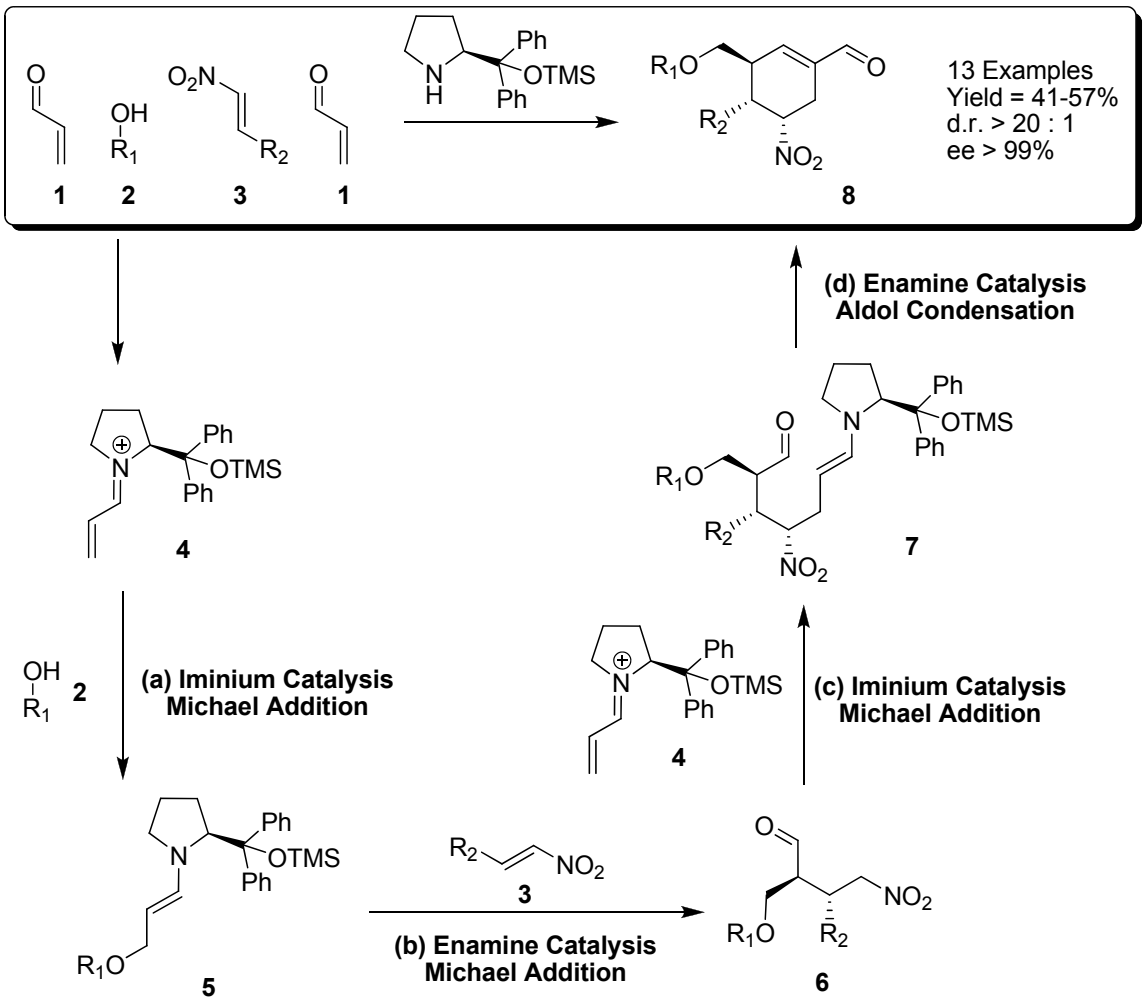
To achieve atom economy and efficiency in the current status of organic chemistry, multicomponent cascade reactions have been utilized for the efficient and stereoselective construction of complex molecules from easily accessible simple precursors in a one-pot fashion. Inheriting the unprecedented advantages of organocatalysis, the organocatalytic cascade reactions have quickly become a mighty instrument to achieving high molecular complexity. In the organocatalytic cascade process, the combination of various activation catalytic modes provides unexampled opportunity of strategic design of innovative cascade sequences to afford an unobtainable structural topology as well as a high level of stereocontrol.[33, 34]

Thanks to pioneer endeavors of various organic chemists, a number of review articles have been published in the research area of organocatalytic cascade reactions.[33-36] Based on their summary, the aminocatalysts are considered as a widely used catalyst for cascade process than other organocatalysts. The aminocatalysts could have up to three activation modes, while others only have one (Scheme 1.2 and Scheme 1.3). Moreover, the number of combination of activation modes using the same aminocatalyst could be double-cascade, triple-cascade, and even the impressive quadruple-cascades.[37, 38]

Professor Gong and coworkers had discovered an asymmetric organocatalytic four-component quadruple cascade reaction (Scheme 1.4). The oxo-Michael-Michael-Michael-aldol condensation process is catalyzed by a single diphenylprolinol silyl ether aminocatalyst with two equiv. acrolein **1**, simple alcohol **2** and nitroalkene **3** as reactants. The cascade reaction affords highly functionalized trisubstituted cyclohexene carbaldehyde **8** with excellent diastereoselectivity and enantioselectivity. In the first step of the quadruple cascade process, the aminocatalyst associates with acrolein to form an activated iminium intermediate species **4**, which can readily undergo nucleophilic attack from alcohol **2**. The directly formed oxo-Michael adduct **5** is an enamine activated intermediate. In the second step, the activated Michael donor reacts with olefin Michael acceptor **3** to form Michael adduct **6**. Due to electronic withdrawing effect of nitro group, the α-carbon demonstrates nucleophilicity, which renders the nitro compound **6** a good Michael donor. In the third step, another equiv. of iminium activated acrolein **4** reacts with intermediate **6** to form a Michael adduct **7**, which is an enamine activated intermediate. In the last step, intramolecular aldol condensation reaction happens, and the cyclohexene product is formed after dissociation of the aminocatalyst. The iminium-

enamine-iminium-enamine cascade reaction enables the consecutive formation of four new bonds stereoselectively and provides an atom economic access to the functionalized cyclohexene in good yield. And in the quadruple-cascades process, only a single catalyst, one solvent condition and one purification operation are used in a one-pot fashion.[37]

Scheme 1.4. Organocatalytic quadruple cascade reaction and its mechanism



Based on the extensive study of various organocatalysts and their applications in the discovery of novel methodologies, the diarylprolinol silyl ether system is selected as a general organocatalyst. In the development of organic chemistry, the discovery of general catalysts is a longstanding goal in the pursuit of new catalytic systems, which should be capable of mediating a large quantity of stereoselective reactions, through various isolated or consecutive activation modes, with a wide scope of substrate tolerance and high stereoselectivity. The diarylprolinol silyl ether derivatives are capable of promoting various enamine- and iminium-ion- mediated processes, and this renders the catalytic system ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner, leading access to products bearing multiple stereocetners.

1.4. Summary of Dissertation Research

The discovery and development of novel organocatalytic cascade methodologies has become one of the important strategies for modern organic chemists. In the following chapters, I will detail my efforts towards a stepwise fulfillment of such duty. Chapter **2** describes the direct organocatalytic stereoselective α-arylation methodology. In chapter **3,** strategies of stereoselective achieving both *E*- and *Z*- arylation products are scrutinized. Chapter **4** focuses on the concise synthesis of [α]-annulated carbazoles using the stereoselective arylation method. In chapter **5**, the organocatalytic regioselective synthesis of poly-substituted arenes is depicted. Chapter **6** summarizes the pyrrolidine-catalyzed Diels-Alder-retro-Diels-Alder cascade reactions of alkynals with functionalized 2-pyrones. In chapter **7**, the asymmetric Diels-Alder reaction of alkynals using a C2-

symmetric organocatalyst is elaborated.

1.5. Reference

(1) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

(2) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993-3009.

(3) Anderson, E. A. *Org. Biomol. Chem.* **2011**, *9*, 3997-4006.

(4) Robinson, R. J. *Chem. Soc. Trans.* **1917**, 762-768.

(5) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136.

(6) Tietze, L. F.; Rackelmann N. *Pure Appl. Chem.* **2004**, *76*, 1967-1983.

(7) Poulin, J.; Grise-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092-3101.

(8) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619-1665.

(9) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143-2173.

(10) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.

(11) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3417-3421.

(12) Schreiber, S. L. *Science* **2007**, *287*, 1964-1969.

(13) Trost, B. M. *Science* **1991**, *254*, 1471-1477.

(14) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695-705.

(15) Li, C.; Trost, B. M. *Proc. Nat. Acad. Sci.* **2008**, *105*, 13197-13202.

(16) List, B. *Chem. Rev.* **2007**, *107*, 5413-5415.

(17) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304-308.

(18) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chemistry* **2010**, *2*, 167-178.

(19) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007,** *107*, 5471-5569.

(20) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 4243-4244.

(21) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416-5470.

(22) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582-585.

(23) Jang, H.; Hong, J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005.

(24) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494-16495.

(25) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027-5029.

(26) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.

(27) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007,** *107*, 5606-5655.

(28) Dolye, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007,** *107*, 5713-5743.

(29) Akiyama, T. *Chem. Rev.* **2007,** *107*, 5744-5758.

(30) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007,** *107*, 5656-5682.

(31) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724.

(32) Yu, X.; Wang, W. *Chem. Asian. J.* **2008**, *3*, 516-532.

(33) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581.

(34) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037-2046.

(35) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron Asymm.* **2007**, *18*, 693-700.

(36) Albrecht, L.; Jiang, H.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492-8509.

(37) Zhang, F.; Xu, A.; Gong, Y.; Wei, M.; Yang, X. *Chem. Eur. J.* **2009**, *15*, 6815-6818.

(38) Kotame, P.; Hong, B.; Liao, J. *Tetrahedron Lett.* **2009**, *50*, 704-707.

(39) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jorgensen, K. A. *Acc. Chem. Res.* **2011**, DOI: 10.1021/ar200149w.

Chapter 2

Direct Stereoselective α-Arylation of Unmodified Enals with *p*-Bromophenols using an Organocatalytic Cross-Coupling-Like Reaction

2.1. Introduction

Cross-coupling reactions have revolutionized chemical synthesis and, arguably, have become one of the most powerful tools for carbon – carbon bond formation.[1-6] The successful achievement of Csp^2-Csp^2 coupling (Suzuki-Miyaura, etc.), Csp^2-Csp^1 coupling (Sonogashira, etc.), and Csp^3-Csp^2 coupling (C-H activation) renders the cross-coupling methodology a cornerstone in organic synthesis.[7-11]

In recent years, the scope of cross-coupling reactions has moved beyond traditional processes by enabling direct arylation reactions of aromatic C-H bonds. Although great strides have been made in the development of efficient methods for coupling and direct arylation reactions, the strategies devised to date rely on transition-metal-assisted approaches for which new transition metal complexes and ligands have been developed. Moreover, owing to the general inertness of C-H bonds, harsh reaction conditions (for example, strong base used and at high temperature) are generally required to promote transition-metal-catalyzed direct crossing couplings and difficulties associated with the control of chemo-, regio- and stereoselectivity are often problematic. In another perspective, despite tremendous efforts made in creating various environmentally benign

alternatives, the toxicity originated from transition metals was still an Achilles' heel, especially in the realm of medicinal chemistry. [12-20]

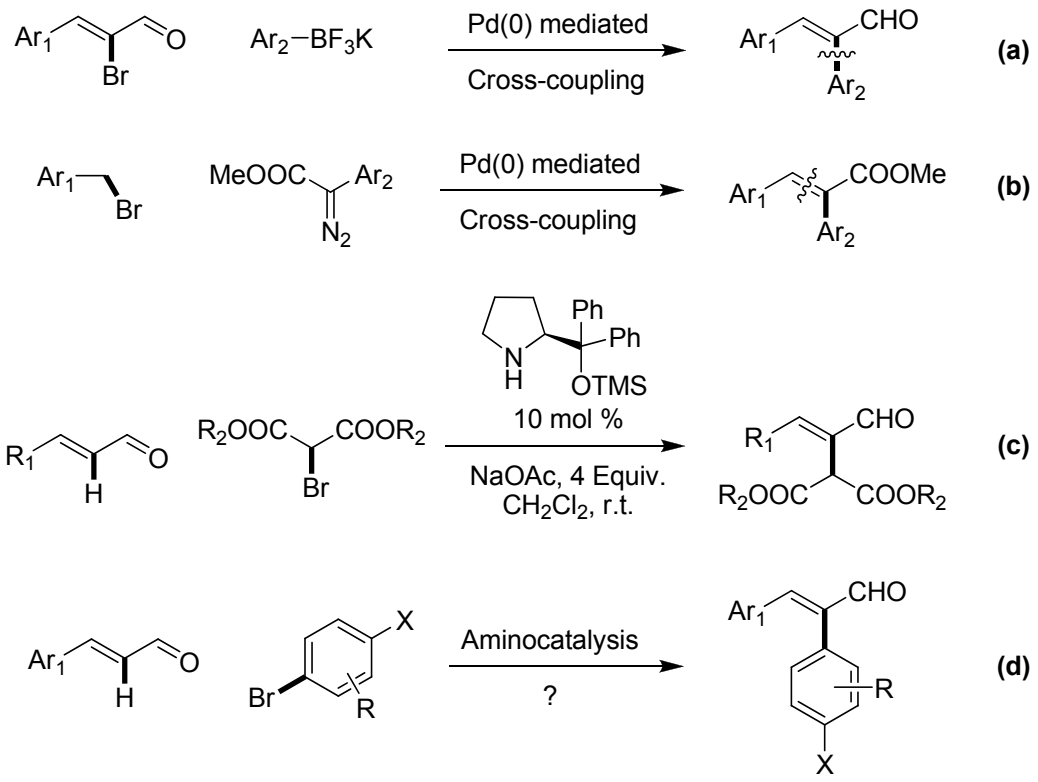
2.2. Organocatalytic Approaches to Functionalized Enals via a Cross-coupling Like Reaction

The pioneering work on respective enamine and iminium catalysis by List and Barbas and MacMillan serve as the conceptual basis for the field of organocatalysis.[21-25] A large number of unprecedented and typically stereoselective organic transformations, which are complementary to transition-metal catalysed processes, have been devised using this chemistry. The success of aminocatalysis can perhaps be attributed to the involvement of unique activation modes that enable stereoselective reactions to proceed under mild conditions and with a broad functional compatibility and operational simplicity. Although the main focus in this area will continue to be the design of highly efficient catalysts that promote existing reactions with greater turnover numbers, expansion of the scope of aminocatalysis to include new reactions is an important yet challenging aim. To our knowledge, the exploration of organocatalysis in the arena of cross-coupling reactions has not been described previously. [26, 27]

Interest in functionalized α, β -unsaturated aldehydes has grown significantly in recent years because of the results of their broad utility in cosmetic[28, 29], pharmaceutical[30-35] and agrochemical[36-39] industries. Moreover, enals are arguably the most widely used substrates in current organocatalytic reactions[21-25]. Therefore, efficient methods for the generation of structurally diverse α, β-unsaturated aldehydes with high levels of E/Z

stereoselectivity (especially E-selective synthesis of α-substituted enals) are highly desirable (Scheme 2.1). Although cross-aldol condensation reactions of two different aldehydes afford facile access to these targets, intrinsic problems associated with poor E/Z stereoselectivity, in which formation of thermodynamically more stable Z isomers are favored, and production of complex product mixtures render this process impracticable. State-of-the-art approaches to these targets use Pd(0)-catalysed cross-coupling protocols, including Suzuki-Miyaura reaction of potassium aryl trifluoroborates with alkenyl bromides (Scheme 2.1.a)[40] and the reaction of benzyl bromides with diazoesters (Scheme 2.1.b)[41].

Scheme 2.1. Approaches to selective (*E*)-α-arylation/alkylation of enals and acrylates



In recent years, we have carried out investigations leading to the development of new organocatalysed reactions and, in particular, those that involve efficient and stereoselective cascade processes.[42] These atom-economical processes serve as powerful approaches to transform readily available chemicals in one-pot operations to useful building blocks for organic synthesis. This effort has recently resulted in the discovery of an organocatalytic, enantioselective Michael-alkylation cascade sequence in which chiral propanes are generated from enals and bromomalonates (Scheme 2.1.c).[43, 44] In this study, an unexpected side reaction was uncovered that produces stereoselectively (*E*)-α-substituted malonate enals. The results from ensuing mechanistic studies revealed that this product is formed through a catalytic Michael-alkylation sequence that gives rise to a cyclopropane intermediate, which then undergoes a stereo-specific ring-opening via an enamine-initiated retro-Michael reaction. Stimulated by these findings, we question whether this chemistry could serve as the foundation of a new transformation involving a Friedel-Craft s alkylation-ring opening cascade (Scheme 2.1.d). If successful, this process would give products derived by direct connection of the α-carbon of an enal with an aryl-ring carbon. To our knowledge, no transformation of this type exists for direct coupling of unmodified enals with arenes.

2.3. Substrate Design

A consideration of the proposed Friedel-Crafts alkylation-ring opening pathway led to the conclusion that the aromatic substrates that participate as Michael donors in the process must be electron rich so that the initial electrophilic aromatic substitution step

can occur efficiently. Although organocatalytic Michael addition reactions of electron-rich aromatic compounds to α, β-unsaturated aldehydes has been intensively studied, to our knowledge no precedent exists for bond formation at *ipso*-positions, which is an essential component of the new α-arylation reaction.[45, 46]

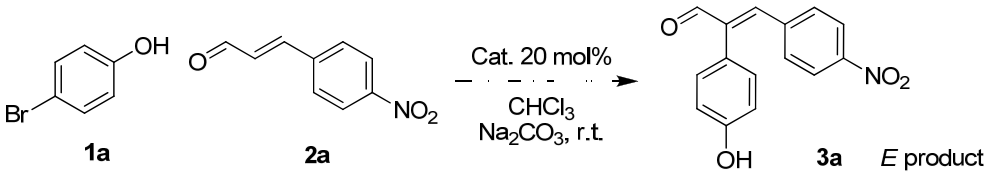
In typical transition-metal-catalysed cross-coupling reactions, the halo-substituent not only polarizes the C-X bond for oxidative insertion of the transition metal, it also functions as a leaving group in the reductive elimination step. In the new 'cross-coupling like' process, the aromatic *ipso*-halogen functions in a similar manner in that it serves as a leaving group in the ensuing alkylation step. More importantly, it functions as an appropriate pool to balance both steric and electronic effects that govern the initial Michael addition process. On the basis of these considerations, we reasoned that bromine would serve optimally in both capacities in that its steric hindrance would be compensated by its electron-donating ability as well as its softness, which would favor conjugated addition. Accordingly, *p*-bromophenol was selected as the substrate in our exploratory investigations of the new process.

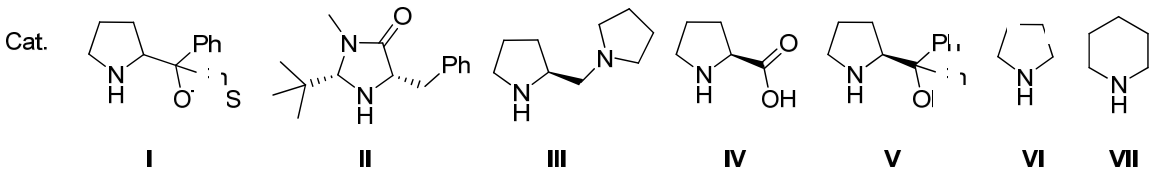
2.4. Optimization of Reaction Conditions

A model cross-coupling-like reaction at room temperature between *p*-bromophenol (**1a**) and *trans*-*p*-nitro-cinnamaldehyde (**2a**) in the presence of Na_2CO_3 and an aminocatalyst was explored in our initial effort (Table 2.1). The cinnamaldehyde with the electronic withdrawing group was selected because of its high electrophilicity after activated by aminocatalyst. Indeed, the reaction occurs to give the desired product **3a**, but

in only a moderate yield before further optimization. The *E*-isomer was observed predominantly as the product, and the structure of compound **3a** was determined by X-ray crystal structural analysis (Figure 2.1).

Table 2.1. Catalyst screening for amine-catalysed direct α-arylation reaction of *trans-p*-nitro-cinnamaldehyde **2a** with *p*-bromophenol **1a**[a]



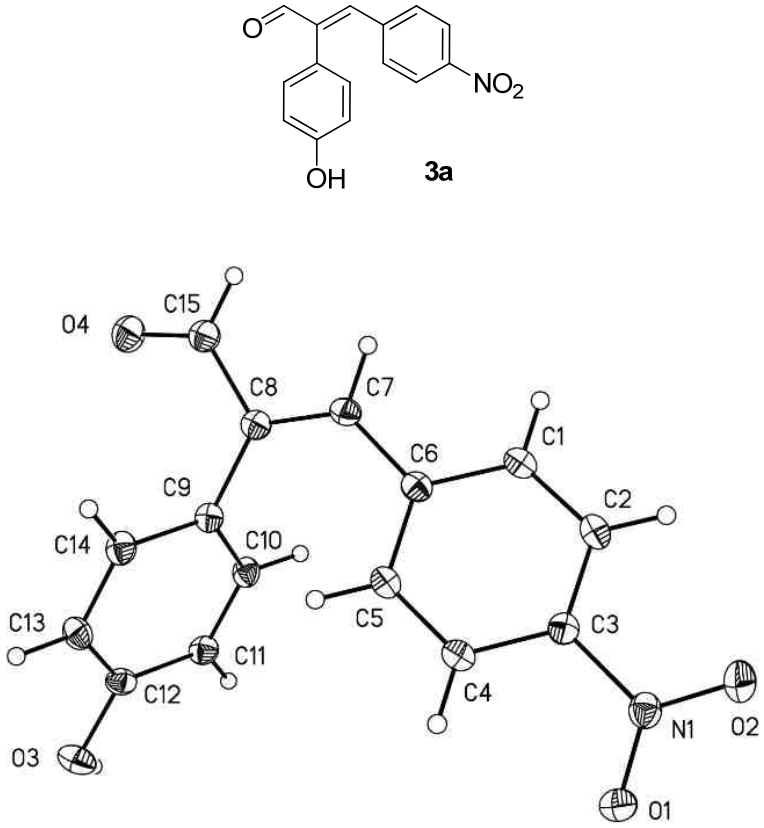


entry	catalyst	time (days)	yield (%)[b]	*E/Z*[c]
1	**I**	4	41	>30:1
2	**II**	6	0	nd[d]
3	**III**	4	19	>30:1
4	**IV**	4	<5	nd[d]
5	**V**	6	0	nd[d]
6	**VI**	8	15	>30:1
7	**VII**	8	11	>30:1

[a]Reaction conditions: unless specified, a mixture of **1a** (0.2 mmol), **2a** (0.1 mmol), designated catalyst (20 % mol, or 0.02 mmol) and Na_2CO_3 additive (0.4 mmol) in

chloroform (1.0 mL, 0.1 *M*) was stirred for a specified time period at room temperature. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Not determined.

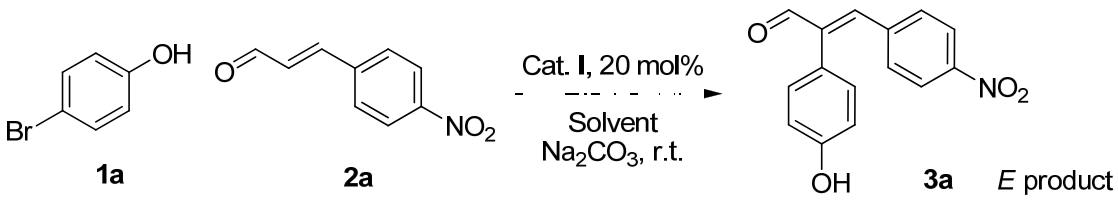
Figure 2.1. Single X-ray crystal structure of **3a** at probability ellipsoids of 20%



A survey of various aminocatalysts was carried out first using the initial model reaction conditions (Table 2.1). The diphenylprolinol TMS ether **I** was found to generate a good yield of 41% with decent *E/Z* stereoselectivity (entry 1). McMillan's 2nd generation catalyst **II** did not show any catalysis under the reaction conditions, and starting materials were recovered (entry 2). The Barbas catalyst **III** could only provide a

yield of 19% (entry 3). When simple *L*-proline **IV** was used as the aminocatalyst, only trace amount of desired product was received (entry 4). Surprisingly, compared with the TMS protected prolinol catalyst **I**, the naked diphenylprolinol catalyst **V** had no catalytic effect (entry 5). Simple secondary amines, such as pyrrolidine **VI** and piperidine **VII**, demonstrated decreased catalytic abilities. When they were used, the reaction could only drive to a completion after 8 days, and the isolated yield was also as low as 15% and 11% respectively (entries 6 and 7). As a result, diphenylprolinol TMS ether **I** was considered as an optimal aminocatalyst.

Table 2.2. Solvent screening for amine-catalysed direct α-arylation reaction of *trans-p*-nitro-cinnamaldehyde **2a** with *p*-bromophenol **1a**[a]



entry	solvent	time (days)	yield (%)[b]	*E*/*Z*[c]
1	toluene	4	34	>30:1
2	Et_2O	4	0	nd[d]
3	THF	4	0	nd[d]
4	MeCN	5	12	>30:1
5	DMF	5	4	>30:1
6	DMSO	5	5	>30:1
7	MeOH	4	10	>30:1

8	acetone	5	0	nd[d]
9	$CHCl_3$	4	41	>30:1

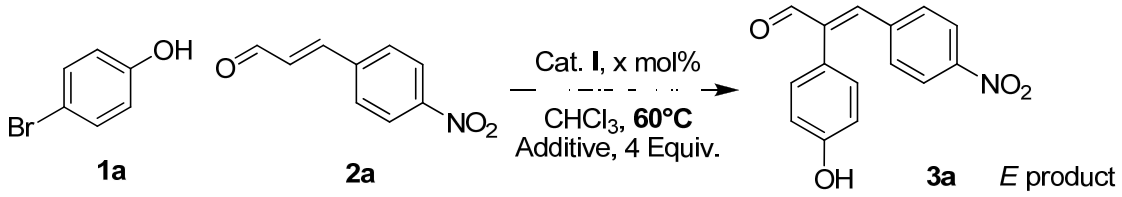
[a]Reaction conditions: unless specified, see footnote *a* and Experimental section. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Not determined.

Ensuing studies showed that the efficiency of formation of the desired cross-coupling-like product was highly solvent dependent (Table 2.2). Toluene is considered as a good alternative, but its efficiency is not as effective as chloroform (entry 1). Additionally, comparing with chloroform, toluene provided poorer solvation environment for the polar reactants and product. In contrast to chloroform (entry 9), reactions taking place in other solvents, such as acetonitrile (entry 4), dimethylformamide (entry 5), dimethylsulfoxide (entry 6) and methanol (entry 7), occur with low yields even when prolonged reaction times are used. Furthermore, when diethyl ether (entry 2), tetrahedrofuran (entry 3) or acetone (entry 9) was used as solvent, the desired transformation was staggered without product formation. As a result, chloroform was chosen as an optimal solvent.

Further optimizations of reaction conditions as well as experimental procedure were carried out (Table 2.3). Elevating the temperature of the reaction in chloroform to 60°C shortens the reaction time significantly without affecting the yield (entry 2). Probing basic additives lead to the conclusion that sodium carbonate is optimal. The weaker base, sodium acetate, could be used to mediate reaction, but with lower efficiency (entry 1). Stronger bases, such as potassium carbonate and cesium carbonate, significantly deteriorated the transformation (entries 3 and 4). An increase in the amount

of **1a** from 2.0 to 4.0 or 8.0 equiv. results in an improvement of the reaction yield (entries 5 and 6). These results suggest that addition of **2a** via a syringe pump over a long period of time would improve yields. The proposal was supported by the observation that the efficiency of the process was enhanced (85% yield, entry 8) when slow addition of 2.0 equiv. of **2a** was used. If a reversed experimental method, syringing **1a** in to a mixture of **2a**, was used, decreasing of efficiency was observed (13% yield, entry 7). Prolongation of the addition time of **2a** would also lead to the reduction of yield (entries 12 and 13). As we known, reducing the catalyst loading resulted in slower transformation due to slow catalyst turnover, and thus longer reaction time would compensate the loss of efficiency, which was generally observed in covalent-bond-mediated aminocatalysis. However, in our cases, under the reaction conditions at relatively high temperature (60 °C comparing with room temperature), although longer reaction time could completely consume the starting materials, the reaction become more complicated with unidentified by-products formed and therefore even lower reaction yields are obtained. As seen, when 10 and 5 mol % catalyst loadings were used, it takes respectively 2 days and 3 days for complete conversion. However, only 39 and 12% yields of desired product **3a** are obtained, respectively (entries 10 and 11). In conclusion, the slowly syringing of enal **2a** into the mixture of *p*-bromophenol and catalytic system in an elevated temperature of 60 °C over the period of 7 hours was considered as the optimal reaction conditions for the cross-coupling-like α-arylation process.

Table 2.3. Optimization of experimental procedure for amine-catalysed direct α-arylation reaction of *trans-p*-nitro-cinnamaldehyde **2a** with *p*-bromophenol **1a**[a]



entry	**1a**:**1b** (ratio)	Cat. x (mol%)	exp. method[a]	additive (4 equiv.)	time (days)	yield (%)[b]	*E*/*Z*[c]
1	2:1	20	***A***	NaOAc	3	20	>30:1
2	2:1	20	***A***	Na_2CO_3	1	43	>30:1
3	2:1	20	***A***	K_2CO_3	1	<5	nd[d]
4	2:1	20	***A***	Cs_2CO_3	1	0	nd[d]
5	4:1	20	***A***	Na_2CO_3	1	58	>30:1
6	8:1	20	***A***	Na_2CO_3	1	70	>30:1
7	2:1	20	***B***	Na_2CO_3	1	13	>30:1
8	2:1	20	***C***	Na_2CO_3	1	85	>30:1
9	3:2	20	***C***	Na_2CO_3	1	72	>30:1
10	2:1	10	***C***	Na_2CO_3	2	39	>30:1
11	2:1	5	***C***	Na_2CO_3	3	12	>30:1
12	2:1	20	***D***	Na_2CO_3	1	57	>30:1
13	2:1	20	***E***	Na_2CO_3	1	11	>30:1

[a]Reaction conditions: **1a** (corresponding amount based on the table above), **2a** (0.1 mmol), catalyst **I** (20 mol%, or 0.02 mmol) and additive (0.4 mmol) were combined according to following methods: ***(A)*** starting materials were mixed together at the same time in a fashion of one-pot; ***(B)*** a solution of **1a** in chloroform (1 mL) was syringed slowly into the mixture of **2a** and other materials in chloroform (1 mL) in the time span

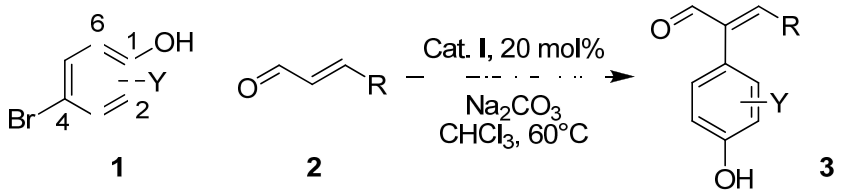
of 7 hours; ***(C)*** a solution of **2a** in chloroform (1 mL) was syringed slowly into the mixture of **1a** and other materials in chloroform (1 mL) in the time span of 7 hours; ***(D)*** a solution of **2a** in chloroform (1 mL) was syringed slowly into the mixture of **1a** and other materials in chloroform (1 mL) in the time span of 15 hours; ***(E)*** a solution of **2a** in chloroform (1 mL) was syringed slowly into the mixture of **1a** and other materials in chloroform (1 mL) in the time span of 22 hours. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d] Not determined.

2.5. Expansion of Substrate Scopes

The scope of the α-arylation reactions of *p*-bromophenols with enals was probed using the optimized conditions described above. As the results in Table 2.4 shown, the diphenylprolinol TMS ether **I** catalysed "cross-coupling-like" reaction displayed broad substrate compatibility. Reactions of a variety of structurally diverse cinnamaldehydes, in which the aromatic ring bears electron-withdrawing, -neutral and -donating substituents, with *p*-bromophenol **1a** as a Michael donor, were explored (entries 1-17). These transformations took place smoothly to give products **3** in moderate to excellent yields (46-99 %). The general conclusion drawn from the results of this effort was that steric effect on reactivity and stereoselectivity were more pronounced than that of electronic effects. For example, relatively lower yields and poorer *E*/*Z* ratios attended reactions of cinnamaldehydes containing *ortho*- and *meta*- versus *para*- aromatic substituents (entries 6-8 and 12-13 versus entries 1-5 and 9-11). The steric effect also reflected in the reaction

of even more hindered β, β-disubstituted enals (for example, *trans*-3-phenyl-but-2-enal): no reaction took place at all.

Table 2.4. Scope of amine-catalysed direct α-arylation reaction of *p*-bromophenols with enals[a]



entry	**R**	**Y**	time (h)	**3**	yield (%)[b]	*E/Z*[c]
1	4-$NO_2C_6H_4$	H	24	**3a**	85	>30:1
2	4-FC_6H_4	H	22	**3b**	92	>30:1
3	4-ClC_6H_4	H	21	**3c**	95	>30:1
4	4-BrC_6H_4	H	13	**3d**	96	>30:1
5	4-CNC_6H_4	H	22	**3e**	86	10:1
6	3-FC_6H_4	H	44	**3f**	62	15:1
7	2-FC_6H_4	H	17	**3g**	77	20:1
8	2-ClC_6H_4	H	24	**3h**	69	7:1
9	Ph	H	19	**3i**	99	>30:1
10	4-$MeOC_6H_4$	H	45	**3j**	99	>30:1
11	4-MeC_6H_4	H	48	**3k**	99	>30:1
12	2-$MeOC_6H_4$	H	60	**3l**	52	19:1
13	2-MeC_6H_4	H	60	**3m**	50	20:1
14	2-Furanyl	H	36	**3n**	46	24:1

15	2-Naphthyl	H	15	**3o**	84	>30:1
16	1-Naphthyl	H	48	**3p**	68	8:1
17	Me	H	72	**3q**	0	nd[d]
18	Ph	2-MeO	96	**3r**	99	>30:1
19	Ph	2,6-Me_2	120	**3s**	86	>30:1
20	Ph	3-Me	168	**3t**	91	>30:1
21	Ph	2-F	120	**3u**	79	>30:1
22	Ph	2-Cl	120	**3v**	62	21:1
23	Ph	3-Cl	168	**3w**	62	>30:1

[a]Reaction conditions: a solution of **2** (0.1 mmol) in chloroform (1mL) was syringed slowly into the mixture of **1** (0.2 mmol), catalyst **I** (20 mol%, 0.02 mmol) and Na_2CO_3 (0.4 mmol) in chloroform (1 mL) in the time span of 7 hours. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Not determined.

Moreover, in general, reactions of electron-withdrawing-substituted cinnamaldehydes yielded products in relatively higher yields and *E/Z* selectivities. In addition, the process could be extended to heterocyclic and conjugated arenes (entries 14-16). Finally, the result demonstrated that an aliphatic enal could not provide the desired product (entry 17). Nevertheless, interestingly, an unexpected 4-methylbenzaldehyde product was obtained in 64% yield. The product was presumably through a [3+3] process, which would be elaborated in Chapter 5.

The effects of varying the substitution pattern (for example, at positions 2, 3 and 6) of the *p*-bromophenol reactants were also investigated (Table 2, entries 18-23). The

results shown that *p*-bromophenol substituents had only a limited influence on yields and stereoselectivities. In general, good to high yields (62-99%) and high *E*/*Z* selectivities were observed in all cases. As they were expected, electronic donating groups were found to facilitate the process (entries 18-20 versus 21-23), whereas the effect of sterics was limited. Finally, we also find that reactions of substrates, in which the phenol -OH group was changed to -OMe, $-NH_2$, -NHMe, $-NMe_2$ and -SH, did not take place (data not shown in the Table 2.4).

2.6. Investigation of Mechanism

Cross-coupling reactions are typically performed by using transition-metal catalysis. Only recently did Sun[47] and Lei[48] independently describe elegant organocatalysed cross-coupling reactions of aryl iodides/bromides with arenes using 1, 10-phenanthroline and *N*, *N'*-dimethylethane-1, 2-diamine as respective catalysts in the presence of *t*-BuOK. It is believed that these processes take place through radical pathways.[47-52] The strategic basis of the new coupling reactions described above are completely different from those reported by Sun, Lei and others.[49-52] The proposed mechanism of the amine **I** catalysed α-arylation reactions of enals (Figure 2.2) involves the intermediacy of iminium ion **4**, derived from the reaction of enal **2** with catalyst **I** followed by a Friedel-Crafts (or Michael addition) reaction with, for example, 4-bromophenol **1a**. This step is the key to success of the overall process, as it must not only take place smoothly to initiate subsequent steps but, more importantly, it must occur regioselectively at a highly crowded *para*-phenol position. Therefore, the facility of the

electrophilic aromatic substitution step requires the presence of an appropriately small halogen, like Br, with a weaker C-X versus C-C bond and an electron-donating or weak-withdrawing capacity.

Figure 2.2. A proposed reaction mechanism for α-arylation reactions of enals with 4-bromophenol

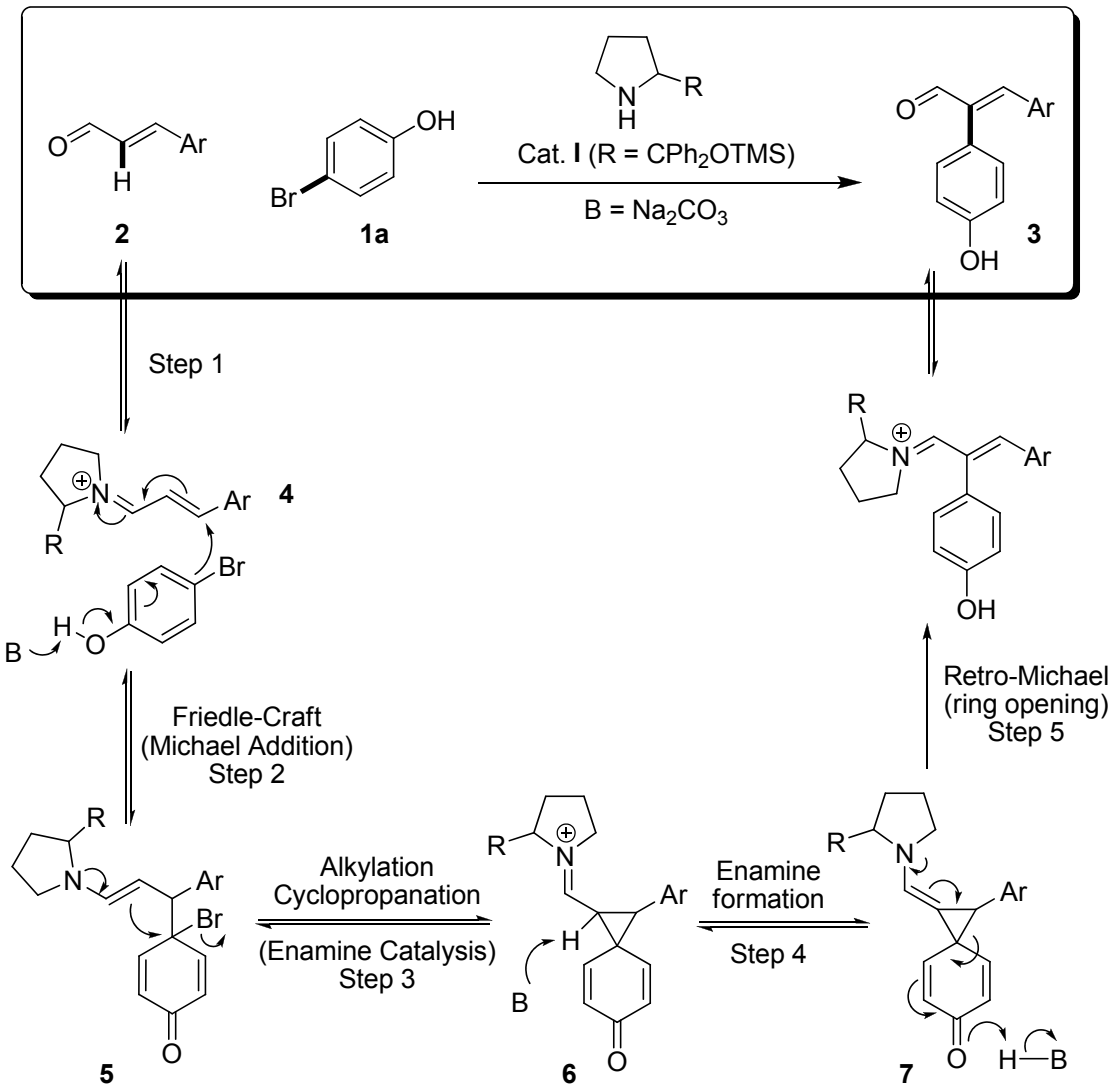
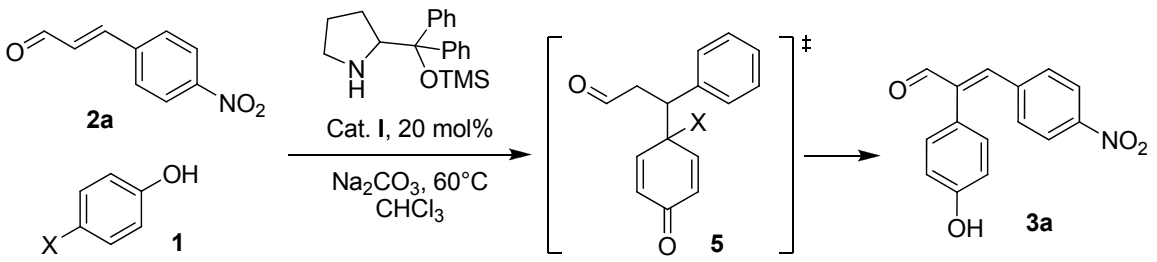


Table 2.5. The effects of leaving groups **X** on the fate of the arylation reactions[a]



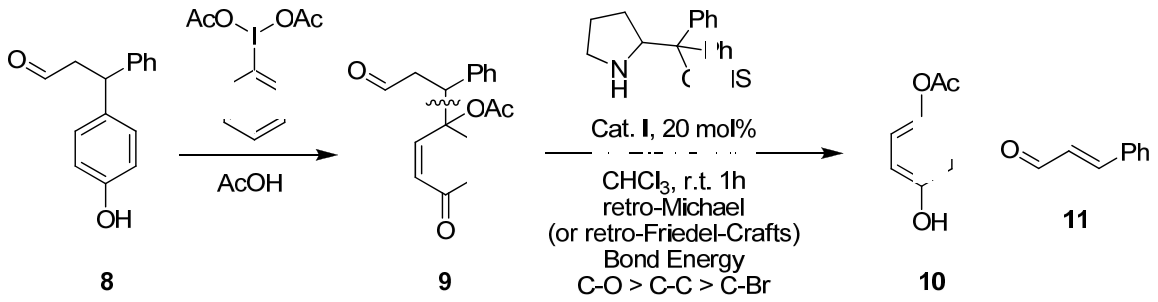
entry	X	**C-X** (kcal mol^{-1})[e]	time (days)	yield (%)[b]	*E*/*Z*[c]
1	H	96-99	2	0	nd[d]
2	OAc	85-91	3	0	nd[d]
3	Cl	79	4	<5	nd[d]
4	Br	66	1	85	>30:1
5	I	52	3	59	>30:1

[a]Reaction conditions: unless specified, see footnote *a* and Experimental section. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Not determined. [e]C-C bond energy: 83-85 kcal mol^{-1}.

Importantly, as mentioned above, to the best of our knowledge, no precedent exists for an organocatalysed Friedel-Crafts reaction of a benzene derivative leading to *ipso*-substitution, a process that is energetically costly as it initially involves de-aromatization of the benzene ring and generation of a highly congested quaternary carbon centre. Moreover, an intramolecular alkylation reaction could compete with retro-Michael addition (Friedel-Crafts). Notably, owing to the relatively weak C-Br (bond energy: 66 kcal mol^{-1}) versus C-C bond (BDE of 83-85 kcal mol^{-1}), C-Br bond cleavage in alkylation process is more favorable than the retro-Michael reaction.[53] To verify this conclusion, studies were carried out with different arene-leaving groups using the same

reaction conditions (Table 2.5). As the results indicate, when the C-X bond energies (for example, C-H and C-O, entries 1 and 2) are larger than that of the C-C bond, retro-Michael addition is dominant and it results in no product formation. When C-X bond energies (for example, C-Br and C-I, entries 4 and 5) are smaller than that of the C-C bond, intramolecular cyclopropanation occurs and leads to a subsequent cascade that delivers product **3a**.

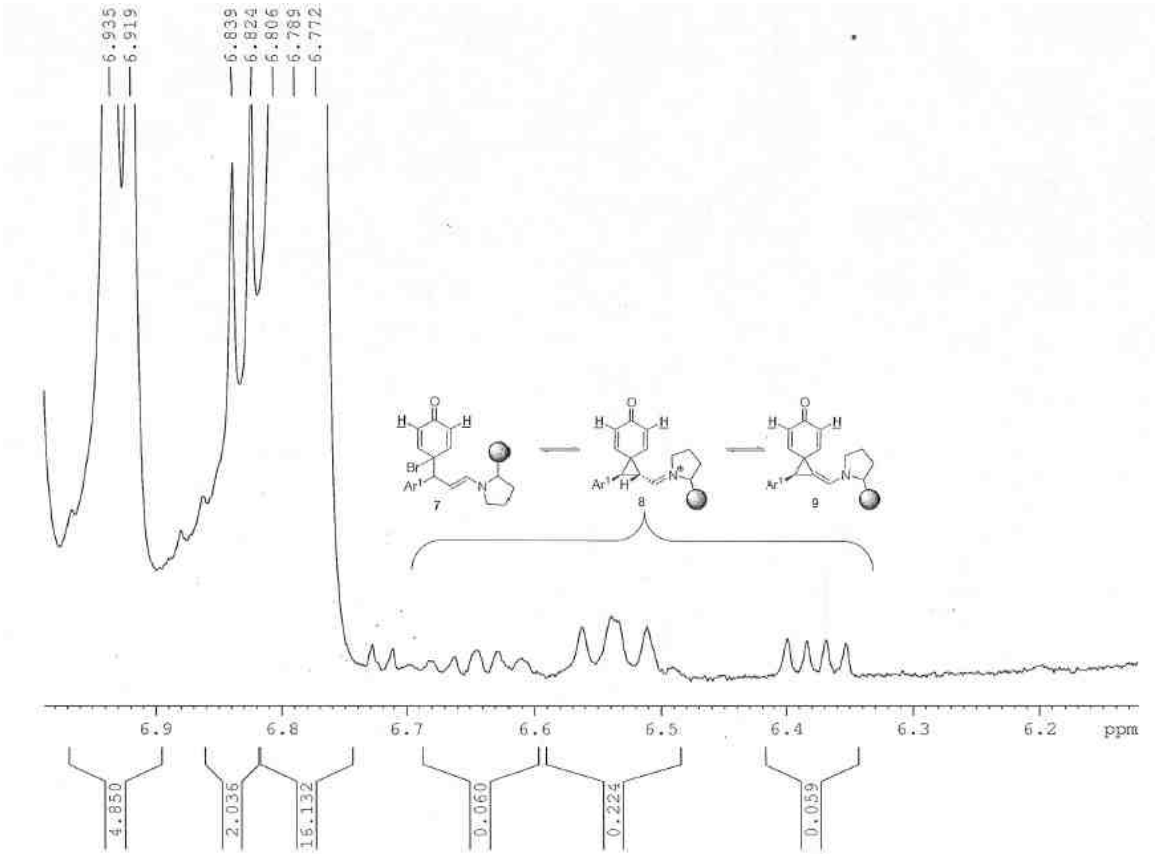
Figure 2.3. Preparation of the stable *p*-acetoxy quinol **9** and catalyst **I** catalyzed retro-Michael addition reaction of **9**



It is expected that reaction with chloro-arenes will not take place (Table 2.5, entry 3) as the C-Cl bond energy is close to that of the C-C bond, and the stronger electron-withdrawing ability of Cl would deactivate the aromatic system for the Friedel-Crafts reaction. In this effort, we have also prepared the stable *p*-acetoxy quinol **9** (Figure 2.3). Treatment of **9** in the presence of catalyst **I** gives 4-acetyloxy phenol **10** and *trans*-cinnamaldehyde **11**. This finding indicates that retro-Michel (retro-Friedel-Crafts) reaction via breaking of the weaker C-C bond rather than the stronger C-O bond prevails

in this process. Taken together, the results described above not only provide support for the proposed reaction mechanism involving a Friedel-Crafts-initiated alkylation-ring-opening cascade process but also can be used to explain why brominated arenes are critical for the success of the organocatalytic α-arylation reactions of enals. The mechanistic pathway outlined in Figure 2.2 also explains why at least 2 equiv of Na_2CO_3 are important for the process. The base is required for the activation of the phenol for the initial Friedel-Crafts reaction (step 2). Furthermore, in step 4, it facilitates formation of enamine **7** for subsequent ring opening. The enamine-retro-Michael sequence has been demonstrated in our early studies of organocatalysed cyclopropanation reaction. As observed earlier, treatment of the cyclopropane products with catalyst **I** in the presence of base (NaOAc) leads to ring opening to give enal products. The cross-coupling-like reaction is proposed to follow a similar pathway. The Michael adduct **5** proceeds an intramolecular alkylation through a favorable *enol-exo-3-exo-tert* attack to produce the strained spiro-cyclopropane intermediate **6**, which spontaneously undergoes formation of enamine **7**, followed by stereoselective retro-Michael reaction (ring opening) to give final product **3** with *E*-configuration. Unlike the earlier cyclopropanation reaction, in the current process, isolation of the highly active intermediate cyclopropane aldehyde, derived from **6,** and species **5** and **7** is not possible. Interestingly, *in situ* ^{1}H NMR studies lead to the detection of resonance associated with the quinols **5-7** (Figure 2.4) at 6.24-6.40, 6.50-6.58 and 6.61-6.68 p.p.m. Finally, the formation of major products **3** with (*E*) stereo-configuration is consistent with the geometry of starting material *trans*-α, β-unsaturated aldehydes due to the essential orbital alignment for selective ring opening.

Figure 2.4. Monitoring quinol formation by ^{1}H NMR



2.7. Summary

In conclusion, in the effort described above, we have developed an unprecedented organocatalytic method for direct, stereoselective α-arylation of simple unfunctionalized α, β-unsaturated aldehydes. A novel iminium-initiated Michael-alkylation-enamine-ring-opening cascade process has been demonstrated by using mechanistic studies. The amine catalysed α -arylation reactions, which occur under mild conditions, display a broad substrate scope for the 4-bromophenols and α, β-unsaturated aldehyde reactants. Notably, synthetically challenging *E*-cross-coupling products are generated in good to high yields

and with good to excellent levels of stereoselectivity. The conceptually novel cross-coupling strategy can also be viewed as a stereoselective C-H functionalization process using an organocatalyst and, as such, adds a new process to the emerging field of organocatalysis. Finally, the unique transformation holds significant potential for applications to a broad spectrum of novel organic reactions, a proposal that will guide our further efforts in this area.

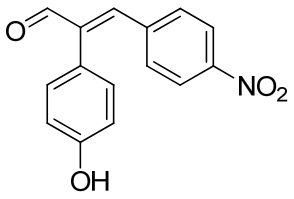
2.8. Experimental Section

General Information:

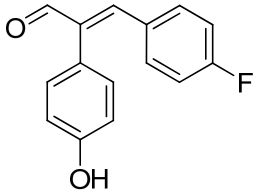
All commercially available reagents were used without further purification. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on Whatman silica gel plates with fluorescence F_{254} indicator. And Merck 60 silica gel was used for chromatography. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance 500. When deuteriorated chloroform ($CDCl_3$) was used to dissolve sample, tetramethylsilane (TMS) was used as an internal reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.

Procedure for (*E*)-α, β-diarylacrylaldehydes (Table 2.4):

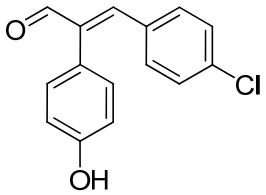
To a mixture of a substituted *p*-bromophenol (**1a**, 35 mg, 0.2 mmol), catalyst **I** (7 mg, 0.02 mmol) and sodium carbonate (42 mg, 0.4 mmol) in 0.5 ml of chloroform at 60°C was added a solution of a α, β -unsaturated aldehyde (**2**, 0.1 mmol) in chloroform (1 ml) slowly via a syringe pump over 7 h. After the aldehyde was totally consumed (determined by TLC analysis), the vial was cooled to room temperature. The solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane. The compound is characterized by ^{1}H and ^{13}C NMR and high-resolution mass spectrometry (HRMS) with > 95 % purity-based ^{1}H NMR.



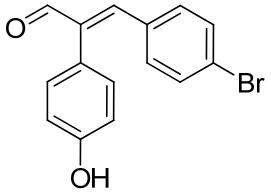
(E)-2-(4-hydroxyphenyl)-3-(4-nitrophenyl)acrylaldehyde (3a). The title compound was prepared according to the typical procedure, as described above in 85 % yield. Melting point (MP) 186-187°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.83 (s, 1H), 8.67 (br, 1H), 8.14 (d, J = 8.5 Hz, 2H), 7.65 (s, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 158.6, 148.4, 146.3, 145.1, 142.1, 131.8, 131.6, 124.0, 116.3; HRMS (ESI) calcd. for $C_{15}H_{11}NO_4$: *m/z* 292.0586 ($[M + Na]^+$), found 292.0583.



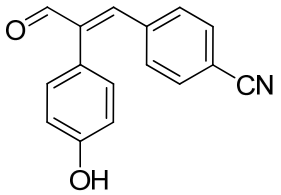
(E)-3-(4-fluorophenyl)-2-(4-hydroxyphenyl)acrylaldehyde (3b). The title compound was prepared according to the typical procedure, as described above in 92 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.73 (s, 1H), 8.62 (br, 1H), 7.51 (s, 1H), 7.37 (m, 2H), 7.06 (t, J = 9.0 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 164.8, 162.8, 158.1, 148.4, 142.4, 133.4, 133.3, 131.9, 131.4, 124.9, 116.2, 116.1, 115.9; HRMS (ESI) calcd. for $C_{15}H_{11}FO_2$: *m/z* 265.0641 ($[M + Na]^+$), found 265.0640.



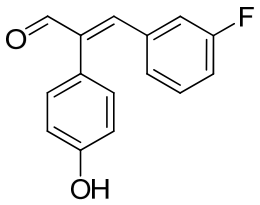
(E)-3-(4-chlorophenyl)-2-(4-hydroxyphenyl)acrylaldehyde (3c). The title compound was prepared according to the typical procedure, as described above in 95 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.75 (s, 1H), 8.64 (br, 1H), 7.50 (s, 1H), 7.32 (s, 4H), 7.00 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 158.2, 148.0, 143.1, 135.6, 134.3, 132.6, 131.4, 129.2, 124.7, 116.2; HRMS (ESI) calcd. for $C_{15}H_{11}ClO_2$: *m/z* 281.0345 ($[M + Na]^+$), found 281.0339.



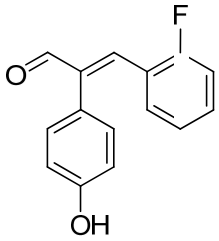
(E)-3-(4-bromophenyl)-2-(4-hydroxyphenyl)acrylaldehyde (3d). The title compound was prepared according to the typical procedure, as described above in 96 % yield. MP 185-186°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.75 (s, 1H), 8.65 (br, 1H), 7.47 (m, 3H), 7.24 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 158.3, 148.1, 143.2, 134.7, 132.8, 131.4, 124.7, 124.1, 116.3; HRMS (ESI) calcd. for $C_{15}H_{11}BrO_2$: *m/z* 324.9840 ([M + Na]$^+$), found 324.9833.



(E)-4-(2-(4-hydroxyphenyl)-3-oxoprop-1-enyl)benzonitrile (3e). The title compound was prepared according to the typical procedure, as described above in 86 % yield. MP 160-162°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.80 (s, 1H), 8.64 (br, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.58 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 158.5, 146.9, 144.7, 140.1, 132.8, 131.5, 128.7, 124.2, 118.8, 116.3, 115.8, 113.1; HRMS (ESI) calcd. for $C_{16}H_{11}NO_2$: *m/z* 272.0687 ([M + Na]$^+$), found 272.0681.

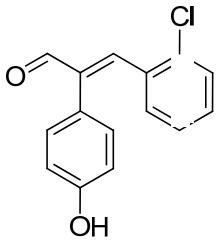


(E)-3-(3-fluorophenyl)-2-(4-hydroxyphenyl)acrylaldehyde (3f). The title compound was prepared according to the typical procedure, as described above in 62 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.77 (s, 1H), 8.60 (br, 1H), 7.53 (s, 1H), 7.34 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.10 (m, 1H), 7.01 (m, 3H), 6.89 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.3, 158.4, 147.9, 143.7, 137.9, 131.4, 131.1, 131.0, 127.4, 124.7, 117.2, 117.1, 117.0, 116.3; HRMS (ESI) calcd. for $C_{15}H_{11}FO_2$: *m/z* 265.0641 ($[M + Na]^+$), found 265.0636.

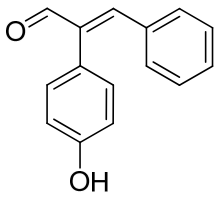


(E)-3-(2-fluorophenyl)-2-(4-hydroxyphenyl)acrylaldehyde (3g). The title compound was prepared according to the typical procedure, as described above in 77 % yield. MP 165-166°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.83 (s, 1H), 8.56 (br, 1H), 7.62 (s, 1H), 7.37 (m, 1H), 7.19 (m, 1H), 7.02 (m, 4H), 6.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 158.3, 144.0, 140.5, 140.4, 132.5, 132.4, 131.5,

131.0, 124.6, 116.5, 116.3, 116.1; HRMS (ESI) calcd. for $C_{15}H_{11}FO_2$: *m/z* 265.0641 ([M + Na]$^+$), found 265.0642.

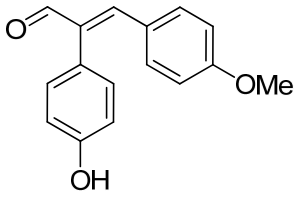


(E)-3-(2-chlorophenyl)-2-(4-hydroxyphenyl)acrylaldehyde (3h). The title compound was prepared according to the typical procedure, as described above in 69 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.87 (s, 1H), 8.58 (br, 1H), 7.68 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.31 (m, 1H), 7.06 (m, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 158.2, 145.0, 144.0, 134.9, 134.1, 131.7, 131.6, 131.3, 130.3, 127.2, 124.0, 115.9; HRMS (ESI) calcd. for $C_{15}H_{11}ClO_2$: *m/z* 281.0345 ([M + Na]$^+$), found 281.0337.

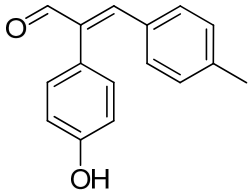


(E)-2-(4-hydroxyphenyl)-3-phenylacrylaldehyde (3i). The title compound was prepared according to the typical procedure, as described above in 99 % yield. MP 152-153°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.72 (s, 1H), 8.55 (br, 1H), 7.47 (s, 1H),

7.25 (m, 5H), 6.97 (d, *J*= 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.3, 158.0, 149.8, 142.6, 135.4, 131.4, 131.1, 130.4, 129.0, 125.1, 116.1; HRMS (ESI) calcd. for $C_{15}H_{12}O_2$: *m/z* 247.0735 ([M + Na]$^+$), found 247.0733.

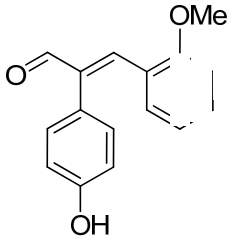


(E)-2-(4-hydroxyphenyl)-3-(4-methoxyphenyl)acrylaldehyde (3j). The title compound was prepared according to the typical procedure, as described above in 99 % yield. MP 180-181°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.68 (s, 1H), 8.57 (br, 1H), 7.43 (s, 1H), 7.27 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.1, 161.9, 157.9, 149.9, 140.7, 133.1, 131.4, 127.9, 125.6, 116.2, 114.5, 55.5; HRMS (ESI) calcd. for $C_{15}H_{12}O_2$: *m/z* 277.0841 ([M + Na]$^+$), found 277.0838.

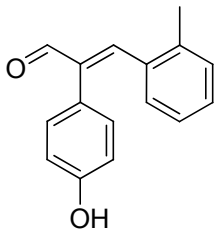


(E)-2-(4-hydroxyphenyl)-3-p-tolylacrylaldehyde (3k). The title compound was prepared according to the typical procedure, as described above in 99 % yield. MP 188-190°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.72 (s 1H), 8.56 (br, 1H), 7.46 (s, 1H),

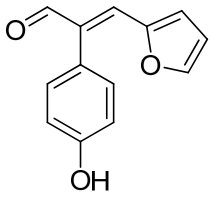
7.20 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.3, 158.0, 150.0, 141.9, 140.9, 132.6, 131.4, 131.2, 129.7, 125.4, 116.1, 21.1; HRMS (ESI) calcd. for $C_{16}H_{14}O_2$: *m/z* 261.0891 ($[M + Na]^+$), found 261.0888.



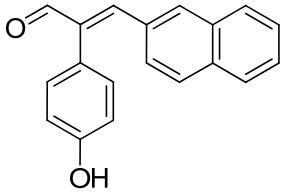
(E)-2-(4-hydroxyphenyl)-3-(2-methoxyphenyl)acrylaldehyde (3l). The title compound was prepared according to the typical procedure, as described above in 52 % yield. MP 173-174°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.76 (s, 1H), 8.47 (br, 1H), 7.74 (s, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 7.5 Hz, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.68 (t, J = 7.5 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.3, 159.0, 158.0, 144.5, 142.1, 132.1, 131.6, 130.8, 125.4, 124.1, 120.6, 116.0, 111.9, 56.0; HRMS (ESI) calcd. for $C_{16}H_{14}O_3$: *m/z* 277.0841 ($[M + Na]^+$), found 277.0835.



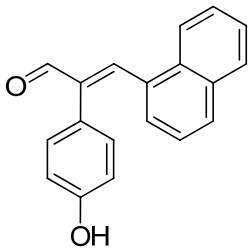
(E)-2-(4-hydroxyphenyl)-3-o-tolylacrylaldehyde (3m). The title compound was prepared according to the typical procedure, as described above in 50 % yield. MP 161-162°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.83 (s, 1H), 8.45 (br, 1H), 7.69 (s, 1H), 7.19 (d, J = 5.0 Hz, 1H), 7.17 (m, 1H), 6.95 (m. 4H), 6.76 (d, J = 8.5 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.5, 158.0, 148.5, 143.1, 138.3, 134.9, 131.9, 131.0, 130.0, 129.8, 126.1, 124.8, 115.8, 19.9; HRMS (ESI) calcd. for $C_{16}H_{14}O_2$: *m/z* 261.0891 ($[M + Na]^+$), found 261.0889.



(E)-3-(furan-2-yl)-2-(4-hydroxyphenyl)acrylaldehyde (3n). The title compound was prepared according to the typical procedure, as described above in 46 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.68 (s, 1H), 8.55 (br, 1H), 7.68 (s, 1H), 7.36 (s, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.50 (d, J = 2.0 Hz, 1H), 6.34 (d, J = 3.5 Hz, 1H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 193.2, 158.2, 151.8, 146.3, 139.5, 135.9, 131.3, 130.8, 125.3, 116.6, 116.0, 113.4; HRMS (ESI) calcd. for $C_{13}H_{10}O_3$: *m/z* 237.0528 ($[M + Na]^+$), found 237.0525.

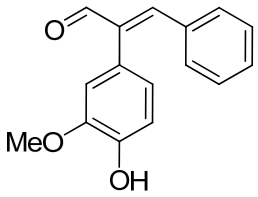


(E)-2-(4-hydroxyphenyl)-3-(naphthalen-2-yl)acrylaldehyde (3o). The title compound was prepared according to the typical procedure, as described above in 84 % yield. MP 151-152°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.81 (s, 1H), 8.62 (br, 1H), 7.98 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (m, 2H), 7.51 (m, 2H), 7.27 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.3, 158.2, 149.7, 142.7, 134.4, 133.8, 133.2, 132.3, 131.6, 129.2, 128.3, 128.2, 128.1, 127.2, 127.1, 125.1, 116.1; HRMS (ESI) calcd. for $C_{19}H_{14}O_2$: *m/z* 297.0891 ($[M + Na]^+$), found 297.0890.

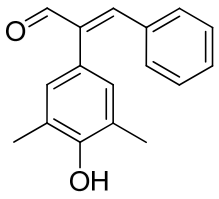


(E)-2-(4-hydroxyphenyl)-3-(naphthalen-1-yl)acrylaldehyde (3p). The title compound was prepared according to the typical procedure, as described above in 68 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.00 (s, 1H), 8.45 (br, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.20 (s, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.58 (m, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.5, 157.9, 147.6,144.3, 134.4, 132.9, 132.4,

131.9, 130.9, 130.1, 129.4, 128.5, 127.5, 127.0, 125.8, 124.7, 115.8; HRMS (ESI) calcd. for $C_{19}H_{14}O_2$: *m/z* 297.0891 ($[M + Na]^+$), found 297.0884.

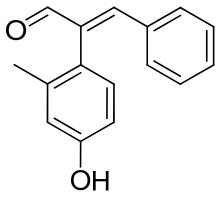


(E)-2-(4-hydroxy-3-methoxyphenyl)-3-phenylacrylaldehyde (3r). The title compound was prepared according to the typical procedure, as described above in 99 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.75 (s, 1H), 7.79 (br, 1H), 7.51 (s, 1H), 7.31 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.3, 149.7, 148.3, 147.4, 142.7, 135.4, 131.2, 130.5, 129.1, 125.5, 123.1, 116.0, 113.6, 56.1; HRMS (ESI) calcd. for $C_{16}H_{14}O_3$: *m/z* 277.0841 ($[M + Na]^+$), found 277.0837.

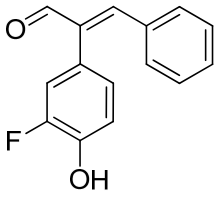


(E)-2-(4-hydroxy-3,5-dimethylphenyl)-3-phenylacrylaldehyde (3s). The title compound was prepared according to the typical procedure, as described above in 86 % yield. MP 148-149°C; ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.74 (s, 1H), 7.47 (s, 2H), 7.30 (m, 5H), 6.75 (s, 2H), 2.20 (s, 6H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.5,

153.9, 149.5, 142.9, 135.5, 131.2, 130.5, 129.9, 129.0, 125.3, 124.9, 16.4; HRMS (ESI) calcd. for $C_{17}H_{16}O_2$: *m/z* 275.1048 ($[M + Na]^+$), found 275.1046.

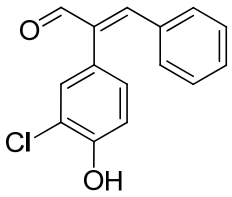


(E)-2-(4-hydroxy-2-methylphenyl)-3-phenylacrylaldehyde (3t). The title compound was prepared according to the typical procedure, as described above in 91 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.77 (s, 1H), 8.40 (br, 1H), 7.29 (m, 6H), 6.80 (d, 2H), 6.72 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.4, 158.1, 150.6, 142.8, 138.2, 135.6, 131.0, 130.8, 129.3, 125.6, 117.7, 114.0, 19.6; HRMS (ESI) calcd. for $C_{16}H_{14}O_2$: *m/z* 261.0891 ($[M + Na]^+$), found 261.0891.

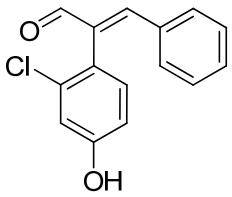


(E)-2-(3-fluoro-4-hydroxyphenyl)-3-phenylacrylaldehyde (3u). The title compound was prepared according to the typical procedure, as described above in 79 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.74 (s, 1H), 8.88 (br, 1H), 7.57 (s, 1H), 7.31 (m, 5H), 7.02 (t, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 12 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 193.9, 153.0, 151.1, 150.4, 145.5, 145.4, 141.4, 135.1,

131.1, 130.7, 129.1, 126.6, 126.0X2, 118.6, 118.0, 117.8; HRMS (ESI) calcd. for $C_{15}H_{11}FO_2$: *m/z* 265.0641 ($[M + Na]^+$), found 265.0635.

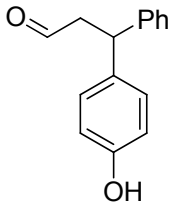


(E)-2-(3-chloro-4-hydroxyphenyl)-3-phenylacrylaldehyde (3v). The title compound was prepared according to the typical procedure, as described above in 62 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.75 (s, 1H), 9.05 (br, 1H), 7.58 (s, 1H), 7.32 (m, 6H), 7.18 (s, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.0, 153.6, 150.6, 141.2, 135.1, 131.6, 131.2, 130.8, 130.1, 129.2, 126.7, 121.0, 117.6; HRMS (ESI) calcd. for $C_{15}H_{11}ClO_2$: *m/z* 281.0345 ($[M + Na]^+$), found 281.0344.

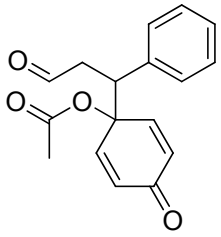


(E)-2-(2-chloro-4-hydroxyphenyl)-3-phenylacrylaldehyde (3w). The title compound was prepared according to the typical procedure, as described above in 62 % yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.76 (s, 1H), 7.72 (s, 1H), 7.33 (m, 6H), 7.02 (d, J = 2.5 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 8.0, 2.5 Hz, 1H); ^{13}C NMR (Acetone -

d_6, 125 MHz): δ = 193.4, 159.1, 151.1, 140.6, 135.2, 134.2, 132.6, 131.0, 129.4, 125.0, 117.1, 115.6; HRMS (ESI) calcd. for $C_{15}H_{11}ClO_2$: *m/z* 281.0345 ($[M + Na]^+$), found 281.0342.



3-(4-Hydroxyphenyl)-3-phenylpropanal (8). The title compound was synthesized according to a known procedure.[55] ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.73 (s, 1H), 7.37-7.18 (m, 5H), 7.09 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 4.62 (br, 1H), 4.56 (t, J = 8.0 Hz, 1H), 3.13 (dd, J = 8.0 2.0 Hz, 2H).



4-Oxo-1-(3-oxo-1-phenylpropyl)cyclohexa-2,5-dienyl acetate (9). The title compound was synthesized according to a known procedure.[56] (Diacetoxyiodo)benzene (0.5 mmol) was added to a solution of 3-(4-hydroxyphenyl)-3-phenylpropanal (0.5 mmol) in glacial AcOH (2mL) at 0°C. After starting material was totally consumed, the reaction was concentrated and purified by flash chromatography. ^{1}H NMR ($CDCl_3$, 500 MHz): δ =

9.60 (s, 1H), 7.30-7.18 (m, 5H), 6.73 (m, 2H), 6.31 (d, J = 10.0 Hz, 1H), 6.24 (d, J = 10.0 Hz, 1H), 3.81 (m, 1H), 2.95 (m, 2H), 2.10 (s, 3H).

^{1}H NMR study of the formation of quinols:

Trans-p-nitro-cinnamaldehyde (**2a**, 18 mg, 0.1 mmol) and 4-bromophenol (**1a**, 26 mg, 0.15 mmol) and catalyst (0.02 mmol) were dissolved in 0.8 ml of $CDCl_3$ and the reaction mixture was transferred into a NMR tube. A small magnetic stir bar was used to stir the mixture, and it was removed before ^{1}H NMR measurement. The reaction mixture was monitored with designated period of time (2, 8, and 10, 49 h, and 3 days).

2.9. Reference

(1) Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, **2004**, *2nd ed.* Wiley-VCH.

(2) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

(3) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555-1564.

(4) Liu, C.; Jin, L; Lei, A. *Synlett* **2010**, *2010*, 2527-2536.

(5) Wu, X.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9047-9050.

(6) Negishi, E.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3151-3182.

(7) Martin, R.; Buchwald, S. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

(8) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874-922.

(9) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082-1146.

(10) Chen, X.; Engle, K.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115.

(11) Brennfuhrer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114-4133.

(12) Jones, W.; Fehe, F. *Acc. Chem. Res.* **1989**, *22*, 91-100.

(13) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507-514.

(14) Dyker, G. *Handbook of C-H Transformations. Applications in Organic Synthesis* **2005**, Wiley-VCH.

(15) Godula, K.; Sames, D. *Science* **2006**, *312*, 67-72.

(16) Bergman, R. G. *Nature* **2007**, *446*, 391-393.

(17) Chen, X.; Engle, K. M.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115.

(18) Knappke, C. E. I.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3568-3570.

(19) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540-548.

(20) Sun, C.; Li, B.; Shi, Z. *Chem. Rev.* **2011**, *111*, 1293-1314.

(21) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

(22) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

(23) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

(24) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79-87.

(25) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416-5470.

(26) Berkessel, A.; Groeger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* **2005**, Wiley-VCH.

(27) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582-585.

(28) Cochiara, J.; Letizia, C. S.; Lalko, J.; Lapczynski, A.; Api, A. M. *Food Chem. Toxicol.* **2005**, *43*, 867-923.

(29) Friedman, M.; Kozukue, N.; Harden, L. A. *J. Agric. Food. Chem.* **2000**, *48*, 5702-5709.

(30) Brackman, G. *et al. BMC Microbiol.* **2008**, *16*, 149.

(31) Lee. C. W. *et al. J. Pharmacol. Sci.* **2007**, *104*, 19-28.

(32) Sato, K.; Krist, S.; Buchbaruer, G. *Biol. Pharm. Bull.* **2006**, *29*, 2292-2294.

(33) Moreau, A.; Chen, Q.; Praveen Rao, P. N.; Knaus, E. E. *Bioorg. Med. Chem.* **2006**, *14*, 7716-7727.

(34) Jonnalagadda, S. S.; Haar, E. T.; Hamel, E.; Lin, C. M.; Magarian, R. A.; Day, B. W. *Bioorg. Med. Chem.* **1997**, *5*, 715-722.

(35) Nodiff, E. A. *et al. J. Med. Chem.* **1971**, *14*, 921-925.

(36) Lee, E. J.; Kim, J. R.; Choi, D. R.; Ahn, Y. J. *J. Econ. Entomol.* **2008**, *101*, 1960.

(37) Rodriguez, A.; Nerin, C.;Batlle, R. *J. Agric. Food Chem.* **2008**, *56*, 6364-6469.

(38) Chang, S. T.; Cheng, S. S *J. Agric. Food Chem.* **2002**, *50*, 1389-1392.

(39) Park, I. K.; Lee, H. S.; Lee, S. G.; Park, J. D.; Ahn, Y. J. *J. Agric. Food Chem.* **2000**, *48*, 2528-2531.

(40) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743-5747.

(41) Yu, W.; Tsoi, Y.; Zhou, Z.; Chang, A. S. *Org. Lett.* **2009**, *11*, 469-472.

(42) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037-2046.

(43) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886-10894.

(44) Rios, R.; Sunden, H.; Vesely, J.; Zhao, G.; Dziedzic, P.; Cordova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028-1032.

(45) Paras, N.; MacMillan, D. *J. Am. Chem. Soc.* **2001**, *124*, 4370-4371.

(46) Marques-Lopez, E.; Diez-Martinez, A.; Merino, P.; Herrera, R. P. *Curr. Org. Chem.* **2009**, *13*, 1585-1609.

(47) Sun, C.; Li, H.; Yu, D.; Yu, M.; Zhou, X.; Lu, X.; Huang, K.; Zheng, S.; Li, B.; Shi, Z. *Nat. Chem.* **2010**, *2*, 1044-1049.

(48) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 13737-16740.

(49) Yanagisawa, S.; Ueda, K.; Tanigushi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673-4676.

(50) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C. *Chem. Eur. J.* **2009**, *15*, 333-337.

(51) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1668-1669.

(52) Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5018-5022.

(53) Bond energy values (BDV). Smith, M. B.; March, J. (ed) *March's Advanced Organic Chemistry 5th ed.* **2004**, 24, Wiley-VCH.

(54) Zhang, S. *et al*. *Nat. Commun.* **2011**, *2*, 211.

(55) Caschi, S.; Ta Torre, F.; Palmieri, G. *J. organometal. Chem.* **1984**, *268*, c48-c51.

(56) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.***2008**, *130*, 404-405.

Chapter 3

Direct Stereoselective α-Arylation of Simple Enals with Bromonaphthols using an Organocatalytic Cross-Coupling-Like Approach

3.1. Introduction to Functionalized Naphthol Frameworks

The bicyclic privileged structural frameworks of naphthols exist ubiquitously in natural products possessing a wide spectrum of important biological activities such as antibacterial, anticancer, antiviral, mutagenicity, antiproliferative, antitumor, *etc*.[1-8] Both metal or Lewis acid mediated methodologies[9-12] and organocatalytic strategies[13-18] have been developed for the construction of various functionalized naphthol containing frameworks.

As a class of electronic rich bicyclic arenes, naphthols are readily participating in the Friedel-Crafts reaction enantioselectively as well as regioselectively. Erker and coworkers reported the first Lewis acid catalyzed enantioselective Friedel-Crafts reaction of 1-naphthols and ethyl pyruvates as early as in 1990.[9] Recently, Jørgensen and coworkers demonstrated the first organocatalytic asymmetric Friedel-Crafts amination of 2-naphthols to generate atropisomers[13,14], and Chen and coworkers also reported the enantioselective Friedel-Crafts alkylation/cascade reaction of naphthols and nitroolefins catalyzed by thiourea-tertiary amine based bifunctional organocatalyst[15]. Discovery of

novel methodologies towards versatile functionalized naphthols is a rewarding task in the circumstance of modern organic synthesis.

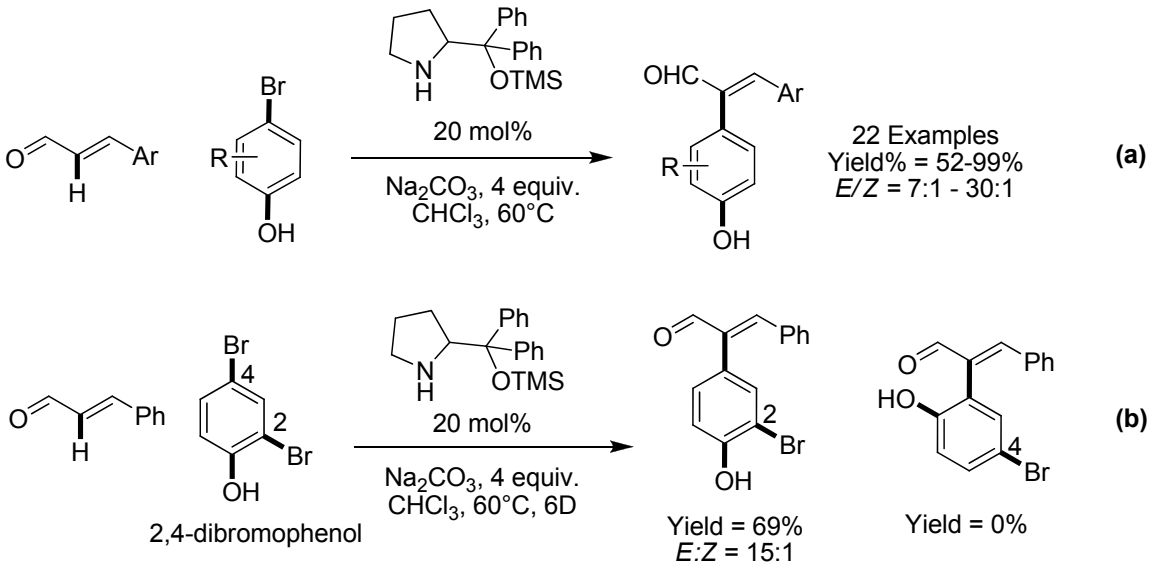
3.2. Substrate Design

Recently we reported an unprecedented organocatalytic cross-coupling-like strategy for the direct α-arylation of unmodified α, β-unsaturated aldehydes with 4-bromophenols (Scheme 3.1, equation a).[19] The synthetically challenging *E*-α,β-diarylacrylaldehydes were obtained via a novel iminium initiated Michael-alkylation-enamine-ring opening cascade process. Besides 4-bromophenols, we also probe 2-bromophenol for the reaction. No reaction occurs and only starting materials are recovered. Furthermore, when 2, 4-dibromophenol was used as Michael donor, an exclusive regioselectivity favoring *para*-phenol position over *ortho*-position was also discovered (Scheme 3.1, equation b). In the 2, 4-dibromophenol, both para and ortho positions are potential Michael donation sites. However, after it is submitted to optimized reaction conditions, α-arylation only happens at *para*-position of the phenol (with 69% yield).

The observation of high regioselectivity could be directly led to a seemingly convenient conclusion that *ortho*-bromophenol is less reactive than *para*-bromophenol. It is believed that 2-bromophenol framework is more crowded than 4-bromophenol for the cross-coupling process, and such an effect becomes significant in the initial Michael addition reaction, which is steric sensitive, as results of the generation of a highly crowded quaternary carbon center and requires high energy for dearomatization.[19] In

order to overcome such an energy barrier, we proposed that 1-bromo-2-naphthol, which is considered as an reactive analogue of 2-bromophenol, should be a good candidate sufficing the investigation of the *ortho*-bromophenol framework in direct α-arylation methodology.

Scheme 3.1. Cross-coupling-like strategy for the direct α-arylation of unmodified α, β-unsaturated aldehydes with 4-bromophenols

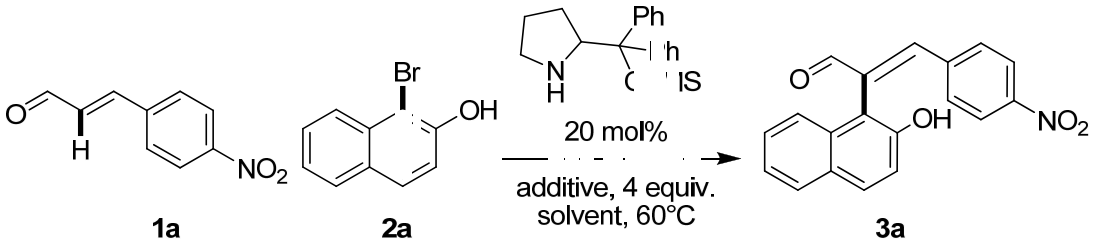


3.3. Optimization of Reaction Conditions

A model reaction at 60^0C using *trans-p*-nitrocinnamaldehyde and 1-bromo-2-naphthol in the presence of sodium acetate and diphenylprolinol TMS ether catalyst was set up according to a typical α-arylation reaction condition we previously developed (Table 3.1). After initial screening of various solvents and solvents combination, acetonitrile was found to be the optimal solvent which provided maximum yield of 56%

after 3 days reaction under 60^0C (Table 3.1, entry 8). It was found that the organic solvents with high polarity usually provided higher yield (entries 5-8 and entries 1-3). Although water was more polarized than acetonitrile, after mixing the water with acetonitrile in different volume ratios, the reaction accomplished much faster but the yield decreased significantly (data not shown here).

Table 3.1. Reaction conditions optimization of amine-catalyzed direct α-arylation reaction of *trans-p*-nitrocinnamaldehyde with 1-bromo-2-naphthol[a]



entry	solvent	additive	time(days)	yield(%)[b]	*E/Z*[c]
1	CHCl3	NaOAc	3	<5	nd[d]
2	THF	NaOAc	3	<5	nd[d]
3	Toluene	NaOAc	3	<5	nd[d]
4	DMF	NaOAc	3	13	>30:1
5	MeOH	NaOAc	3	39	>30:1
6	EtOH	NaOAc	3	41	>30:1
7	Acetone	NaOAc	3	50	>30:1
8	MeCN	NaOAc	3	56	>30:1
9	MeCN	K_2CO_3	3	<5	nd[d]
10	MeCN	Na_2CO_3	3	22	>30:1

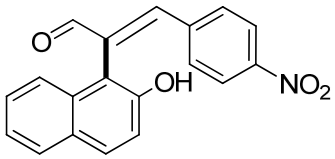
11	MeCN	$NaHCO_3$	3	24	>30:1
12	MeCN	LiOAc	2	32	>30:1
13	MeCN	LiOAc	3	61	>30:1
14	MeCN	LiOAc-$2H_2O$	3	68	>30:1

[a]Unless stated otherwise, the reaction was carried out with *trans*-*p*-nitrocinnamaldehyde (0.2 mmol), 1-bromo-2-naphthol (0.4 mmol), additive (0.8 mmol) and aminocatalyst (0.04 mmol) in solvent (1 mL) for a specified time. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Not determined.

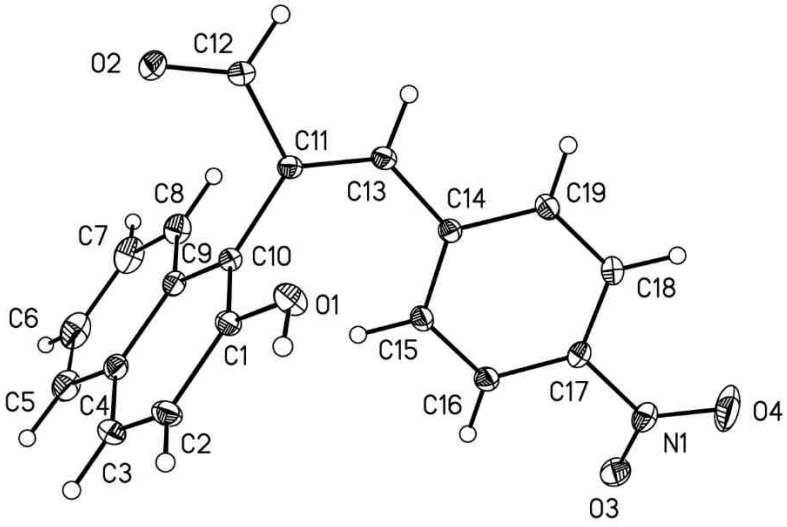
It was also know that the inorganic salts gave significant influence towards the overall yield of the model reaction. After submitting various salts into the reaction mixtures, lithium acetate double hydrate provides a better yield of 68% (Table 3.1, entry 14). The optimal reaction conditions were not established, until series of temperature and time control studies were carried out (data not shown here). Based on our previously experience, the slow addition of a limiting reagent into an exceeding reagent usually give higher yield. However, when 1-bromo-2-naphthol was used as Michael donor, such a slow syringing technique provided a lower overall yield. As a result, one pot reaction condition is considered as a better experimental method than slow syringing in this specific reaction process.

As expected, the *E*-isomer was observed predominantly as the product, and the structure of compound **3a** was determined by X-ray crystal structural analysis (Figure 3.1).

Figure 3.1. Single X-ray crystal structure of **3a** at probability ellipsoids of 20%



3a



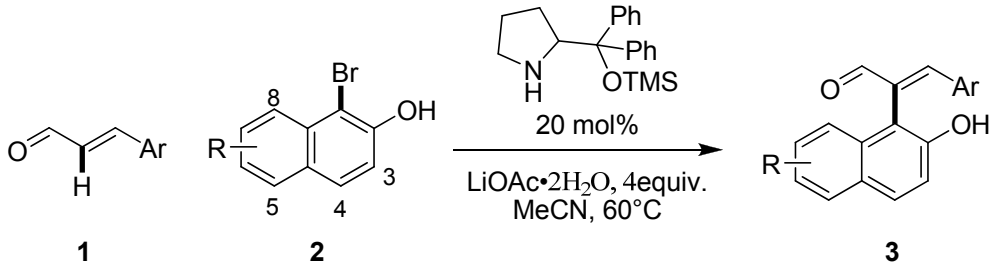
3.4. Expansion of Substrate Scopes

After reaction condition was optimized, the substrate scope was expanded accordingly (Table 3.2). Generally speaking, the scope of the direct α-arylation of enals with 1-bromo-2-naphthols follows the same trend of the scope of *p*-bromophenols as well as 3-bromoindoles. Most of the products give excellent *E/Z* ratio of more than 30:1 (entries except 3, 13 and 15). In some of the cases, poor overall yields of the *E*-isomer were obtained (entries 5 and 12). Enal substrates with electronic withdrawing groups generated relative higher yields than those with electronic donating groups (entries 1, 3, 4, and 8 comparing with entries 13 and 14). If compared with substrates bearing the same

substitutes on *para*-position of phenyl ring, *ortho*-substitutes usually brought down the yields because of large steric hindrance (entries 1 and 2; entries 4 and 5; entries 6 and 7). The reason of the relatively low yields comparing with the results of α-arylation of *p*-bromophenols is that the *E*-isomeric products could easily undergo reversed-aldol-condensation process.

Further on, various brominated naphthol derivatives were submitted to the same optimized reaction conditions (Table 3.2, entries 15-18). As described in our previous report, if the brominated aromatic system contains a strong electron withdrawing substituent, it usually demonstrated decreased reactivity. This experimental rule was also useful for the brominated naphthol systems. The electron deficient property of the quinoline ring rendered the 5-bromo-6-hydroxyquinoline inert to the cross-coupling like reaction (data not shown here). If a weak electron withdrawing group was integrated to the 1-bromo-2-naphthol skeleton, expected product could be obtained with decent yields. As demonstrated, when bromo- substituent was attached at 3, 6, or 7-position of the 1-bromo-2-naphthol ring, the cross-coupling like C-C bond formation happened exclusively at 2-position with good regioselectivity as well as stereoselectivity (entries 15, 16 and 17). When a carboxylic ester group was attached to the naphthol framework, expected α-arylation product was also obtained with 41% yield (entry 18). Comparing with 1-bromo-2-naphthol, the 2-bromo-1-naphthol demonstrated decreased reactivity and provided only a trace amount of desired product. As one of its close derivative, 3-bromo-4-hydroxycoumarine also generated similar negative results (data not shown in the table).

Table 3.2. Substrates scope of amine-catalyzed direct α-arylation reactions of 1-bromo-2-naphthols with enals[a]



1 **2** **3**

entry	Ar	R	time(day)	**3**	yield(%)[b]	*E/Z*[c]
1	4-$NO_2C_6H_4$	H	3	**3a**	68	> 30 : 1
2	2-$NO_2C_6H_4$	H	3	**3b**	34	> 30 : 1
3	4-CNC_6H_4	H	3	**3c**	57	7 : 1
4	4-$CF_3C_6H_4$	H	3	**3d**	73	> 30 : 1
5	2-$CF_3C_6H_4$	H	3	**3e**	13	> 30 : 1
6	4-FC_6H_4	H	3	**3f**	46	> 30 : 1
7	2-FC_6H_4	H	3	**3h**	43	> 30 : 1
8	4-ClC_6H_4	H	3	**3i**	65	> 30 : 1
9	4-BrC_6H_4	H	3	**3j**	42	> 30 : 1
10	Ph	H	4	**3k**	51	> 30 : 1
11	2-Naphthyl	H	3	**3l**	45	> 30 : 1
12	2-Furanyl	H	3	**3m**	12	> 30 : 1
13	4-$MeOC_6H_4$	H	5	**3n**	31	6 : 1
14	2-$MeOC_6H_4$	H	4	**3o**	33	> 30 : 1
15	4-$NO_2C_6H_4$	3-Br	4	**3p**	49	14:1
16	4-$NO_2C_6H_4$	6-Br	4	**3q**	56	> 30 : 1
17	4-$NO_2C_6H_4$	7-Br	4	**3r**	62	> 30 : 1
18	4-$NO_2C_6H_4$	3-COOMe	6	**3s**	41	> 30 : 1

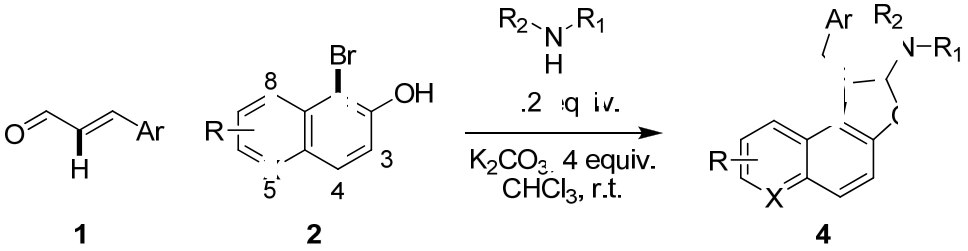
[a]Unless stated otherwise, the reaction was carried out with enals (0.2 mmol), 1-bromo-2-naphthols (0.4 mmol), lithium acetate dihydrate (0.8 mmol) and diphenyl prolinol TMS ether catalyst (0.04 mmol) in acetonitrile (1 mL) for a specified time. [b]Isolated yield. [c]Determined by ^{1}H NMR of crude reaction mixture.

3.5. Amine Integrated Three-Component Reaction

As demonstrated in our previous work and also in the above mentioned results, diphenylprolinol TMS ether, was found as an optimal organocatalyst for the direct α-arylation of enals with various brominated aromatic systems. Due to the large steric hindrance brought by the TMS protecting group, *E*-isomeric product was received almost exclusively in most of cases. Surprisingly, in the extensive exploration of the cross-coupling-like reactions of enals and bromonaphthols, when secondary amines with smaller steric hindrance were used, the amine-integrated *Z*-isometric three-component products were obtained for instead. Compared with abovementioned direct α-arylation process, the three component reaction demonstrated much higher efficiency, and the reaction was usually driven to a completion within hours at room temperature (Table 3).

Various secondary amines, enals and bromonaphthols were submitted to the three-component reaction conditions (Table 3.3). Cyclic secondary amines, such as piperidine and pyrrolidine, usually generate three-component adducts with decent yields and excellent Z/E ratio within 2 hours at room temperature (entries 1 and 2). The *Z*-isomer was observed predominantly as the product, and the structure of compound **4a** was determined by X-ray crystal structural analysis (data not shown here). Acyclic

Table 3.3. Three component reactions of 1-bromo-2-naphthols and enals with stoichiometric amount of amines[a]



entry	Ar	R, X	amine	time (h)	**4**	yield (%)[b]	*Z*/*E*[c]
1	4-$NO_2C_6H_4$	H, CH	piperidine	2	**4a**	91	>30:1
2	4-$NO_2C_6H_4$	H, CH	pyrrolidine	1	**4b**	99	>30:1
3	4-$NO_2C_6H_4$	H, CH	diethylamine	36	**4c**	88	>30:1
4	Ph	H, CH	pyrrolidine	2	**4d**	60	>30:1
5	2-$NO_2C_6H_4$	H, CH	pyrrolidine	4	**4e**	48	>30:1
6	4-$CF_3C_6H_4$	H, CH	pyrrolidine	2	**4f**	94	>30:1
7	4-ClC_6H_4	H, CH	pyrrolidine	2	**4h**	95	>30:1
8	4-CNC_6H_4	H, CH	pyrrolidine	2	**4i**	82	6 : 1
9	4-$MeOC_6H_4$	H, CH	pyrrolidine	4	**4j**	16	4 : 1
10	COOEt	H, CH	pyrrolidine	4	**4k**	59	5 : 1
11	4-$NO_2C_6H_4$	H, N	pyrrolidine	48	**4l**	72	>30:1
12	4-$NO_2C_6H_4$	3-Br, CH	pyrrolidine	2	**4m**	82	>30:1
13	4-$NO_2C_6H_4$	6-Br, CH	pyrrolidine	2	**4n**	80	>30:1
14	4-$NO_2C_6H_4$	7-Br, CH	pyrrolidine	2	**4o**	87	>30:1
15	4-$NO_2C_6H_4$	3-COOMe, CH	pyrrolidine	6	**4p**	85	>30:1

[a]Unless stated otherwise, the reaction was carried out with enals (0.2 mmol), 1-bromo-2-naphthols (0.2 mmol), potassium carbonate (0.8 mmol) and amines (0.24 mmol) in

chloroform (1 mL) for a specified time. [b]Isolated yield. [c]Determined by ^{1}H NMR of crude reaction mixture.

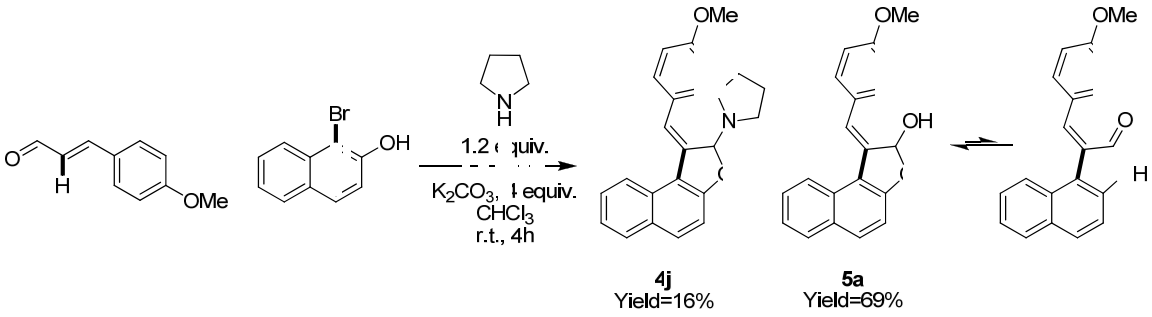
secondary amines that possess larger special hindrance than cyclic one, usually prolong reaction time, decrease yields (entry 3). As a result, pyrrolidine was chosen as an effective amine component during the following substrate scope expansion.

Structurally modified cinnamaldehydes with electron-withdrawing, electron-neutral, and weak electron-donating substituents bearing on the phenyl ring usually provide 3-component products with decent yield and good Z/E selectivity (entries 4-9). While in the case of cinnamaldehyde bearing methoxide group on phenyl ring, the profound effect of the cleavage of amine moiety from the 3-component product was observed (Table 3, entry 9; Scheme 3.2). As a result, the three component product **4j** was collected with the yield of only 16% (entry 9), and the two component α-arylation product **5a** was gathered with 69% yield in favor of *Z*-isomer. The intramolecular hemiacetal **5a** exhibited weak fluorescence because of hyper-conjugation of aromatic systems.

Due to high efficiency of the 3-component reaction process, substrates that were inert to *E*-selective α-arylation pathway, such as aliphatic enal or electron-deficient brominated naphthols, could participated in the *Z*-selective 3-component pathway smoothly. The (*E*)-methyl 4-oxobut-2-enoate, which is an aliphatic enal without γ-proton, could take part in the three-component α-arylation reaction effectively (entry 10). Moreover, electronic deficient aromatic system, such as 5-bromo-6-hydroxyquinoline,

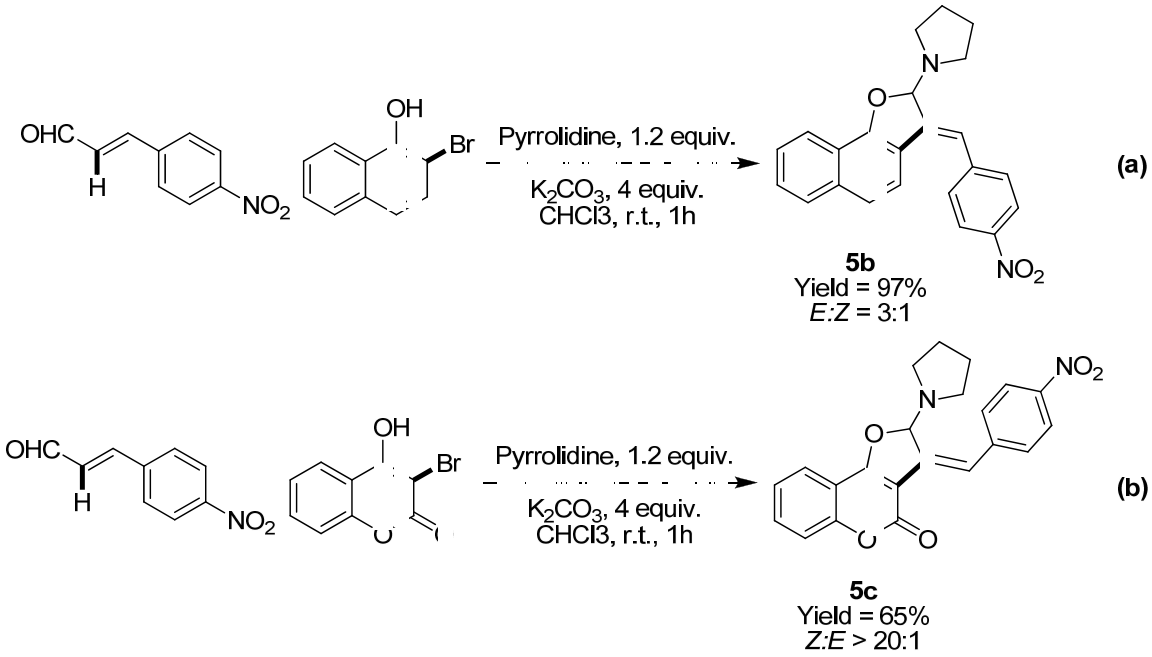
was also feasible for the direct α-arylation process, and the decent yield of 72% was obtained after an elevated reaction time of two days in room temperature (entry 11). Other substituted 1-bromo-2-naphthols were also able to generate desired product smoothly within hours (entries 12-15).

Scheme 3.2. The α-arylation reaction of *trans-p*-methoxy-cinnamaldehyde with 1-bromo-2-naphthol



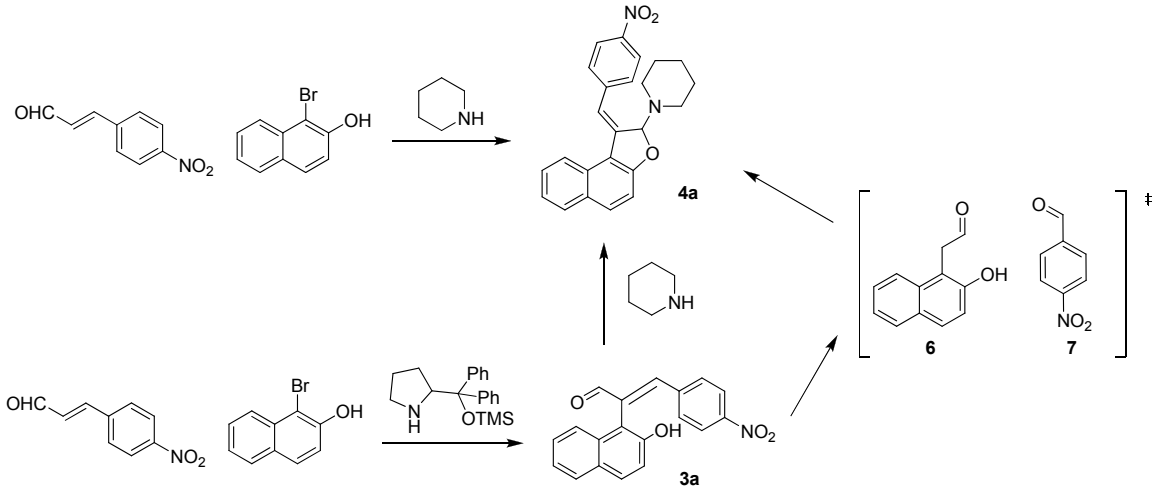
Similarly, although they were left intact during the bulky diphenylprolinol TMS ether catalyzed α-arylation reaction, 2-bromo-1-naphthol and its derivatives could be implanted in the 3-component reaction in excellent efficiency. Mediated by pyrrolidine, enal and 2-bromo-1-naphthol provide desired three-component product with 97% yield and preference of *E*-isomer (Scheme 3.3, equation a). The 3-bromo-4-hydroxycoumarine, which has similar structural framework, could also participate in the α-arylation process with excellent stereoselectivity (Scheme 3.2, equation b).

Scheme 3.3. Three-component α-arylation reaction of enals with 2-bromo-1-naphthol and 3-bromo-4-hydroxycoumarine



Interestingly, α-arylation *E*-isomeric product **3a** can be quantitatively converted to its *Z*-isomeric three-component-reaction analog **4a** using stoichiometric amount of secondary amine, such as piperidine, under room temperature within hours (Scheme 3.4). The releasing of the steric hindrance in *E*-isomeric two-component α-arylation product, such as **3a**, is considered as a driving force for the *E* to *Z* conversion. Such a transformation mechanism was believed to follow the retro-Aldol condensation (from **3a** to **6** and **7**) tandem Aldol condensation (from **6** and **7** to **4a**) cascade processes.

Scheme 3.4. Conversion from the *E*-isomer **3a** to the three-component *Z*-isomer **4a** using piperidine



3.6. Summary

In conclusion, both *E*- and *Z*- functionalized naphthol frameworks can be stereoselectively constructed by carefully selection of secondary amine mediator used in the direct α-arylation reactions. Catalyzed by bulky diphenylprolinol TMS ether, a cross-coupling-like reaction of α, β-unsaturated aldehydes and 1-bromo-2-naphthols was described, and (*E*)-α,β-diarylacrylaldehydes were obtained in moderate to good yields and excellent *E/Z* ratios. Additionally, stoichiometric amount of cyclic secondary amines could mediate the reaction in the generation of *Z*-isomeric three-component product with higher efficiency.

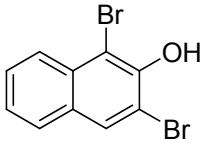
3.7. Experimental Section

General Information:

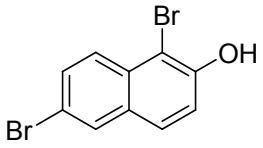
All commercially available reagents were used without further purification. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on Whatman silica gel plates with fluorescence F_{254} indicator. And Merck 60 silica gel was used for chromatography. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance 500. When deuteriorated chloroform ($CDCl_3$) was used to dissolve sample, tetramethylsilane (TMS) was used as an internal reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.

Procedure for the mono-bromination of various substituted naphthols

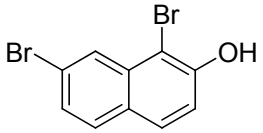
To a mixture of substituted naphthol (1 mmol) and ammonium acetate (10 mol %) in MeCN (5mL), NBS (1.05 mmol) was added in one portion. The reaction mixture was stirred at room temperature until the naphthol was totally consumed (determined by TLC analysis). The solvent was evaporated, and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane.



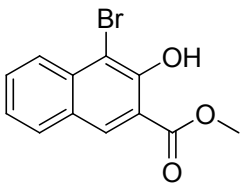
1,3-Dibromonaphthalen-2-ol. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.97 (d, J = 7.5 Hz, 1H), 7.94 (s, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 6.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 147.2, 131.8, 131.6, 129.8, 128.2, 127.4, 125.8, 125.2, 110.8, 106.5.



1,6-Dibromonaphthalen-2-ol. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89 (d, J = 1.8 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.58 (m, 2H), 7.24 (d, J = 9.0 Hz, 1H).



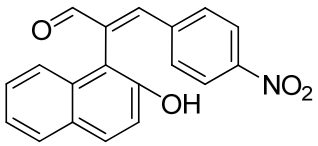
1,7-Dibromonaphthalen-2-ol. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.17 (s, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 1.8 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 5.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 151.7, 133.8, 130.1, 129., 128.4, 127.9, 122.8, 117.9, 105.2.



Methyl 4-bromo-3-hydroxy-2-naphthoate. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.24 (s, 1H), 8.44 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.2, 153.4, 136.4, 132.2, 130.8, 130.0, 127.7, 126.1, 124.9, 114.4, 107.3, 53.3.

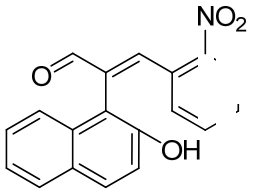
Typical procedure for the synthesis of (*E*)-α-(2-hydroxynaphthalen-1-yl)-β-Arylacrylaldehyde

To the mixture containing 0.2 mmol of *α,β*-unsaturated aldehyde, 0.4 mmol of 1-bromo-2-naphthol, 20 % mol of diphenylprolinol TMS ether as catalyst, and 0.8 mmol of lithium acetate dehydrate, 1mL acetonitrile was added in one portion. The reaction mixture was heated at 60^{0}C until the aldehyde was totally consumed (determined by TLC analysis). The solvent was evaporated after the reaction was cooled to room temperature. The residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane.

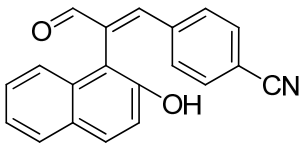


(E)-2-(2-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylaldehyde (3a). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.98 (s, 1H), 8.76 (s, 1H), 8.13 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.87 (m, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.0, 1H), 7.30 (m, 3H); ^{13}C NMR

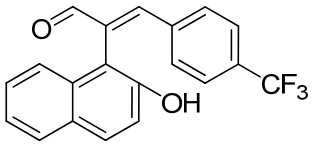
(DMSO-d_6, 125 MHz): δ = 194.5, 152.6, 148.8, 147.6, 140.9, 139.9, 132.0, 130.5, 130.1, 128.3, 127.9, 126.8, 123.6, 123.0, 122.9, 118.3, 112.2.



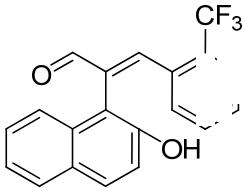
(E)-2-(2-hydroxynaphthalen-1-yl)-3-(2-nitrophenyl)acrylaldehyde (3b). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.05 (s, 1H), 8.70 (s, 1H), 8.39 (s, 1H), 8.05 (dd, J = 8.0, 1.2 Hz, 1H), 7.74 (t, J = 8.3 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.42 (td, J = 7.7, 1.5 Hz, 1H), 7.33 (td, J = 7.5, 1.2 Hz, 1H), 7.25 (m, 4H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 193.5, 153.8, 148.5, 148.2, 140.2, 133.9, 133.7, 131.8, 130.7, 130.6, 129.3, 128.9, 127.3, 125.1, 124.1, 123.7, 118.4, 113.6.



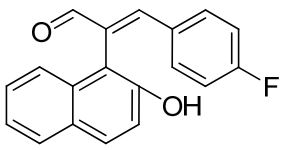
(E)-4-(2-(2-hydroxynaphthalen-1-yl)-3-oxoprop-1-enyl)benzonitrile (3c). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.96 (s, 1H), 8.61 (br, 1H), 8.05 (s, 1H), 7.87 (m, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.43 (m, 3H), 7.28 (m, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.0, 153.0, 149.5, 140.4, 140.0, 133.2, 132.8, 131.0, 129.5, 129.1, 128.6, 127.5, 124.1, 123.9, 118.8, 118.6, 113.8, 113.5.



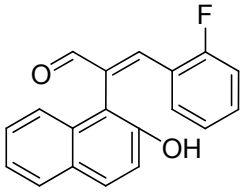
(E)-2-(2-hydroxynaphthalen-1-yl)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde (3d). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.98 (s, 1H), 8.58 (br, 1H), 8.07 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.48 (m, 5H), 7.29 (m, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.1, 152.9, 149.9, 139.9, 139.4, 133.2, 131.3, 131.0, 130.9, 129.5, 129.0, 127.4, 125.9, 125.7, 124.1, 123.8, 118.8, 114.0.



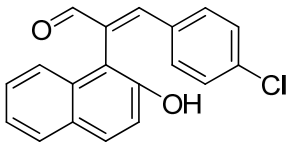
(E)-2-(2-hydroxynaphthalen-1-yl)-3-(2-(trifluoromethyl)phenyl)acrylaldehyde (3e). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.02 (s, 1H), 8.73 (s, 1H), 8.24 (s, 1H), 7.77 (m, 3H), 7.39 (m, 2H), 7.24 (m, 5H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 192.8, 152.8, 145.7, 140.3, 133.2, 132.5, 131.6, 130.0, 129.5, 128.4, 128.1, 127.5, 126.4, 125.7X2, 123.2, 122.8, 117.6, 112.9.



(E)-3-(4-fluorophenyl)-2-(2-hydroxynaphthalen-1-yl)acrylaldehyde (3f). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.91 (s, 1H), 8.44 (br, 1H), 7.98 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.28 (m, 5H), 6.95 (t, J = 9.0 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.1, 165.2, 163.2, 153.0, 151.0, 137.4, 133.3, 133.2, 133.1, 132.2, 130.7, 129.6, 129.0, 127.3, 124.3, 123.8, 118.9, 116.3, 116.1, 114.4.

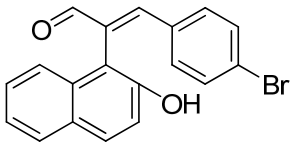


(E)-3-(2-fluorophenyl)-2-(2-hydroxynaphthalen-1-yl)acrylaldehyde (3h). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.99 (s, 1H), 8.55 (br, 1H), 8.17 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.28 (m, 4H), 7.17 (t, J = 9.5 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.1, 160.7, 153.1, 142.5, 139.3, 133.4, 133.0, 132.9, 130.8, 129.8, 129.5, 129.1, 127.4, 125.0, 124.2, 123.8, 123.6, 123.4, 118.9, 116.3, 116.1, 114.3.

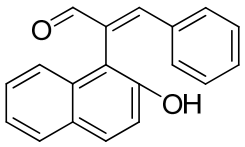


(E)-3-(4-chlorophenyl)-2-(2-hydroxynaphthalen-1-yl)acrylaldehyde (3i). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.92 (s, 1H), 8.48 (br, 1H), 7.97 (s, 1H), 7.85 (m, 2H), 7.42

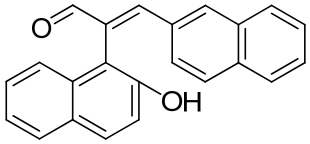
(m, 1H), 7.25 (m, 7H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.0, 152.9, 150.6, 138.3, 136.1, 134.5, 133.3, 132.2, 130.7, 129.5, 129.3, 129.0, 127.4, 124.2, 123.8, 118.9, 114.3.



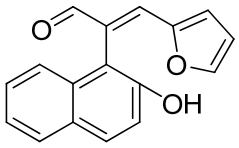
(E)-3-(4-bromophenyl)-2-(2-hydroxynaphthalen-1-yl)acrylaldehyde (3j). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.92 (s, 1H), 8.47 (br, 1H), 7.96 (s, 1H), 7.85 (m, 2H), 7.42 (m, 1H), 7.38 (d, J = 15 Hz, 2H), 7.29 (m, 3H), 7.20 (d, J = 15 Hz, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.1, 152.9, 150.7, 138.4, 134.8, 133.3, 132.4, 132.3, 130.8, 129.5, 129.0, 127.4, 124.6, 124.2, 123.8, 118.9, 114.3.



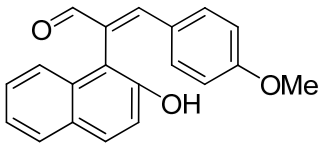
(E)-2-(2-hydroxynaphthalen-1-yl)-3-phenylacrylaldehyde (3k). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.93 (s, 1H), 8.39 (br, 1H), 7.98 (s, 1H), 7.85 (m, 2H), 7.44 (m, 1H), 7.27 (m, 6H), 7.15 (m, 2H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 152.9, 152.5, 137.6, 135.6, 133.4, 130.9, 130.5, 129.5, 129.2, 128.9, 127.2, 124.3, 123.7, 118.9, 114.7.



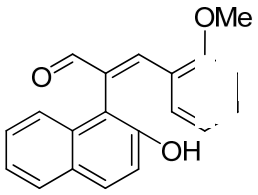
(E)-2-(2-hydroxynaphthalen-1-yl)-3-(naphthalen-2-yl)acrylaldehyde (3l). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.00 (s, 1H), 8.50 (br, 1H), 8.15 (s, 1H), 7.97 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 9.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.46 (m, 3H), 7.31 (d, J = 9.0 Hz, 1H), 7.26 (m, 2H), 7.19 (d, J = 8.5 Hz, 1H), ; ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.2, 153.0, 152.3, 137.8, 134.6, 133.7, 133.5 133.3, 132.4, 130.6, 129.5, 129.2, 128.9, 128.6, 127.2, 126.5, 124.3, 123.7, 118.9, 114.8.



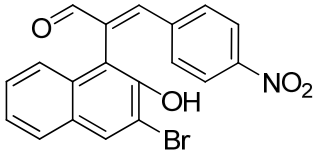
(E)-3-(furan-2-yl)-2-(2-hydroxynaphthalen-1-yl)acrylaldehyde (3m). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.88 (s, 1H), 8.33 (br, 1H), 7.85 (m, 3H), 7.62 (s, 1H), 7.43(d, J = 14 Hz, 2H), 7.29 (m, 2H), 6.34 (s, 1H), 5.85 (d, J = 5.5 Hz, 1H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 192.9, 152.8, 151.9, 146.5, 138.5, 134.7, 133.4, 130.6, 129.6, 128.9, 127.2, 124.3, 123.7, 119.0, 116.3, 114.6, 113.6.



(E)-2-(2-hydroxynaphthalen-1-yl)-3-(4-methoxyphenyl)acrylaldehyde (3m). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.86 (s, 1H), 8.29 (s, 1H), 7.87 (m, 3H), 7.44 (m, 1H), 7.28 (m, 3H), 7.20 (d, J = 15 Hz, 2H), 6.72 (d, J = 15 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.0, 162.3, 152.8, 152.5, 135.1, 134.4, 133.0, 130.4, 129.6, 129.0, 128.2, 127.2, 124.5, 123.7, 119.0, 115.0, 114.7, 55.5.

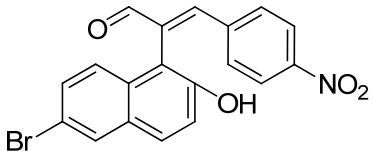


(E)-2-(2-hydroxynaphthalen-1-yl)-3-(2-methoxyphenyl)acrylaldehyde (3o). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.92 (s, 1H), 8.41 (br, 1H), 8.33 (s, 1H), 7.82 (t, J = 9.0 Hz, 2H), 7.43 (t, J = 9.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.25 (m, 4H), 7.01 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.45 (t, J = 7.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (Acetone -d_6, 125 MHz): δ = 194.1, 158.8, 152.9, 146.1, 137.0, 133.4, 132.5, 130.3, 129.5, 129.4, 128.8, 127.0, 124.3, 124.1, 123.5, 120.7, 118.8, 115.0, 111.7, 56.0.

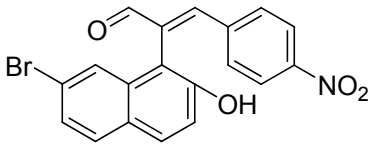


(E)-2-(3-bromo-2-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylaldehyde (3p). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.93 (s, 1H), 8.30 (s, 1H), 8.19 (s, 1H), 8.04 (d, J = 8.7

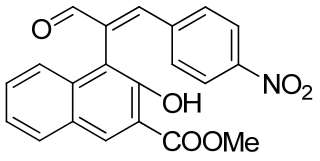
Hz, 2H), 7.86 (m, 1H), 7.49 (d, J = 8.7 Hz, 2H), 7.43 (m, 1H), 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.7, 149.4, 148.9, 141.4, 139.9, 133.5, 132.2, 131.5, 130.3, 128.3, 128.1, 125.2, 124.4, 124.3, 116.1, 113.5.



(E)-2-(6-bromo-2-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylaldehyde (3q). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 9.98 (s, 1H), 8.84 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 8.03 (d, J = 9.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 193.9, 153.6, 149.4, 148.8, 141.7, 140.3, 131.9, 131.3, 131.0, 130.7, 130.4, 130.3, 126.4, 124.2, 120.1, 117.0, 114.0.



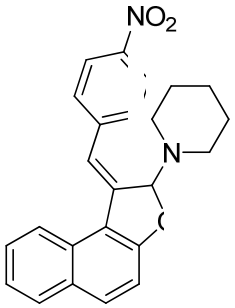
(E)-2-(7-bromo-2-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylaldehyde (3r). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.02 (s, 1H), 8.92 (s, 1H), 8.18 (s, 1H), 8.07 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.41 (dd, J = 8.7 1.8 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.0, 154.1, 149.7, 148.9, 141.7, 140.1, 134.7, 131.4, 131.2, 127.9, 127.1, 126.1, 124.2, 121.6, 119.5, 113.1.



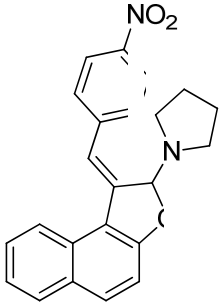
(E)-methyl 3-hydroxy-4-(1-(4-nitrophenyl)-3-oxoprop-1-en-2-yl)-2-naphthoate (3s). ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.77 (s, 1H), 10.02 (s, 1H), 8.72 (s, 1H), 8.20 (s, 1H), 8.03 (m 3H), 7.53 (d, J = 9.0 Hz, 2H), 7.48 (m, 2H), 7.39 (m, 1H)4.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 193.7, 171.0, 154.4, 149.4, 148.8, 141.7, 140.1, 136.0, 134.1, 131.3, 130.9, 130.7, 127.9, 125.1, 124.2, 124.1, 115.7, 114.8, 53.3.

Typical procedure for the three-component reaction

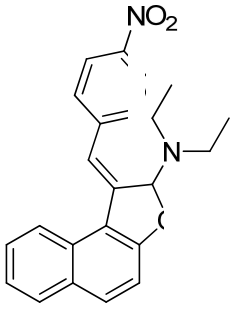
To the mixture containing 0.2 mmol of *α,β*-unsaturated aldehyde, 0.2 mmol of 1-bromo-2-naphthol, 0.24 mmol of secondary amine, and 0.8 mmol of potassium carbonate, 1mL chloroform was added in one portion. The reaction mixture was stirred at room temperature until the aldehyde was totally consumed (determined by TLC analysis). The solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane.



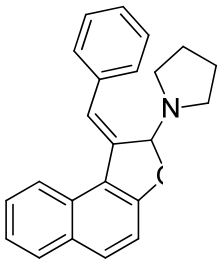
(Z)-1-(1-(4-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)piperidine (4a). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.35 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 5.92 (s, 1H), 2.90 (m, 2H), 1.45 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.1, 146.1, 144.5, 142.9, 133.8, 130.4, 130.1, 130.0, 129.1, 128.5, 123.8, 122.4, 122.3, 116.7, 112.6, 101.4, 26.2, 24.5.



(Z)-1-(1-(4-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4b). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.35 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 8.5 Hz, 2H), 7.87 (m, 3H), 7.79 (d, J = 9.0 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.51 (s, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 6.22 (s, 1H), 2.95 (m, 2H), 2.82 (s, 2H), 1.76 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.5, 146.1, 144.5, 143.4, 133.8, 130.1, 129.5, 128.5, 123.9, 123.8, 122.3, 121.6, 116.1, 112.5, 96.9, 46.3, 24.6.

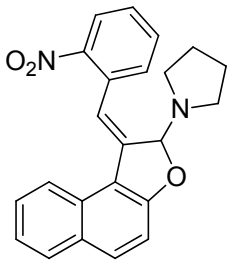


(Z)-N,N-diethyl-1-(4-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-amine (4c). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.37 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.54 (s, 1H), (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.20 (s, 1H), 2.88 (m, 4H), 1.07 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.2, 146.1, 144.5, 143.2, 133.8, 130.3, 130.2, 130.0, 129.3, 129.5, 123.7, 122.3, 122.0, 116.8, 112.9, 100.1, 30.0, 13.5.

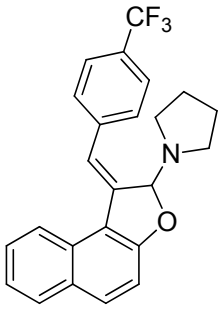


(Z)-1-(1-benzylidene-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4d). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.39 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.50 (m, 3H), 7.58 (t, J = 7.5 Hz, 1H), 7.50 (s, 1H), 7.38 (m, 3H), 7.27 (m, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.23 (s, 1H), 2.97 (m, 2H), 2.83 (m, 2H), 1.75 (m, 4H) ; ^{13}C NMR ($CDCl_3$, 125

MHz): δ = 161.1, 138.7, 137.9, 132.0, 130.0, 129.9, 129.4, 128.6, 127.9, 127.1, 124.5, 123.3, 122.5, 116.8, 112.3, 96.9, 46.2, 24.5.

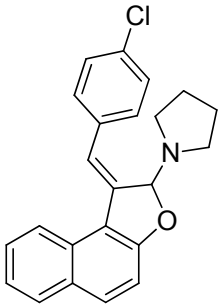


(Z)-1-(1-(2-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4e). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.80 (m, 4H), 7.59 (m, 2H), 7.39 (m, 2H), 7.10 (d, J = 9.0 Hz, 1H), 6.15 (s, 1H), 2.78 (m, 2H), 2.53 (m, 2H), 1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.5, 148.7, 141.1, 133.9, 133.2, 132.8, 131.0, 129.9, 129.8, 128.4, 127.7, 124.6, 123.6, 122.5, 118.6, 115.8, 112.6, 97.5, 46.2, 24.5.

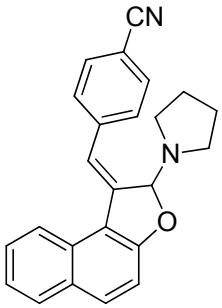


(Z)-1-(1-(4-(trifluoromethyl)benzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4f). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.34 (d, J = 8.5 Hz, 1H), 7.82 (m,

3H), 7.73 (d, J = 8.5 Hz, 1H), 7.59 (m, 3H), 7.47 (s, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.16 (s, 1H), 2.93 (m, 2H), 2.79 (m, 2H), 1.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 161.8, 141.3, 132.9, 130.1, 130.0, 129.8, 129.5, 128.8, 128.3, 128.2, 126.5, 125.4, 124.3, 123.5, 122.9, 122.6, 122.4, 116.3, 112.4, 96.8, 46.2, 24.5.

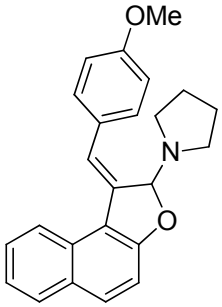


(Z)-1-(1-(4-chlorobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4h). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.34 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.70 (m, 3H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (s, 1H), 7.34 (m, 3H), 7.11 (d, J = 8.7 Hz, 1H), 6.15 (s, 1H), 2.94 (m, 2H), 2.79 (m, 2H), 1.73 (m, 4H) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 161.4, 139.3, 136.4, 132.9, 132.3, 131.0, 130.0, 129.9, 129.4, 128.7, 127.9, 123.4, 123.0, 122.4, 116.5, 112.3, 96.7, 46.2, 24.5.



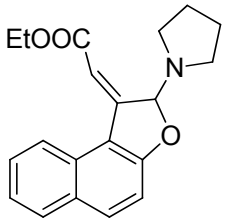
(Z)-4-((2-(pyrrolidin-1-yl)naphtho[2,1-b]furan-1(2H)-ylidene)methyl)benzonitrile

(4i). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.36 (d, J = 8.5 Hz, 1H), 7.83 (m, 4H), 7.63 (m, 3H), 7.47 (d, J = 1.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.21 (s, 1H), 2.98 (m, 2H), 2.82 (m, 2H), 1.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.2, 142.5, 142.4, 133.4, 132.7, 132.2, 130.0, 129.4, 128.3, 123.7, 122.3, 122.1, 119.5, 116.1, 112.4, 109.8, 96.846.3, 24.5.

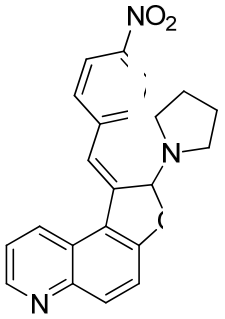


(Z)-1-(1-(4-methoxybenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine

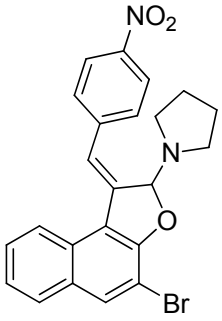
(4j). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.38 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.73 (m, 3H), 7.56 (t, J = 7.5 Hz, 1H), 7.45 (s, 1H), 7.36 (m, 1H), 7.25 (s, 1h), 7.11 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.19 (s, 1H), 3.85 (s, 3H), 2.97 (m, 2H), 2.83 (m, 2H), 1.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.7, 159.0, 136.5, 131.5, 131.3, 130.8, 130.0, 129.9, 129.4, 127.7, 124.2, 123.2, 122.6, 117.1, 114.1, 112.3, 96.9, 55.6, 46.2, 24.6.



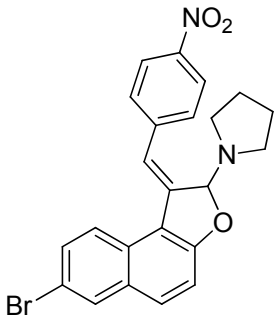
(Z)-ethyl 2-(2-(pyrrolidin-1-yl)naphtho[2,1-b]furan-1(2H)-ylidene)acetate (4k). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.16 (d, J = 8.4 Hz, 1H), 7.81 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 6.83 (s, 1H), 6.68 (s, 1H), 4.25 (q, J = 7.0 Hz, 2H), 2.84 (m, 4H), 1.72 (m, 4H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.9, 164.8, 154.0, 135.8, 130.0, 129.8, 128.8, 123.9, 122.4, 114.2, 112.8, 110.6, 98.5, 60.3, 46.8, 24.6, 14.6.



(Z)-1-(4-nitrobenzylidene)-2-(pyrrolidin-1-yl)-1,2-dihydrofuro[3,2-f]quinoline (4l). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.81 (s, 1H), 8.67 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 7.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.49 (m, 1H), 7.41 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 6.28 (s, 1H), 2.95 (m, 2H), 2.82 (m, 2H), 1.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.2, 147.7, 146.3, 145.4, 143.8, 142.6, 134.8, 130.1, 124.8, 123.8, 122.5, 115.9, 97.7, 46.3, 24.6.

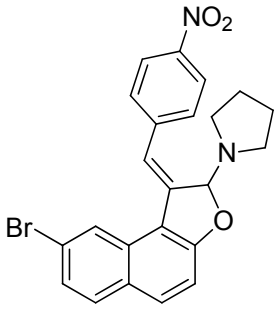


(Z)-1-(4-bromo-1-(4-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4m). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8;.29 (d, J = 8.5 Hz, 1H), 8.20 (d, J =8.0 Hz, 2H), 7.97 (s, 1H), 7.84 (d, J =8.0 Hz, 2H), 7.75 (d, J =8.5 Hz, 1H), 7.60 (t, J =7.5 Hz, 1H), 7.49 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 6.26 (s, 1H), 2.96 (m, 2H), 2.80 (m, 2H), 1.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 158.8, 146.4, 143.8, 142.8, 134.8, 130.9, 130.2, 129.2, 128.5, 128.4, 124.5, 123.9, 123.2, 122.3, 117.5, 105.8, 97.7, 46.4, 24.5.

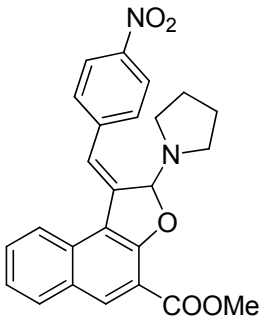


(Z)-1-(7-bromo-1-(4-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4n). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.22 (m, 3H), 8.00 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.69 (m, 2H), 7.44 (d, J =2.0 Hz, 1H), 7.15 (d, J = 9.0 Hz,

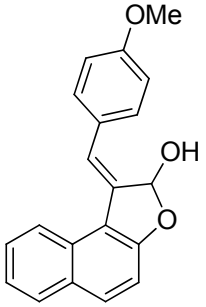
1H), 6.22 (s, 1H), 2.93 (m, 2H), 2.80 (m, 2H), 1.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 162.6, 146.3, 144.2, 142.8, 132.6, 132.0, 131.5, 131.4, 130.2, 127.9, 124.0, 123.9, 122.2, 117.2, 116.4, 113.7, 97.2, 46.3, 24.6.



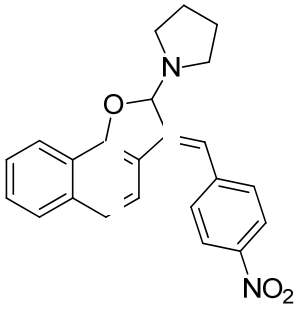
(Z)-1-(8-bromo-1-(4-nitrobenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-yl)pyrrolidine (4o). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.44 (s, 1H), 8.21 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.72 (m, 2H), 7.45 (dd, J = 8.7 1.8 Hz, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.19 (s, 1H), 2.94 (m, 2H), 2.78 (m, 2H), 1.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.0, 146.3, 144.1, 142.5, 133.5, 131.5, 130.5, 130.2, 128.4, 127.1, 124.7, 123.8, 123.3, 121.9, 115.4, 112.9, 97.2, 46.3, 24.6.



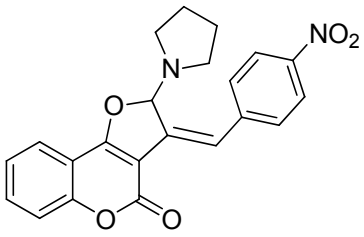
(Z)-methyl-1-(4-nitrobenzylidene)-2-(pyrrolidin-1-yl)-1,2-dihydronaphtho[2,1-b]furan-4-carboxylate (4p). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.48 (s, 1H), 8.35 (d, J = 8.7 Hz, 1H), 8.23 (d, J = 8.7 Hz, 2H), 7.91 (m, 3H), 7.70 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 1.5Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 6.30 (s, 1H), 2.99 (m, 2H), 2.80 (m, 2H), 1.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.4, 160.6, 146.3, 144.0, 142.2, 136.5, 131.4, 131.3, 130.6, 130.2, 128.9, 124.4, 123.9, 122.8, 122.2, 118.3, 115.1, 97.6, 52.5, 46.4, 24.4.



(Z)-1-(4-methoxybenzylidene)-1,2-dihydronaphtho[2,1-b]furan-2-ol (5a). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.27 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.48 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1h), 6.93 (d, J = 7.5 Hz, 2H), 6.35 (s, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 159.6, 158.5, 136.4, 132.3, 131.8, 130.9, 130.5, 129.9, 129.4, 127.9, 126.5, 123.8, 122.6, 114.5, 114.4, 112.8, 100.2, 55.6.

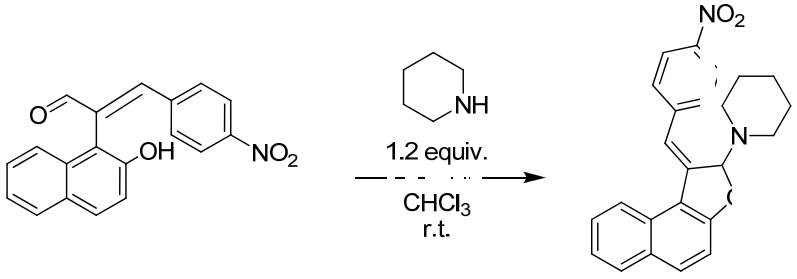


(E)-1-(3-(4-nitrobenzylidene)-2,3-dihydronaphtho[1,2-b]furan-2-yl)pyrrolidine (5b). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.21 (d, J = 8.5 Hz, 2H), 8.07 (m, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.53 (m, 2H), 7.47 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 2.97 (m, 2H), 2.91 (m, 2H), 1.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (mixture of E and Z isomers) = 159.9, 146.4, 144.1, 142.8, 136.5, 130.8, 130.6, 129.6, 129.0, 128.1, 127.6, 126.6, 124.0, 123.3, 123.0, 122.6, 121.5, 121.1, 120.5, 119.6, 119.0, 118.4, 100.0, 99.2, 46.6, 24.9.



(Z)-3-(4-nitrobenzylidene)-2-(pyrrolidin-1-yl)-2H-furo[3,2-c]chromen-4(3H)-one (5c). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.18 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.63 (m, 2H), 7.36 (m, 2H), 6.95 (s, 1H), 3.01 (m, 4H), 1.78 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.9, 158.8, 155.2, 146.3,

Typical Procedure for the conversion from E-isomer to its Z-isomeric analog using secondary amine



To the vial containing 0.1 mmol of *E*-isomeric α-arylation product, such as (E)-2-(2-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylaldehyde, dissolved in 1mL chloroform, 0.12 mmol of cyclic secondary amine, such as piperidine, was added in one portion. The reaction mixture was stirred at room temperature until the aldehyde was totally consumed (determined by TLC analysis). The solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane.

3.8. Reference

(1) Horton, D. a; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930.

(2) Maloney, D. J.; Deng, J.-Z.; Starck, S. R.; Gao, Z.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 4140-4141.

(3) Wilkinson, J.; Foretia, D.; Rossington, S.; Heagerty, A.; Leonard, J.; Hussain, N.; Austin, C. *European Journal of pharmacology* **2007**, *561*, 160-163.

(4) Han, C.; Zhang, J.; Zheng, M.; Xiao, Y.; Li, Y.; Liu, G. *Molecular Diversity* **2011**, *15*, 857-876.

(5) Posakony, J.; Hirao, M.; Stevens, S.; Simon, J.; Bedalov, A. *J. Med. Chem.* **2004**, *47*, 2635-2644.

(6) Neugebauer, R. C.; Uchiechowska, U.; Meier, R.; Hruby, H.; Valkov, V.; Verdin, E.; Sippl, W.; Jung, M. *J. Med. Chem.* **2008**, *51*, 1203-1213.

(7) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem.* **2008**, *51*, 1706-1718.

(8) Ramachary, D. B.; Kishor, M. *Organic & Biomolecular chemistry* **2010**, *8*, 2859-2867.

(9) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem., Int. Ed.* **1990**, *29*, 512.

(10) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596-13597.

(11) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850-10851.

(12) Shen, X.; Jones, G. O.; Watson, D.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278-11287.

(13) Brandes, S.; Bella, M.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147-1151.

(14) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2006**, *12*, 6039-6052.

(15) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Comm.* **2007**, 2228-2230.

(16) Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6881-6884.

(17) Ramachary, D. B.; Babul Reddy, G.; Mondal, R. *Tetrahedron Letters* **2007**, *48*, 7618-7623.

(18) Wang, X.-S.; Zheng, C.-W.; Zhao, S.-L.; Chai, Z.; Zhao, G.; Yang, G.-S. *Tetrahedron: Asymmetry* **2008**, *19*, 2699-2704.

(19) Song, X.-X.; Song, A.-G.; Zhang, F.; Li, H.-X.; Wang, W. *Nat. Commun.* **2011**, *2*, 524, DOI: 10.1038/ncomms1541.

Chapter 4

Direct Stereoselective α-Arylation of Unmodified Enals with 3-Bromoindoles via an Organocatalytic Cross-Coupling-Like Strategy

4.1. Introduction

Functionalized indoles are important building blocks in organic synthesis and privileged structures in drug discovery.[1,2] In the realms of organocatalysis, it usually serves as a good nucleophile in stereoselective Friedel-Crafts reactions.[3] The applications of indoles in asymmetric organocatalytic Michael addition towards enals[4-7], unsaturated ketones[8-12] and nitro-olefins[13-17], and 1,2-addition towards imines and carbonyl compounds[18-26] have already been scrutinized in the last decade, and various functionalized indoles are received as synthetically useful products for further elaborations.

Compared to benzene, indole is usually considered as an electron-rich hetero-aromatic system that demonstrates enhanced reactivity in electrophilic aromatic substitutions. The most reactive site of indole towards electrophilic substitution is the C3 position, which is about 10^{13} times more reactive than benzene.[27] The high reactivity of indole usually renders a possible access to organic reactions that are unfeasible for benzene and similar arenes. As for the methodologies that are already feasible for benzene and its derivatives, indole is usually a good alternative substrate after a careful

assessment of the reaction conditions as well as additives to suppress undesired poly-substitution events on the indolyl ring.

4.2. Optimization of Reaction Conditions

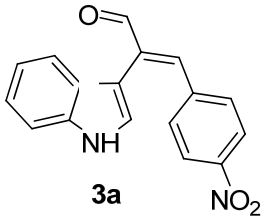
The success of the diphenyl prolinol TMS ether promoted direct α-arylation of enals with *p*-bromophenols as well as bromonaphthols prompts us to explore the ability of non-phenolic substrates to serve as aromatic coupling partners.[28] We envision that 3-bromoindoles would be good substrates for the reaction as the integrated indole frameworks are electron-rich species and they have already been used in organocatalysed enantioselective Friedel-Craft s reactions previously.

The model reaction between 3-bromoindole **2a** and *trans-p*-nitrocinnamaldehyde **1a** was set up for reaction condition optimization (Table 4.1). The *E*-isomer was observed predominantly as the product, and the structure of compound **3a** was determined by X-ray crystal structural analysis (Figure 4.1).

At first, various aminocatalysts were screened (Table 4.1). Neither McMillan's 1st (**I**) nor 2nd (**II**) generation catalyst provide any stable product, and the reactions were sluggish (entries 1 and 2). Babar's Catalyst (**III**) gave 27% yield, but the *E*-to-*Z* ratio is poor (entry 3). Wang's Catalyst (**IV**) gave relative good *E/Z* value, but the yield is low (entry 4). When proline (**V**) and the unprotected diphenylprolinol (**VII**) were used to catalyze the reaction, there was no catalyst turn over at all (entries 5 and 7). Diphenylprolinol TMS ether provided best result among all the aminocatalysts, and single *E*-isomer was obtained with 52% yield (entry 6). Since the 3-bromoindole suffered

from significant decomposition and polymerization even in solid form at room temperature, it should be noticed that two fold equiv. of 3-bromoindole was used to zero out the deterioration in reaction solution.

Figure 4.1. Single X-ray crystal structure of **3a** at probability ellipsoids of 20%



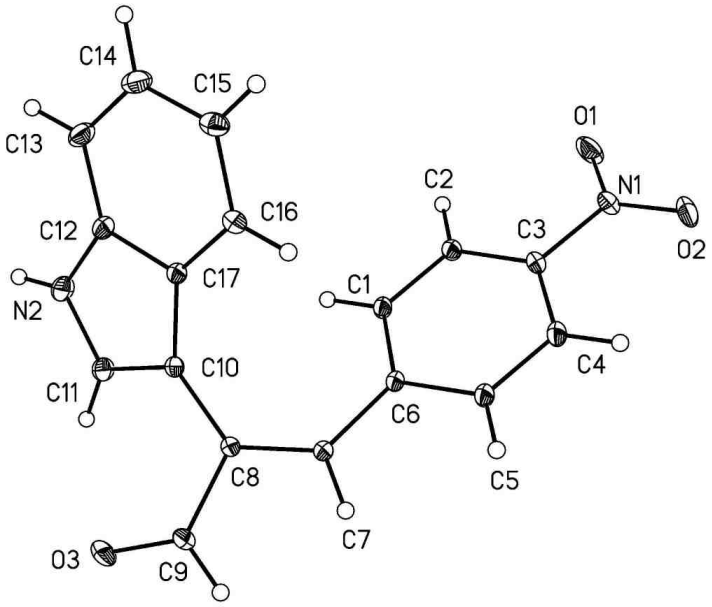
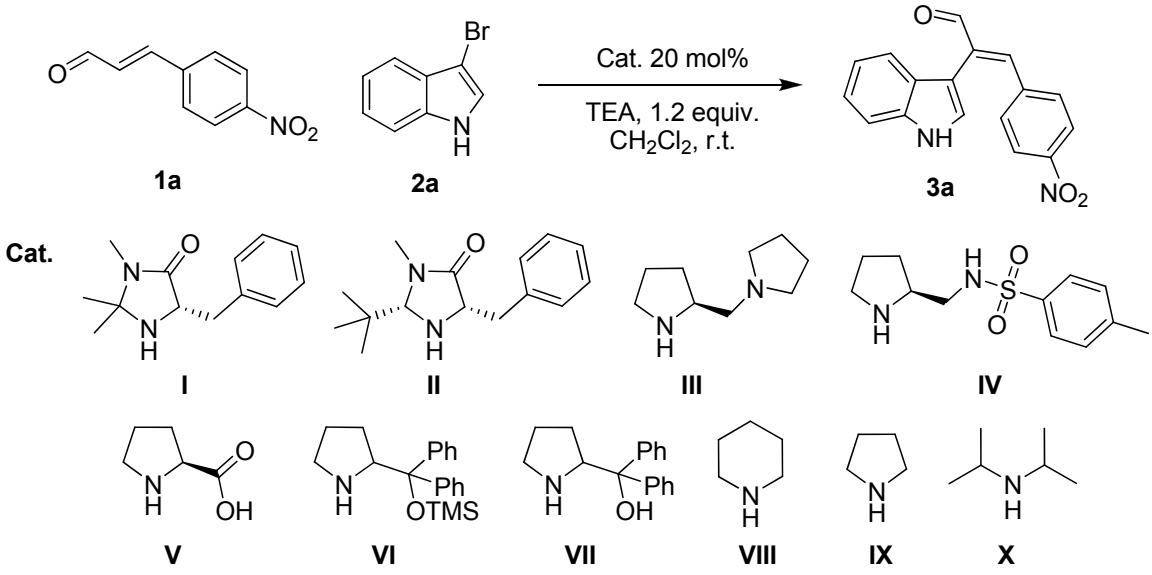


Table 4.1. Screening of catalysts for the cascade reactions using enal **1a** and 3-bromoindole **4a**[a]



entry	catalyst	time (days)	yield (%)[b]	*E*/*Z*[c]
1	**I**	6	0	nd[d]
2	**II**	6	0	nd[d]
3	**III**	5	27	81:19
4	**IV**	5	25	98:2
5	**V**	6	6	nd[d]
6	**VI**	3	52	>99:1
7	**VII**	6	9	nd[d]
8	**VIII**	5	38	98:2
9	**IX**	5	21	98:2
10	**X**	8	<5	nd[d]

[a]Reaction conditions: unless specified, a mixture of **1a** (0.1 mmol), **2a** (0.2 mmol), designated catalyst (20 mol%, or 0.02 mmol) and triethylamine additive (1.2 equiv.) in

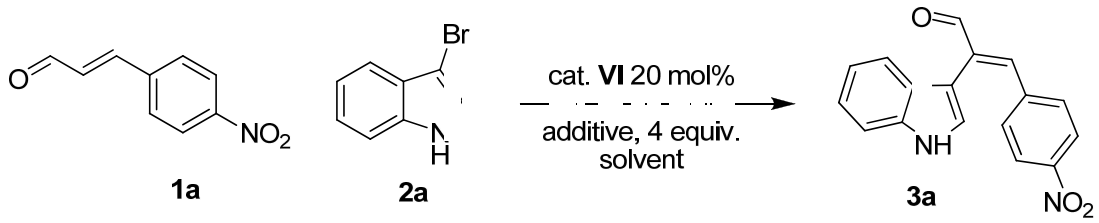
dichloromethane (0.5 mL) was stirred for a specified time period at room temperature. [b]Isolated yields. [c]Determined by ^{1}H NMR of crude reaction mixture. [d]Not determined.

After the catalyst **VI** was found as the optimal catalyst, other reaction parameters were screened to improve product yield (Table 4.2). As demonstrated, the organic bases, such as triethylamine and 2, 6-lutidine, provide lower yield, compared with inorganic bases (Table 4.2, entry 1 and entries 2 to 4). Among the three inorganic sodium salts, sodium acetate was selected as the best additive (entries 2, 3 and 4). Solvent screen came next. Although the methodology could tolerant a large spectrum of solvents, chloroform was found to be the optimized solvent (entries 5 to 12). At last, reaction time was shortened from 3 days to 7 hours by increasing the temperature from 25° to 60 °C (entry 13). If the reaction time was prolonged from 7 hours to 24 hours, neither significant yield increase nor decomposition of the product was observed (entry 14). Furthermore, E/Z ratio did not decrease during the prolonged heating. Additional control reactions demonstrated that the sodium acetate base is crucial to the catalyst turn over. When sodium acetate was not added, reaction yield is limited to as low as 20% which is about the amount of the catalyst used in the reaction system.

In conclusion, the results of extensive exploratory and optimization studies of the model reaction between 3-bromoindole **2a** with *trans-p*-nitrocinnamaldehyde **1a** revealed that catalyst **VI** , chloroform as solvent at 60 °C, and sodium acetate, instead of sodium carbonate, represent optimal conditions. It is noteworthy that, in contrast to reactions of

4-bromophenols, the process can be performed in one pot without the need for gradual addition of the 3-bromoindoles.

Table 4.2. Effect of additives and solvents on the synthesis of (*E*)-α-indolyl-β-arylacrylaldehyde **3a**[a]



entry	solvent	additive	temp.(°C)	time (days)	yield (%)[b]
1	CH_2Cl_2	2,6-lutidine	25	5	46
2	CH_2Cl_2	NaOAc	25	3	73
3	CH_2Cl_2	$NaHCO_3$	25	3	66
4	CH_2Cl_2	Na_2CO_3	25	3	71
5	$CHCl_3$	NaOAc	25	3	81
6	MeOH	NaOAc	25	3	79
7	MeCN	NaOAc	25	3	52
8	THF	NaOAc	25	3	73
9	Toluene	NaOAc	25	3	78
10	Et_2O	NaOAc	25	3	66
11	DMF	NaOAc	25	3	59
12	Acetone	NaOAc	25	3	77
13	$CHCl_3$	NaOAc	60	0.3	89
14	$CHCl_3$	NaOAc	60	1	90

[a]Reaction conditions: unless specified, a mixture of **1a** (0.1 mmol), **2a** (0.2 mmol), designated catalyst (20 mol%, or 0.02 mmol) and the specific additive (1.2 equiv.) in dichloromethane (0.5 mL) was stirred for a specified time period at the designated temperature. [b]Isolated yields.

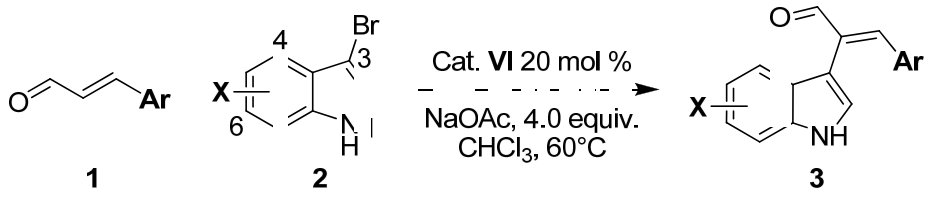
4.3. Expansion of Substrate Scopes

The scope of V**I**-catalysed direct α-arylation reactions of 3-bromoindoles **2** with enals **1** is examined (Table 4.3). The results show that the processes serve as a general and efficient method to prepare a variety of (*E*)-α-indolyl-β-arylacrylaldehyde. Notably, high yields (65-100 %) and good to high *E*-selectivities (9:1 to >30:1) attend these processes. Furthermore, the reactions generally proceed faster and with higher yields and *E*-stereoselectivities than those with 4-bromophenols. In addition, as observed with reactions of 4-bromophenols, electron-withdrawing (entries 1-6), electron-neutral (entry 7) and electron-donating substituents (entries 8-11) or a combination (entry 12) on enals **1** are found to have limited effects on these processes. Reactions of 3-bromoindoles also occur in high yields with other heterocycles (entry 13) and with other conjugated aromatic systems (entries 14-15). Again, steric effects are found to influence the efficiency of these reactions more than electronic effects. In general, more hindered substrates react with diminished *E*/*Z* selectivities (entries 4-6, 10-11 and 15).

A survey of the structural tolerance of 3-bromoidoles indicates that, in all cases, good to high yields (65-100%) and high stereoselectivities (16:1 to >30:1) are achieved (entries 16-20), regardless of the size and electronic characteristics of substituents. To our

dismay, N-Boc protected 3-bromoindole was not active enough to transform to desired product, and was left intact after heated at 60 °C for 5 days (data not shown here). Surprisingly, although they provide large steric hindrance, 2-substituted 3-bromoindoles did react smoothly with enal 1a, and the reactions afforded quantitative yields and good E/Z ratios (entries 16 and 17). Interestingly, in case of 5-methoxyindole (entry 20), a 2-brominated product is unexpectedly obtained.

Table 4.3. Scope of amine-catalysed direct α-arylation reactions of 3-bromoindoles with enals[a]



1 2 3

entry	**Ar**	**X**	time (h)	**3**	yield (%)[b]	*E/Z*[c]
1	4-$NO_2C_6H_4$	H	22	**3a**	90	>30:1
2	4-ClC_6H_4	H	22	**3b**	79	>30:1
3	4-BrC_6H_4	H	22	**3c**	>99	>30:1
4	4-CNC_6H_4	H	22	**3d**	81	12:1
5	2-ClC_6H_4	H	22	**3e**	>99	9:1
6	2-BrC_6H_4	H	22	**3f**	>99	9:1
7	Ph	H	22	**3g**	87	>30:1
8	4-$MeOC_6H_4$	H	22	**3h**	75	>30:1
9	4-MeC_6H_4	H	22	**3i**	90	>30:1
10	2-$MeOC_6H_4$	H	22	**3j**	89	13:1

11	2-MeC_6H_4	H	22	**3k**	97	10:1
12	4-AcO-3-$MeOC_6H_4$	H	22	**3l**	94	>30:1
13	2-Furanyl	H	22	**3m**	90	16:1
14	2-Naphthyl	H	22	**3n**	78	>30:1
15	1-Naphthyl	H	22	**3o**	96	10:1
16	4-$NO_2C_6H_4$	2-Me	28	**3p**	>99	>30:1
17	4-$NO_2C_6H_4$	2-Ph	28	**3q**	>99	16:1
18	4-$NO_2C_6H_4$	5-NO_2	48	**3r**	65	>30:1
19	4-$NO_2C_6H_4$	5-Br	22	**3s**	>99	>30:1
20[d]	4-$NO_2C_6H_4$	5-MeO	22	**3t**	87	>30:1

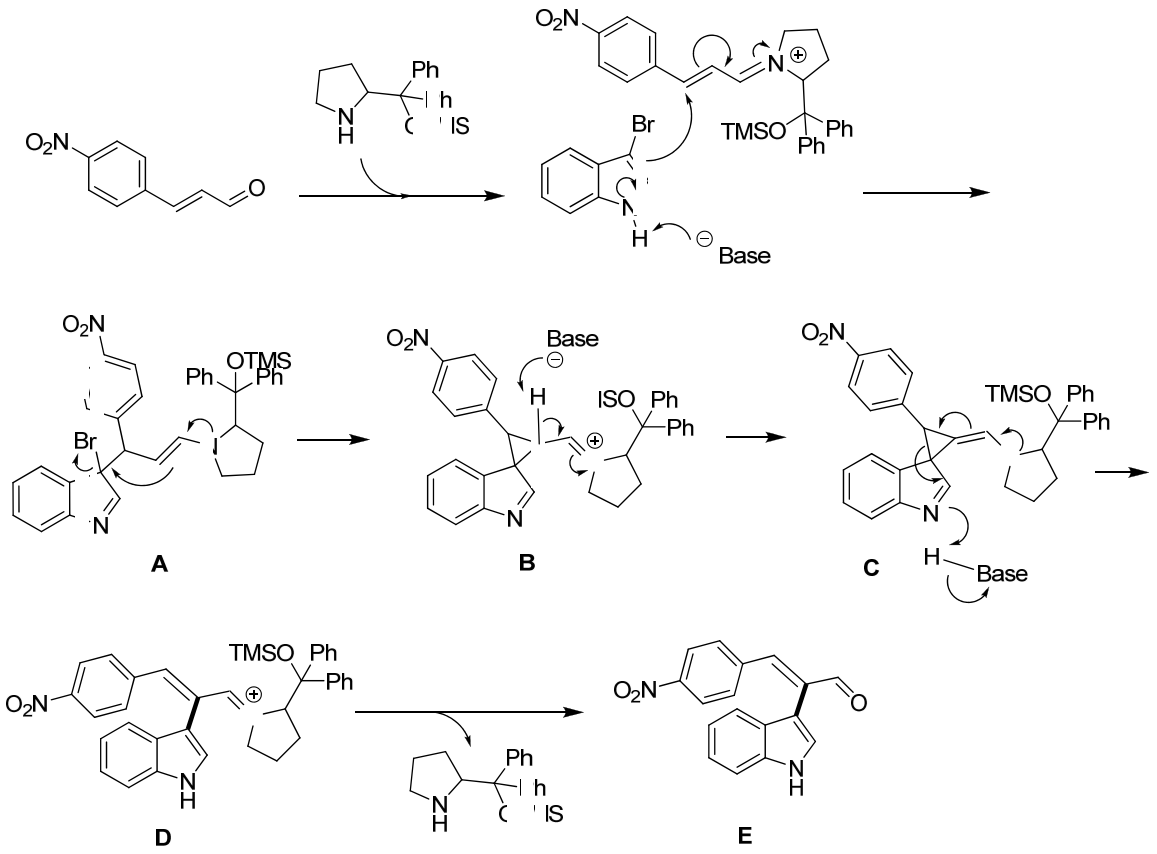
[a]Reaction conditions: unless specified, a mixture of **1a** (0.1 mmol), **2a** (0.2 mmol), designated catalyst (20 mol%, or 0.02 mmol) and sodium acetate additive (1.2 equiv., 0.4 mmol) in dichloromethane (0.5 mL) was stirred for a specified time period at 60 °C. [b]Isolated yields. [c]Determined by ^{1}H NMR of crude reaction mixture. [d]2-bromonated product formed.

4.4. Proposed Reaction Mechanism

Based on previously studies of the mechanism for the direct α-arylation of enals with 4-bromophenols, a plausible mechanism was also proposed for the stereoselective organocatalytic synthesis of (*E*)-α-Indolyl-β-aryl-acrylaldehydes (Figure 4.2). The process started from the iminium activation of enal by the aminocatalyst **VI**. The 3-bromoindole attacked the iminium species, and the Michael adduct **A** was formed accordingly. Intramolecular alkylation happened in the following step, and the intermediate **B** was produced with the framework of cyclopropane ring. After the opening

of the cyclopropane ring, α-indolyl intermediate **D** was obtained. Noticed that the α-indolyl moiety was connected with the iminium moiety through a single C-C bond which could rotate freely, and the two conjugated moieties were not conjugated. This framework was verified by the X-ray structural analysis of compound **3a** which possesses a dihedral angle between the two planar moieties. The *E*-conformation was favored due to large steric hindrance brought by the diphenylprolinol TMS ether.

Figure 4.2. A proposed reaction mechanism for α-arylation reactions of enals with 3-bromoindole



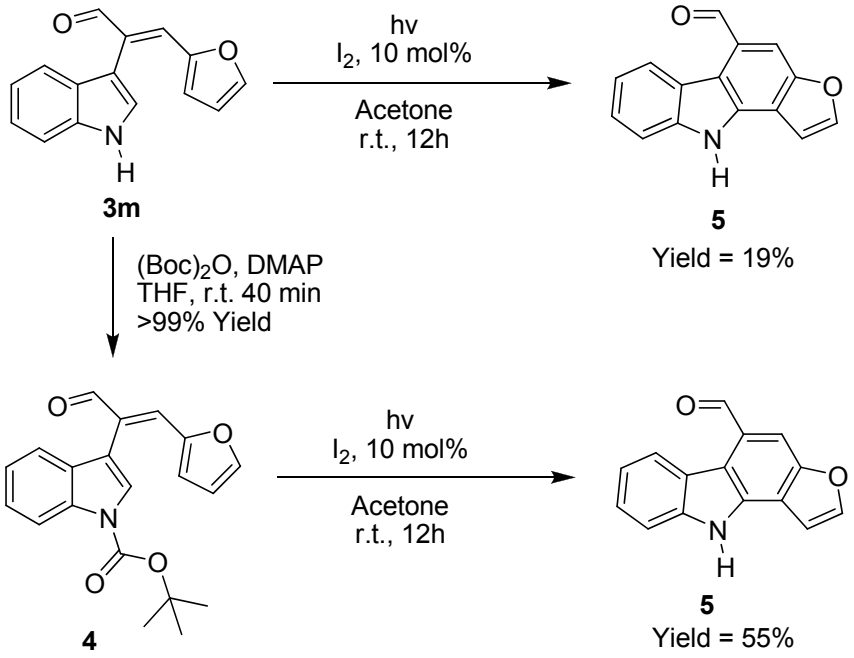
4.5. Photosynthesis of Furocarbazole

As a kind of aryl- and heteroaryl-annulated carbazoles (AHACs), [α]-annulated carbazoles is an important class of compounds with fascinating biological properties such as anti-tumour, anti-microbial and anti-fungal activities.[29] Moreover, recently, their application has been expanded to the areas of molecular imaging and material chemistry.[30-31] Generally speaking, there are two major strategies for the synthesis. Although photochemical cycliszation method was usually used in the annulations process, the substrates submitted for the irradiation were difficult to make, which renders the method lacking of generality.[32] A newly developed indium-catalyzed annulation methodology provides a more general and straightforward strategy for the [α]-annulated carbazoles synthesis. Since the method focused on further material application, the products generated lack functional groups, and cannot be conveniently diversified without further modification in the purpose of biological research.[33]

The (*E*)-α-indolyl-β-arylacrylaldehydes **3** can serve as valuable precursors for the efficient synthesis of [α]-annulated carbazoles. As demonstrated, for instance, compound **3m** can be efficiently transformed to furocarbazole **5** through a photoelectronic cyclization-photoinduced decarboxylation cascade (Figure 4.3). Although the compound **3m** could be directly transformed to furocarbazole **5** after UV irradiation for 12 hours in acetone with catalytic amount of iodine, the yield is as low as 19%. A cascade process which combines photoelectronic cyclization with photoinduced decarboxylation could improve the yield up to 55% after the substrate's indole moiety was protected with Boc-protecting group. It is known that furocarbazole **5** and its analogues are of considerable

biological interest. They can be potentially used for the treatment of various infections and poisonous snake bites.[34,35]

Figure 4.3. Synthesis of furocarbazoles **5** via photoelectronic cycliszation-photoinduced decarboxylation cascade process



4.6. Summary

As demonstrated above, a general method for the stereoselective synthesis of (*E*)-α-indolyl-β-aryl-acrylaldehyde was established. Organocatalyst was used to mediate the cross-coupling-like transformation from α, β-unsaturated aldehydes and 3-bromoindoles to tri-substituted alkene products stereoselectively in favor of the *E*-isomer formation. Various aromatic enals and brominated indoles could be tolerated in such a direct α-

arylation cascade process. Furthermore, the (*E*)-α-indolyl-β-aryl-acrylaldehyde framework also served as the crucial template in the concise construction of [α]-annulated carbazoles via photoelectronic cyclization-photoinduced decarboxylation cascade.

4.7. Experimental Section

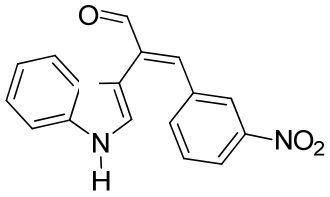
General Information:

All commercially available reagents were used without further purification. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on Whatman silica gel plates with fluorescence F_{254} indicator. And Merck 60 silica gel was used for chromatography. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance 500. When deuteriorated chloroform ($CDCl_3$) was used to dissolve sample, tetramethylsilane (TMS) was used as an internal reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.

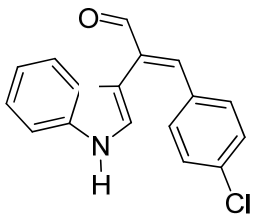
Procedure for (*E*)-α-indolyl-β-aryl-acrylaldehydes (Table 4.3)

3-Bromoindole (0.2 mmol), α,β-unsaturated aldehyde (0.1 mmol), NaOAc (42 mg, 0.4 mmol) and catalyst V**I** (20 mmol %, 7 mg, 0.02 mmol) were dissolved in chloroform (0.2 M relative to aldehyde, 0.5 mL) at room temperature, and the reaction mixture were

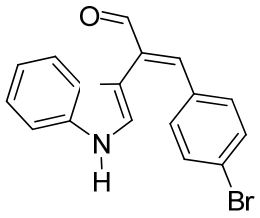
heated to 60 °C. After the aldehyde was totally consumed (determined by TLC analysis), the vial was cooled to room temperature. The solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane. The compound is characterized by ^{1}H and ^{13}C NMR and HRMS with >95 % purity-based ^{1}H NMR.



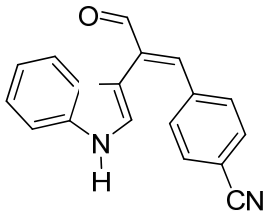
(*E*)-2-(1 *H* -indol-3-yl)-3-(4-nitrophenyl)acrylaldehyde (3a) . The title compound was prepared according to the typical procedure as described above in 90% yield. MP 211-212°C; ^{1}H NMR (acetone-d_6 , 500 MHz): δ = 10.82 (br, 1H), 9.93 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.69 (s, 1H), 7.62 (m, 3H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.5, 1H), 6.81 (t, *J* = 7.5, 1H), 6.74 (d, *J* = 8.0 Hz, 1H); 13 C NMR (acetone-d_6 , 125 MHz): δ = 194.7, 148.3, 144.4, 143.2, 138.3, 137.6, 131.7X2, 128.3, 125.7, 124.1X2, 122.7, 121.0, 120.4, 112.8, 107.1; HRMS (ESI) calcd. for $C_{17}H_{12}N_2O_3$: *m/z* 315.0746 ($[M+Na]^+$), found 315.0742.



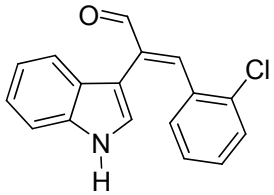
(E)-3-(4-chlorophenyl)-2-(1H-indol-3-yl)acrylaldehyde (3b). The title compound was prepared according the typical procedure, as described above in 79% yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.65 (br, 1H), 9.86 (s, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 7.47 (d, J = 8 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.90-6.81 (m, 2H); ^{13}C NMR (Acetone-d_6, 125 MHz): δ = 194.6, 146.8, 137.4, 136.1, 135.3, 135.2, 132.4X2, 129.1X2, 127.4, 125.8, 122.3, 120.9, 120.0, 112.5, 107.3; HRMS (ESI) calcd. for $C_{17}H_{12}ClNO$: *m/z* 304.0505 ($[M+Na]^+$), found 304.0503.



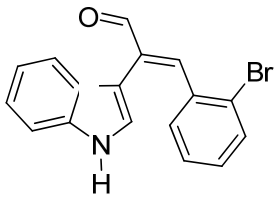
(E)-3-(4-bromophenyl)-2-(1H-indol-3-yl)acrylaldehyde (3c). The title compound was prepared according the typical procedure, as described above in 100% yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.65 (br, 1H), 9.86 (s, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 7.47 (d, J = 8 Hz, 1H), 7.39-7.33 (m, 4H), 7.08 (t, J = 7.5 Hz, 1H), 6.87-6.82 (m, 2H); ^{13}C NMR (Acetone-d_6, 125 MHz): δ = 194.6, 146.8, 137.4, 136.1, 135.5, 132.6X2, 132.1X2, 127.4, 125.8, 123.7, 122.3, 120.9, 120.0, 112.5, 107.3; HRMS (ESI) calcd. for $C_{17}H_{12}BrNO$: *m/z* 348.0000 ($[M+Na]^+$), found 379.9993.



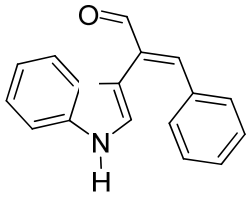
(E)-4-(2-(1H-indol-3-yl)-3-oxoprop-1-enyl)benzonitrile (3d). The title compound was prepared according the typical procedure, as described above in 81% yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.74 (br, 1H), 9.91 (s, 1H), 7.65 (s, 1H), 7.60-7.55 (m, 5H), 7.47 (d, J = 8 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 125 MHz): δ = 194.7, 145.2, 141.1, 137.8, 137.5, 132.7X2, 131.4X2, 128.1, 125.7, 122.6, 120.9, 120.3, 119.1, 112.8, 112.7, 107.1; HRMS (ESI) calcd. for $C_{18}H_{12}N_2O$: *m/z* 295.0847 ($[M+Na]^+$), found 295.0841.



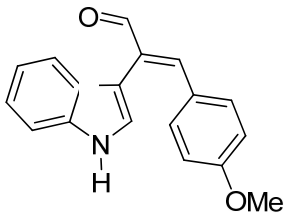
(E)-3-(2-chlorophenyl)-2-(1H-indol-3-yl)acrylaldehyde (3e). The title compound was prepared according the typical procedure, as described above in 100% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.92 (s, 1H), 8.49 (br, 1H), 7.72 (s, 1H), 7.52-7.43 (m, 2H), 7.33 (d, J = 8 Hz, 1H), 7.15-7.09 (m, 3H), 6.88 (t, J = 7.5 Hz, 1H), 6.82-6.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.9, 144.7, 136.3, 136.0, 134.9, 134.0, 130.8, 130.7, 129.9, 126.8, 126.7, 125.1, 122.5, 120.8, 120.3, 111.5, 107.2; HRMS (ESI) calcd. for $C_{17}H_{12}ClNO$: *m/z* 304.0505 ($[M+Na]^+$), found 304.0503.



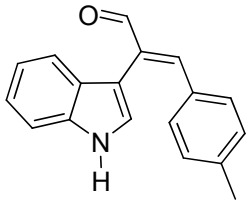
(E)-3-(2-bromophenyl)-2-(1H-indol-3-yl)acrylaldehyde (3f). The title compound was prepared according the typical procedure, as described above in 100% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.93 (s, 1H), 8.46 (br, 1H), 7.65 (d, J = 8 Hz, 1H), 7.64 (s, 1H), 7.44 (s, 1H), 7.33 (d, J = 8 Hz, 1H), 7.11-7.09 (m, 2H), 7.05 (t, J = 7.5, 1H), 6.89-6.80 (m, 3H), ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.8, 147.06, 136.3, 135.9, 133.1, 131.0, 130.7, 127.4, 127.2, 126.6, 125.4, 125.1, 122.5, 120.9, 120.3, 111.5, 107.2; HRMS (ESI) calcd. for $C_{17}H_{12}BrNO$: *m/z* 348.0000 ($[M+Na]^+$), found 379.9996.



(E)-2-(1H-indol-3-yl)-3-phenylacrylaldehyde (3g). The title compound was prepared according the typical procedure, as described above in 87% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.15 (s, 1H), 9.86 (br, 1H), 7.53 (s, 1H), 7.40-7.35 (m, 4H), 7.25 (m, 1H), 7.19-7.13 (m, 3H), 6.94-6.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.1, 149.8, 136.4, 135.2, 134.6, 130.7X2, 130.1, 128.6X2, 125.9, 125.4, 122.5, 121.0, 120.2, 111.6, 107.8; HRMS (ESI) calcd. for $C_{17}H_{13}NO$: *m/z* 270.0895 ($[M+Na]^+$), found 270.0892.

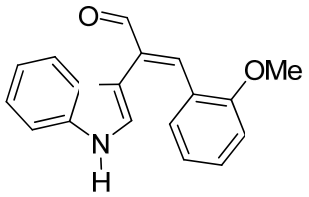


(E)-2-(1H-indol-3-yl)-3-(4-methoxyphenyl)acrylaldehyde (3h). The title compound was prepared according the typical procedure, as described above in 75% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.80 (s, 1H), 8.52 (br, 1H), 7.44 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.1, 161.3, 150.2, 136.4, 132.8X2, 132.5, 127.9, 125.6X2, 122.4, 121.0, 121.2, 114.1X2, 111.6, 108.1, 55.5; HRMS (ESI) calcd. for $C_{18}H_{15}NO_2$: *m/z* 300.1000 ($[M+Na]^+$), found 300.0995.

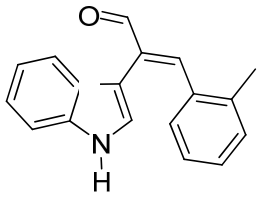


(E)-2-(1H-indol-3-yl)-3-p-tolylacrylaldehyde (3i). The title compound was prepared according the typical procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.83 (s, 1H), 8.49 (br, 1H), 7.46 (s, 1H), 7.38 (d, J = 8 Hz, 1H), 7.34 (d, J = 2.5 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.99-6.92 (m, 4H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.1, 150.3, 140.7, 136.4, 133.7, 132.4, 130.9X2,

129.4X2, 125.7, 125.5, 122.4, 121.1, 120.2, 111.6, 108.0, 21.8; HRMS (ESI) calcd. for $C_{18}H_{15}NO$: *m/z* 284.1051 ($[M+Na]^+$), found 284.1047.

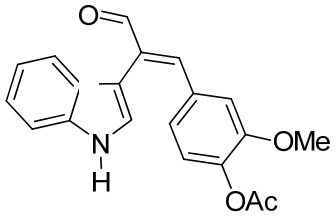


(E)-2-(1H-indol-3-yl)-3-(2-methoxyphenyl)acrylaldehyde (3j). The title compound was prepared according the typical procedure, as described above in 89% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.88 (s, 1H), 8.47 (br, 1H), 7.87 (s, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 7.34 (d, *J* = 8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.13-7.10 (m, 2H), 6.97-6.88 (m, 3H), 6.52 (t, *J* = 7.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.4, 158.1, 144.5, 136.4, 134.2, 131.5, 130.3, 125.9, 125.3, 124.4, 122.3, 121.1, 120.4, 120.0, 111.5, 110.8, 108.1, 55.9; HRMS (ESI) calcd. for $C_{18}H_{15}NO_2$: *m/z* 300.1000 ($[M+Na]^+$), found 300.0999.

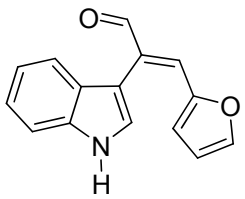


(E)-2-(1H-indol-3-yl)-3-o-tolylacrylaldehyde (3k). The title compound was prepared according the typical procedure, as described above in 97% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.90 (s, 1H), 8.40 (br, 1H), 7.61 (s, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.33 (d, *J* =

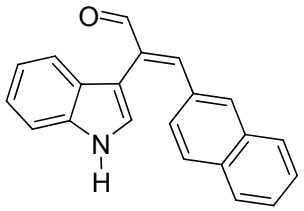
8.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.14-7.08 (m, 3H), 6.85 (t, J = 7.5 Hz, 1H), 6.80-6.77 (m, 2H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.0, 147.4, 137.6, 136.3, 135.3, 134.7, 130.6, 129.6, 129.4, 126.3, 125.9, 125.3, 122.3, 121.0, 120.1, 111.4, 107.9, 20.5; HRMS (ESI) calcd. for $C_{18}H_{15}NO$: *m/z* 284.1051 ($[M+Na]^+$), found 284.1046.



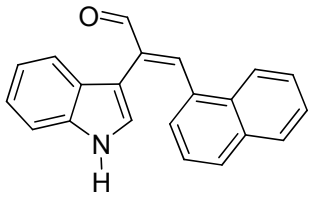
(E)-4-(2-(1H-indol-3-yl)-3-oxoprop-1-enyl)-2-methoxyphenyl acetate (3l). The title compound was prepared according the typical procedure, as described above in 94% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.85 (s, 1H), 8.57 (br, 1H), 7.44 (s, 1H), 7.36 (d, J = 8, 1H), 7.30 (s, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8Hz, 1H), 7.00-6.95 (m, 3H), 6.85 (s, 1H), 3.02 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.0, 169.0, 150.8, 148.9, 141.2, 136.3, 134.4, 133.8, 125.8, 125.3, 124.8, 122.8, 122.7, 121.1, 120.4, 114.1, 111.6, 107.6, 55.2, 20.9; HRMS (ESI) calcd. for $C_{20}H_{17}NO_4$: *m/z* 358.1055 ($[M+Na]^+$), found 358.1053.



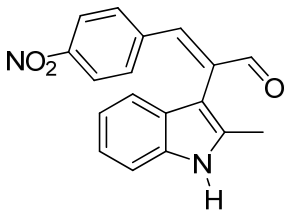
(E)-3-(furan-2-yl)-2-(1H-indol-3-yl)acrylaldehyde (3m). The title compound was prepared according the typical procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.78 (s, 1H), 8.49 (br, 1H), 7.47 (s, 1H), 7.43 (d, J = 8 Hz, 1H), 7.40 (s, 1H), 7.36 (d, J = 2.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.32-6.31 (m, 1H), 6.20 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 193.8, 151.4, 145.4, 136.3, 136.0, 131.3, 125.6, 125.5, 122.5, 121.0, 120.2, 116.8, 113.1, 111.7, 107.9; HRMS (ESI) calcd. for $C_{15}H_{11}NO_2$: *m/z* 260.0687 ($[M+Na]^+$), found 260.0684.



(E)-2-(1H-indol-3-yl)-3-(naphthalen-2-yl)acrylaldehyde (3n). The title compound was prepared according the typical procedure, as described above in 78% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.91 (s, 1H), 8.49 (br, 1H), 7.94 (s, 1H), 7.71-7.69 (m, 2H), 7.65 (s, 1H), 7.51-7.40 (m, 5H), 7.35 (d, J = 9 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.0, 149.7, 136.4, 134.6, 134.0, 133.3, 133.0, 132.0, 128.9, 128.0, 127.9, 127.6, 126.8, 126.7, 126.0, 125.7, 122.6, 121.1, 120.3, 111.6, 108.1. HRMS (ESI) calcd. for $C_{21}H_{15}NO$: *m/z* 320.1051 ($[M+Na]^+$), found 320.1050.

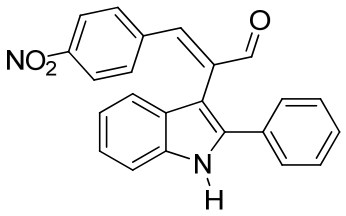


(E)-2-(1H-indol-3-yl)-3-(naphthalen-1-yl)acrylaldehyde (3o). The title compound was prepared according the typical procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.04 (s, 1H), 8.38 (br, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.89 (d, J = 8.0, 1H), 7.74 (d, J = 8.0, 1H), 7.64 (t, J = 7.5, 1H), 7.57 (t, J = 7.5, 1H), 7.47 (d, J = 2.5, 1H), 7.35-7.30 (m, 2H), 7.15-7.04 (m, 2H), 6.72-6.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.9, 145.9, 136.3, 136.1, 133.8, 132.3, 131.9, 130.1, 129.2, 128.0, 127.2, 126.7, 126.4, 125.4, 123.9, 122.6, 122.3, 121.1, 120.1, 111.4, 108.0; HRMS (ESI) calcd. for $C_{21}H_{15}NO$: *m/z* 320.1051 ($[M+Na]^+$), found 320.1046.

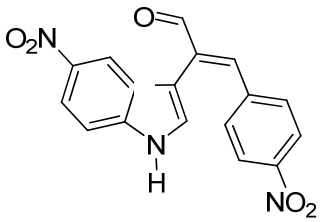


(E)-2-(2-methyl-1H-indol-3-yl)-3-(4-nitrophenyl)acrylaldehyde (3p). The title compound was prepared according the typical procedure, as described above in 100% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.90 (s, 1H), 8.33 (br, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.60 (s, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.0 Hz, 1H), 6.99 (m, 2H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.4, 147.9, 145.9,

141.6, 138.2, 136.1, 134.5, 130.9X2, 126.9, 123.9X2, 122.2, 120.6, 119.4, 111.1, 104.9, 13.2; HRMS (ESI) calcd. for $C_{21}H_{15}NO$: *m/z* 329.0902 ($[M+Na]^+$), found 329.0900.

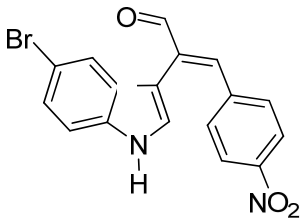


(E)-3-(4-nitrophenyl)-2-(2-phenyl-1H-indol-3-yl)acrylaldehyde (3q). The title compound was prepared according the typical procedure, as described above in 100% yield. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.76 (s, 1H), 8.68 (br, 1H), 7.94 (d, *J* = 8.5, 2H), 7.66 (s, 1H), 7.42-7.34 (m, 5H), 7.27-7.25 (m, 3H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06-7.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 194.0, 147.9, 145.0, 141.4, 138.1, 137.1, 136.7, 132.3, 130.8X2, 129.3X2, 128.6, 127.3X2, 127.3, 123.8X2, 123.5, 121.1, 120.0, 111.8, 105.4; HRMS (ESI) calcd. for $C_{21}H_{15}NO$: *m/z* 391.1059 ($[M+Na]^+$), found 391.1052.

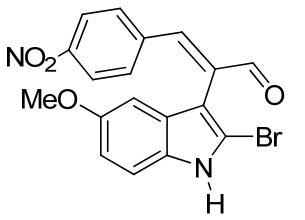


(E)-2-(5-nitro-1H-indol-3-yl)-3-(4-nitrophenyl)acrylaldehyde (3r). The title compound was prepared according the typical procedure, as described above in 65% yield. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.93 (s, 1H), 9.09 (br, 1H), 8.08-8.04 (m, 3H),

7.80 (d, J = 1.5 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 193.6, 148.2, 146.7, 142.5, 141.0, 139.3, 136.2, 130.9X2, 129.6, 124.6, 124.0X2, 118.6, 117.5, 112.1, 109.2; HRMS (ESI) calcd. for $C_{17}H_{11}N_3O_5$: *m/z* 360.0596 ($[M+Na]^+$), found 360.0592.



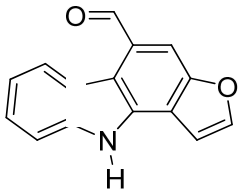
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-nitrophenyl)acrylaldehyde (3s). The title compound was prepared according the typical procedure, as described above in 100% yield. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 10.90 (br, 1H), 9.93 (s, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.75 (s, 1H), 7.64 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.90 (s, 1H); ^{13}C NMR (Acetone-d_6, 125 MHz): δ = 194.5, 148.4, 145.4, 143.0, 137.8, 136.2, 131.7X2, 129.7, 127.6, 125.3, 124.2X2, 123.4, 114.5, 113.2, 106.7; HRMS (ESI) calcd. for $C_{17}H_{11}BrN_2O_3$: *m/z* 392.9851 ($[M+Na]^+$), found 392.9847.



(E)-2-(2-bromo-5-methoxy-1H-indol-3-yl)-3-(4-nitrophenyl)acrylaldehyde (3t). The title compound was prepared according the typical procedure, as described above in 87% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.89 (s, 1H), 8.65 (br, 1H), 8.05 (d, J = 8.5 Hz, 2H), 7.70 (s, 1H), 7.45 ((d, J = 8.5 Hz, 2H), 7.21 (d, J = 9.0 Hz, 1H), 6.83 (dd, J = 9.0, 2.0 Hz, 1H), 6.47 (d, J = 2.0 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 193.1, 155.2, 148.2, 146.9, 141.1, 136.4, 131.8, 131.0X2, 127.3, 124.0X2, 113.6, 112.2, 110.2, 108.5, 101.2, 55.9; HRMS (M = $C_{18}H_{13}BrN_2O_4$, for Br-79 isotope): $[M+Na]^+$ = 422.9956 (cal. = 422.9956).

Typical Procedure for the photoelectronic cyclization

A solution of (*E*)-3-(furan-2-yl)-2-(1H-indol-3-yl)acrylaldehyde (0.2 mmol) dissolved in acetone (7 mL) in the presence of a catalytic amount of I_2 was irradiated for 11 h in a reactor with an HPK-125W Philips high-pressure mercury vapor UV lamp in a water-jacketed immersion well. The solvent was evaporated and the residue was purified by chromatography on silica gel.



10H-furo[3,2-a]carbazole-5-carbaldehyde (5). The title compound was prepared according the typical procedure, as described above in 55% yield. ^{1}H NMR (Acetone-d_6,

500 MHz): δ = 11.29 (br, 1H), 10.50 (s, 1H), 9.13 (d, J = 8.5 Hz, 1H), 8.17 (s, 1H), 8.09 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.38 (s, 1H), 7.26 (t, J = 7.5 Hz, 1H), ; ^{13}C NMR (Acetone-d_6, 125 MHz): δ = 193.1, 154.2, 149.2, 141.1, 134.6, 130.0, 126.4, 126.1, 123.8, 120.3, 118.6, 116.1, 112.6, 111.8, 105.6; HRMS (ESI) calcd. for $C_{15}H_9NO_2$: *m/z* 258.0531 ($[M+Na]^+$), found 258.0528.

4.8. Reference

(1) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644.

(2) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9533-9537.

(3) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, *2010*, 2635-2655.

(4) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173.

(5) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5482-5487.

(6) King, H.; Meng, Z.; Denhart, D.; Mattson, R. *Org. Lett.* **2005**, *7*, 4467-4470.

(7) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847-1850.

(8) Rueping, M.; Nachtsheim, B. J.; Moreth, S.; Bolte, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 593-596.

(9) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Comm.* **2006**, *2006*, 799-801.

(10) Zhou, W.; Xu, L.-W.; Li, L.; Yang, L.; Xia, C.-G. *Eur. J. Org. Chem.* **2006**, *2006*, 5225-5227.

(11) Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. *Eur. J. Org. Chem.* **2008**, *2008*, 1406-1410.

(12) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403-1405.

(13) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576-6579.

(14) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016-4018.

(15) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Bio. Chem.* **2005**, *3*, 2566-2571.

(16) Habib, P. M.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron Lett.* **2008**, *49*, 7005-7007.

(17) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037-7042.

(18) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 3086-3089.

(19) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565-5567.

(20) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Syn. Cat.* **2007**, *349*, 1863-1867.

(21) Yu, P.; He, J.; Guo, C. *Chem. Comm.* **2008**, *2008*, 2355-2357.

(22) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292-293.

(23) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484-1485.

(24) Raheem, I. T.; Thiara, P. S.; Peterson, E. a; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404-13405.

(25) Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063-4065.

(26) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609-2611.

(27) S. Lakhdar; M. Westermaier; F. Terrier; R. Goumont; T. Boubaker; A. R. Ofial; H. Mayr *J. Org. Chem.* **2006**, *71*, 9088-9095.

(28) Song, X.; Song, A.; Zhang, F.; Li, H.-X.; Wang, W. *Nat. Comm.* **2011**, *2*, 524.

(29) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303-4427.

(30) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823-15835.

(31) Zhao, H.-P.; Tao, X.-T.; Wang, F.-Z.; Ren, Y.; Sun, X.-Q.; Yang, J.-X.; Yan, Y.-X.; Zou, D.-C.; Zhao, X.; Jiang, M.-H. *Chem. Physic. Lett.* **2007**, *439*, 132-137.

(32) Wu, T.-S.; Huang, S.-C.; Wu, P.-L.; Kuoh, C.-S. *Phytochemistry* **1999**, *52*, 523-527.

(33) Curiel, D.; Cowley, A.; Beer, P. D. *Chem. Comm.* **2005**, 236-238.

(34) Yasuhara, A.; Suzuki, N.; Sakamoto, T. *Chemical & pharmaceutical bulletin* **2002**, *50*, 143-145.

(35) Soós, T.; Timári, G.; Hajós, G. *Tetrahedron Letters* **1999**, *40*, 8607-8609.

Chapter 5

Organocatalytic Regio- and Chemo-selective "One-pot" Access to Polysubstituted Arenes from Simple Enals via a Michael-Aldol Condensation-Aromatization Cascade

5.1. Introduction

The 'privileged' status of ubiquitous arenes is underscored by their broad applications in organic synthesis, pharmaceuticals, perfumes and cosmetics, agrochemicals and materials.[1-4] Accordingly, synthesis of functionalized arenes has long-standing interest to chemists. Classic synthetic methods include electrophilic aromatic substitution, such as the Friedel-Crafts reaction, and directed *ortho* metalation in construction of substituted arenes.[5-8] Since they introduce specific substitute groups to pre-existed arenes, the scopes of the reactions is restricted by electronic nature of substrates. Moreover, the rigorous reaction conditions and poor regioselectivity render the methodologies less demanded by organic chemists. Recently transition metal catalyzed direct C-H functionalization of arenes has open new doors for synthesis of functionalized arenes.[9-11] However, generally directing groups and relatively harsh reaction conditions are needed in order to achieve respective high regioselectivity and reactivity.[12-14]

Direct construction of aromatic rings from linear precursors is an important alternative. Transition-metal-catalyzed cycloaddition and ring-closing-metathesis are the

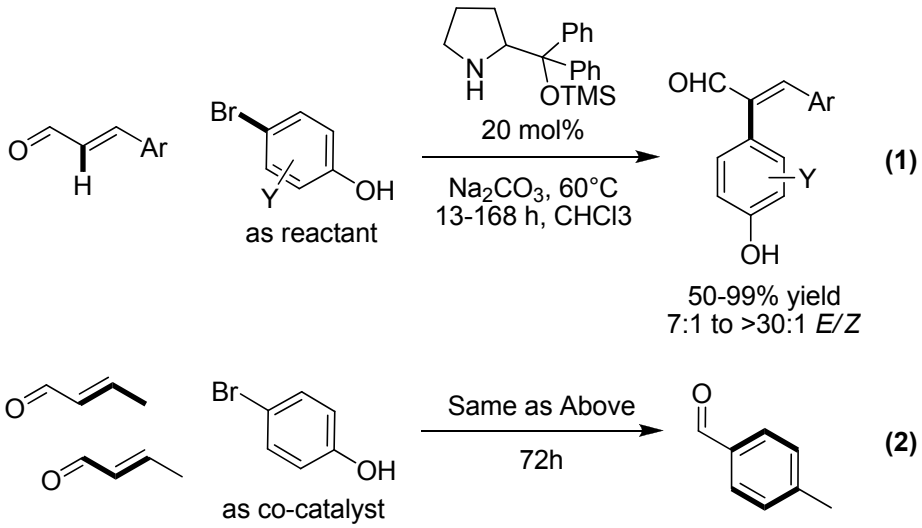
two well developed strategies in the past two decades.[15-21] Although these methodologies provide straightforward assembling routes, the use of less appealing transition metal complexes as catalysts, the poor selective orientation of substituents on aromatic rings and arduously accessible starting materials are the major drawbacks.

In addition to organometallic catalysis, the development of organocatalyzed processes in construction of polysubstituted arenes may be an attractive alternative, but remains elusive. To our knowledge, no such study has been reported. Only a study of *L*-proline catalyzed [3+3] and [4+2] cycloadditions to give 6- membered ring products from enals has been reported by Hong and co-workers.[22,23] However, the products are not arenes; an additional DDQ oxidation is required to generate them. Furthermore, poor regioselectivity resulting from competing [3+3] and [4+2] cycloaddition reactions and high catalyst loading (as high as 50%) render the methodology lack of practical generality.

5.2. Initial Discoveries

Recently we have developed an organocatalytic stereoselective cross-coupling-like α-arylation reaction of aromatic α, β-unsaturated aldehydes with 4-bromophenols (Scheme 5.1, equation 1).[39] However, when an aliphatic crotonaldehyde was subjected to the reaction, an unexpected 4-methyl benzaldehyde was obtained (equation 2). This serendipitous discovery prompted us to investigate this interesting "side reaction".

Scheme 5.1. An unexpected formation of 4-methyl benzaldehyde from the study of cross-coupling-like α-arylation process

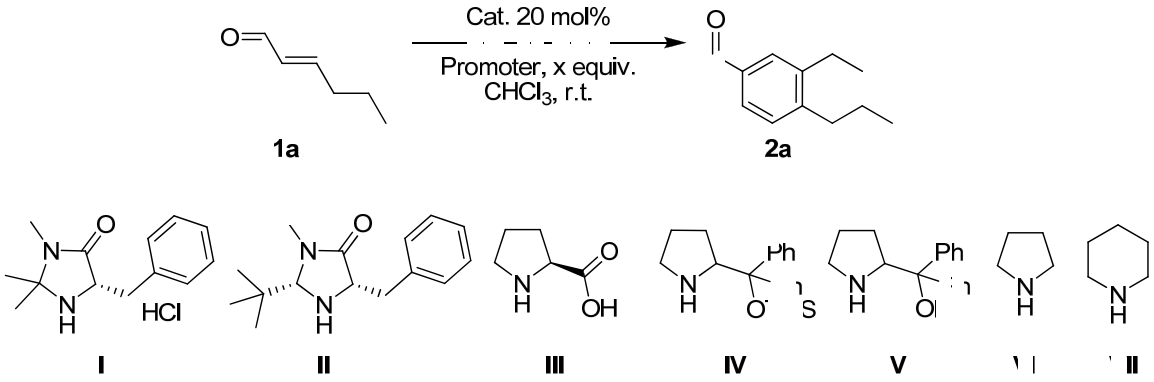


5.3. Optimization of Reaction Conditions

Initial studies were carried out by examining a simple self-dimerization (homo-coupling) of hexenal as sole reactant at r.t. in chloroform in the presence of a secondary amine (Table 5.1). Instead of *p*-bromophenol, unsubstituted phenol was used as mediator to zero out the influence of electronic effect. McMillan's catalysts **I** and **II** did not produce any product, and starting materials were left intact (entries 1 and 2). With *L*-proline (**III**), a catalyst used in Hong's study, the reactant was completely consumed after 3 days, but the desired aromatic product **3a** was obtained in only 6% yield and several byproducts were observed (entry 3). Diphenyl prolinol **V** also displayed low catalytic activity. Only reactant was recovered for 5 d reaction (entry 4). An encouraging result came from diphenyl prolinol TMS ether **IV**, which gave rise to **2a** in 35% (entry 5).

Other amines, such as pyrrolidine **VI** or piperidine **VII** could also drive the reaction to completion, but in much lower yield due to a complicated reaction (entries 6 and 7).

Table 5.1. Optimization of reaction conditions[a]



entry	cat.	promoter (x equiv.)	time (d)	yield (%)[b]
1	**I**	PhOH (1.0)	5	0
2	**II**	PhOH (1.0)	5	0
3	**III**	PhOH (1.0)	3	6
4	**IV**	PhOH (1.0)	3	35
5	**V**	PhOH (1.0)	5	0
6	**VI**	PhOH (1.0)	3	10
7	**VII**	PhOH (1.0)	5	<5
8	**IV**	TEA (1.0)	3	0
9	**IV**	PhCOOH (1.0)	5	11
10	**IV**	PhCOOH (0.5)	5	20
11	**IV**	PhCOOH (0.2)	5	7
12	**IV**	4-MeO-PhOH (1.0)	3	54
13	**IV**	4-Me-PhOH (1.0)	3	56

14	**IV**	4-Br-PhOH (1.0)	2	70
15	**IV**	4-I-PhOH (1.0)	2	77
16	**IV**	4-NO_2-PhOH (1.0)	2	99
17	**IV**	4-NO_2-PhOH (0.5)	2	47
18	**IV**	4-NO_2-PhOH (0.2)	2	52

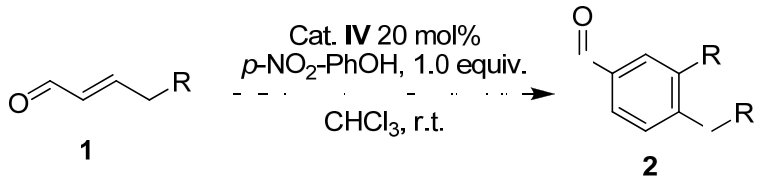
[a]Reaction conditions: enal **1a** (0.4 mmol) dissolved in chloroform (2.0 mL) was followed by addition of a specified amount of promoter and catalyst (0.02 mmol). The reaction mixture was stirred at r.t. for specified time in a loosely capped vial. [b]Isolated yields.

Catalyst **IV** was selected for further studies accordingly. We examined the effect of promoters on the reaction. Acidic reaction environment was crucial for the process, since basic additive, such as triethylamine (TEA), produce no transformation (entry 8). Interestingly, benzoic acid, which possesses stronger acidity than phenol, could also serve as a promoter, but the efficiency was relatively low (entries 9-11). Survey of substituted phenols revealed that a correlation between the acidity derived from electronic property of substituents and the reaction efficiency (e.g., product yield) was observed (entries 4 and 12-16). The acidity of phenol was proportional to the yield. Notably, *p*-nitrophenol gave an almost quantitative yield (entry 16). Further reduction of the amount of *p*-nitrophenol resulted in decreased yields (entries 17 and 18). Chloroform was identified as the choice of reaction medium after screening various solvents. It is worthy of note that no additional oxidant was necessary in our case while required in Hong's protocol.

5.4. Expansion of Substrate Scope

With the optimized reaction conditions in hand, we turned our attention to the scope of the efficient "one-pot" synthesis of arenes with catalyst **IV**. As shown in Table 5.2, the self-dimerized homo-coupling processes with single aliphatic enals proceeded efficiently and regioselectively to give 3,4-substitued benzylaldehydes **2** under the mild reaction conditions. The majority of products were obtained in almost quantitative yields (entries 1 and 3-7). It is noteworthy that crotonaldehyde bearing a benzyloxy functionality in terminal can provide a 3-BnO substituted product in high yield (92%, entry 7).

Table 5.2. Substrate scope of self-dimerization[a]

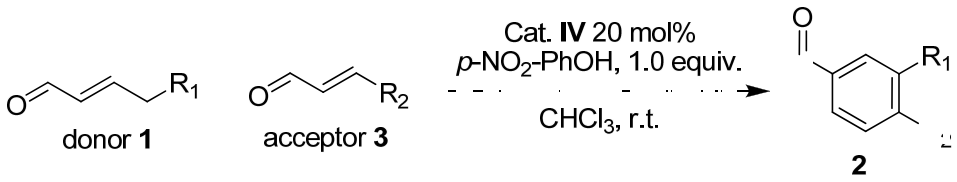


entry	R	**2**	time (d)	yield (%)[b]
1	C_2H_5	**2a**	3	99
2	H	**2b**	2	76
3	CH_3	**2c**	2	94
4	*n*-C_3H_7	**2d**	3	99
5	*n*-C_4H_9	**2e**	3	99
6	*n*-C_8H_{17}	**2f**	3	99
7	OBn	**2g**	3	92

[a]Reaction conditions: unless specified, see footnote *a* in Table 5.1. [b]Isolated yields.

It has been demonstrated that single aliphatic enals can efficiently participate in the arene formation highly regioselectively. However, the employment of two different enals for the process presents a significant challenge because in addition to regioselectivity, chemoselectivity could be an issue and multiple products could be formed. We envisioned that an aliphatic enal as a donor while an aromatic coupling partner as an acceptor might minimize the problem.

Table 5.3. Substrate scope of cross-over dimerization[a]



entry	R_1	R_2	**2**	time (d)	yield (%)[b]
1	H	4-NO_2-Ph	**2h**	3	87
2	CH_3	4-NO_2-Ph	**2i**	3	93
3	C_2H_5	4-NO_2-Ph	**2j**	3	99
4	C_3H_7	4-NO_2-Ph	**2k**	3	99
5	C_4H_9	4-NO_2-Ph	**2l**	4	99
6	C_2H_5	2-NO_2-Ph	**2m**	3	99
7	C_2H_5	4-CN-Ph	**2n**	3	99
8	C_2H_5	2-naphthalenyl	**2o**	4	91
9	C_2H_5	2-furyl	**2p**	4	87
10	C_2H_5	4-CF_3-Ph	**2q**	3	92

11	C_2H_5	4-Cl-Ph	**2r**	3	99
12	C_2H_5	2-Cl-Ph	**2s**	3	96
13	C_2H_5	4-MeO-Ph	**2t**	4	84
14	C_2H_5	2-MeO-Ph	**2u**	4	80
15	C_2H_5	COOEt	**2v**	4	95

[a]Reaction conditions: unless specified, to a solution of a donor enal **1** (0.2 mmol) and an acceptor enal **3** (0.2 mmol) in chloroform (2.0 mL) was added *p*-nitrophenol (0.2 mmol) and catalyst **V** (0.02 mmol, 20% mol). The reaction mixture was stirred at r.t. room for a specified time, and the vial was loosely capped. [b]Isolated yields.

With the concern in mind, we probed a reaction between less hindered crotonaldehyde as a donor and highly active *p*-nitrocinnamaldehyde as an acceptor under the same reaction conditions used in the homo-couplings (Table 5.3, entry 1). To our delight, the process proceeded smoothly. Only a single product was formed chemo- and regioselectively in high yield (87%). Encouraged by the outcome, we attempted to extend to more hindered aliphatic substrates with longer chains (entries 2-5). It appeared that the steric effect was limited. Remarkably, even higher yields of products were achieved (93-99% yields). Furthermore, significantly the substrate scope extended to steric demanding (entries 6, 10, 12 and 13) and less reactive acceptors of aromatic enals (entries 7-12). Besides the aromatic ring carrying electron-withdrawing substitutes (entries 7-10), even electron-donating ones (entries 11 and 12) worked nicely. We were particularly pleased to find that fused aromatic (entry 13), heteroaryl (entry 14) and ester (entry 15) enals could be tolerated to give valuable substituent diversified arenes.

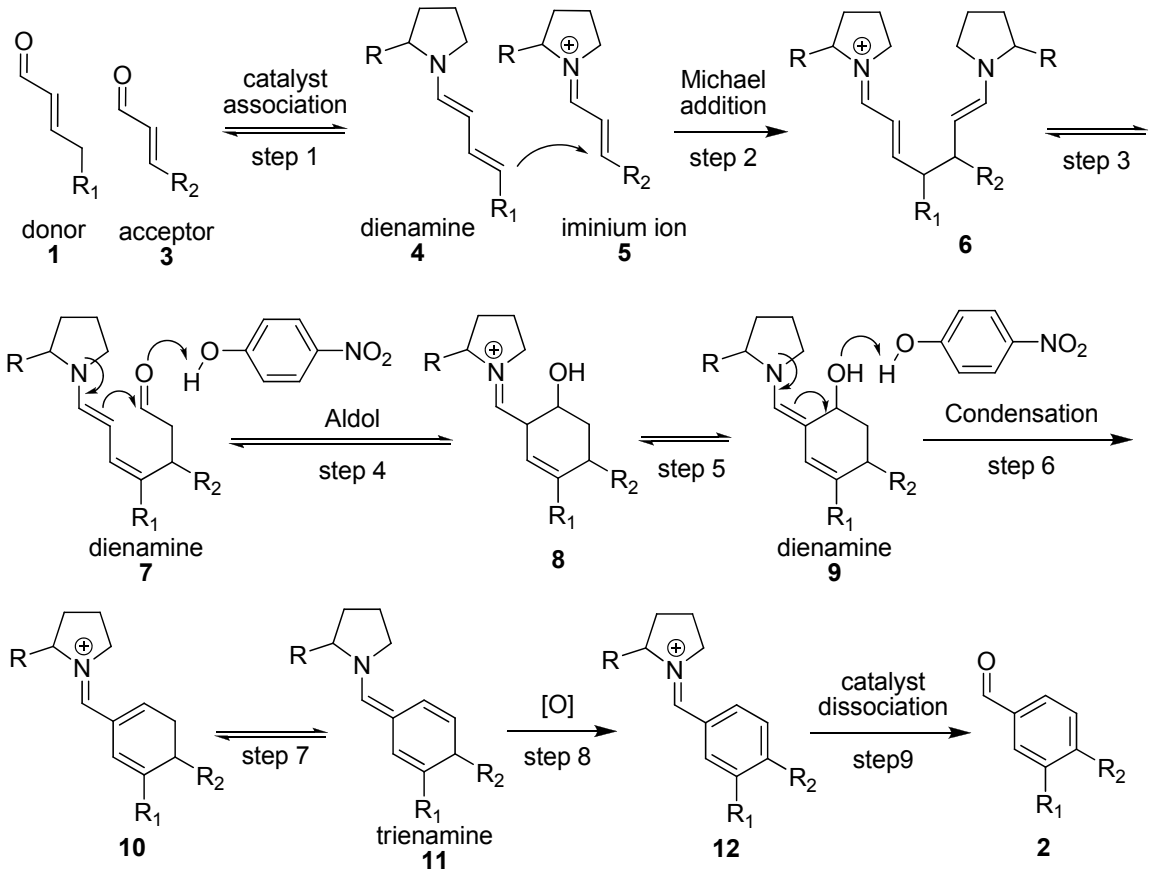
5.5. Investigation of Mechanism

While a mechanism for this transformation is unknown, we propose an amine catalyzed Michael-aldol condensation-aromatization cascade sequence (Scheme 5.2). Catalyst I**V** promoted formation of a dienamine species from a corresponding enal serves as a Michael donor for a conjugate addition reaction with an iminium ion derived from an enal as an acceptor.[40-44] The resulting Michael adduct **6** in the presence of *p*-nitrophenol initiates an intramolecular aldol condensation reaction to give intermediate **10** (steps 3-6). Finally, aromatization of the compound is achieved in the presence of the catalyst to furnish the target **2**. In these transformations several features are deserved to be pointed out. Similar to the reaction pathway proposed by Hong and coworkers in their [3+3]/[4+2] processes,[40-44] the amine activates both substrates for the initial Michael reaction, while an aldol condensation reaction, promoted by acidic *p*-nitrophenol, is proposed for the first time in the cascade sequence. Finally, the subsequent aromatization of the aldol condensation products **10** to final targets **2** occurs efficiently without requiring an additional oxidant. It seems that the catalyst **IV** plays critical and unique roles in these conversions involving multiple reversible iminium ion and enamine transformations.

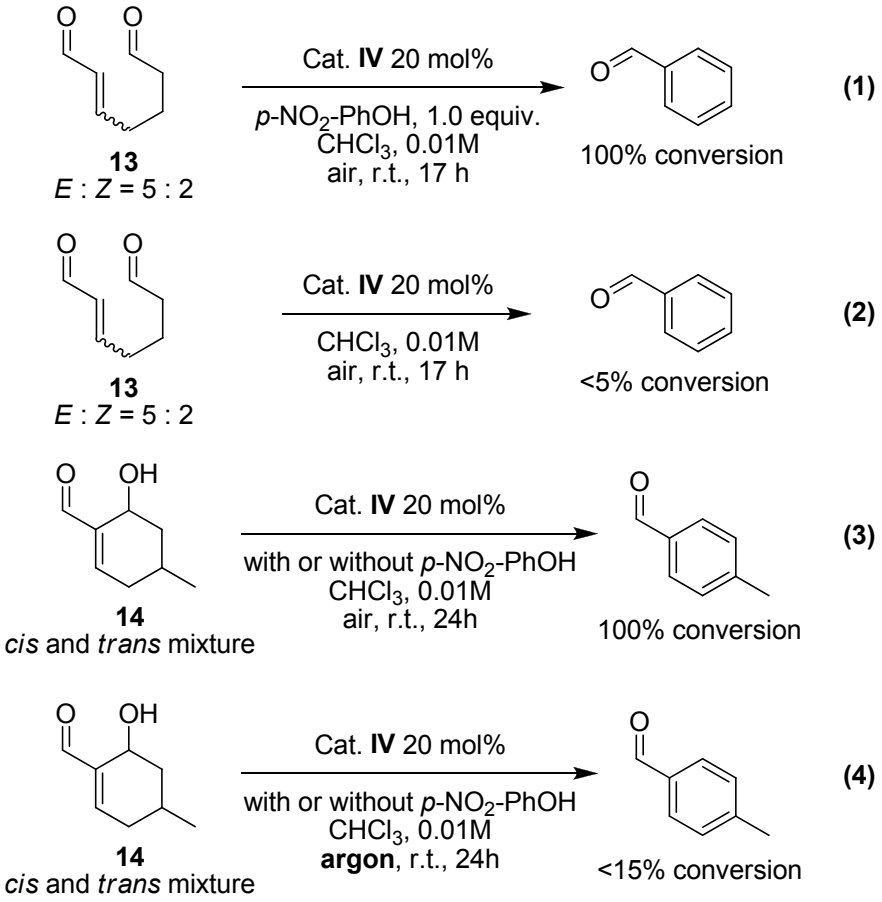
In order to verify the proposed reaction mechanism, we conducted a preliminary mechanistic investigation. In the proposed reaction pathway, two key intermediates **6** and **8** are involved (Scheme 5.2). Therefore two derivatives **13** and **14** were synthesized (Scheme 5.3). When compound **13** was submitted to the same reaction conditions in the presence of I**V** and *p*-nitrophenol, the expected aromatic product benzaldehyde was obtained in quantitative yield (eq. 1). However, a control experiment in the absence of *p*-nitrophenol could not produce the aromatic product, and reactant **13** was recovered (eq.

2). We concluded that *p*-nitrophenol participated in the aldol condensation reaction as a co-catalyst. However, compound **14** in the presence of catalyst I**V** with or without *p*-nitrophenol gave the anticipated product in full conversion (eq. 3). Moreover, without I**V**, almost no reaction occurred. These studies implied that catalyst I**V** was essential for the aromatization through iminium ion and enamine transformations. When the transformation was carried out in argon instead of in air, less than 15% conversion was observed (eq. 4). As a result, oxygen in the air was believed as the oxidant for the aromatization process.

Scheme 5.2. A proposed reaction mechanism



Scheme 5.3. Transformation of two key intermediate analogues **13** and **14** to aromatic compounds in the proposed reaction mechanism involving aldol condensation and aromatization processes



5.6. Summary

In conclusion, we have successfully transformed a "side reaction" discovered in our early study of the cross-coupling-like α-arylation process into a new valuable method for the facile construction of polysubstituted arenes from easily accessible enals. Notably, the cascade process can proceed via two different fashions of self-dimerization of the

same aliphatic enals and hetero-dimerization with two distinct enals regio- and chemoselectively. Polysubstituted arenes bearing a broad spectrum of functionalities are generated in "one-pot" with high yields under mild reaction conditions. Furthermore, an unprecedented highly efficient organocatalyzed Michael-aldol condensation-aromatization process was proposed and verified by preliminary mechanistic studies. The further exploration of the interesting chemistry for new organic transformation and understanding of the reaction mechanism are currently being pursued in our laboratory.

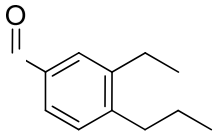
5.7. Experimental Section

General Information:

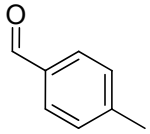
All commercially available reagents were used without further purification. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on Whatman silica gel plates with fluorescence F_{254} indicator. And Merck 60 silica gel was used for chromatography. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance 500. When deuteriorated chloroform ($CDCl_3$) was used to dissolve sample, tetramethylsilane (TMS) was used as an internal reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.

Procedure for synthesis of arenes 2

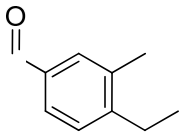
0.1 mmol of enal donor, 0.1 mmol of enal acceptor are dissolved in 2mL of chloroform, following with the addition of 0.2 mmol of p-nitrophenol and 0.04 mmol catalyst (20 % mol relative to the sum of enals). If donor enal and acceptor enal are the same, total amount of 0.2 mmol of the enal is used, and catalyst is 20 % mol relative to the same enal. The reaction mixture is stirred as room temperature, and the seal cap for the vial is loosely attached. After the enal was totally consumed (determined by TLC analysis), solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane.



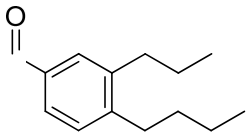
3-Ethyl-4-propylbenzaldehyde (2a, Table 5.2, entry 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.95 (s, 1H), 7.69 (s, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 2.70 (m, 4H), 1.64 (m, 2H), 1.26 (t, J = 12.5 Hz, 3H), 1.00 (t, J = 12.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.6, 148.1, 143.0, 134.9, 130.0, 129.7, 127.7, 35.2, 25.6, 24.1, 15.2, 14.4.



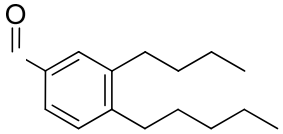
4-Methylbenzaldehyde (2b, Table 5.2, entry 2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.96 (s, 1H), 7.78 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 145.8, 134.5, 130.1, 130.0, 22.2.



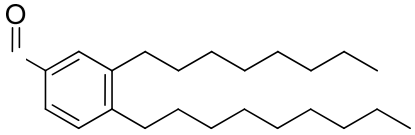
4-Ethyl-3-methylbenzaldehyde (2c, Table 5.2, entry 3). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.94 (s, 1H), 7.65 (m, 2H), 7.32 (d, J = 8Hz, 2H), 2.70 (q, J = 7.5 Hz, 2H), 2.38 (s, 3H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.6, 150.2, 137.1, 134.7, 131.4, 128.8, 128.2, 26.8, 19.4, 14.2.



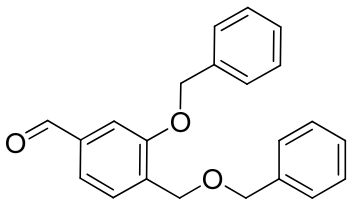
4-Butyl-3-propylbenzaldehyde (2d, Table 5.2, entry 4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.94 (s, 1H), 7.66 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 2.67 (m, 4H), 1.64 (m, 4H), 1.43 (m, 2H), 0.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ =192.7, 148.6, 141.5, 134.7, 130.7, 130.1, 127.7, 34.8, 33.3, 33.0, 24.3, 23.1, 14.4, 14.2.



3-Butyl-4-pentylbenzaldehyde (2e, Table 5.2, entry 5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.94 (s, 1H), 7.66 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 2.67 (m, 4H), 1.60 (m, 4H), 1.37 (m, 6H), 0.95 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.6, 148.6, 141.8, 134.7, 130.6, 130.0, 127.7, 33.4, 33.2, 32.4, 32.1, 30.9, 23.0, 22.8, 14.2.

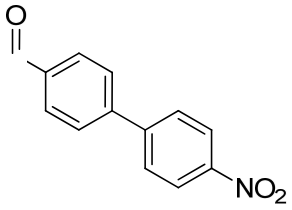


4-Nonyl-3-octylbenzaldehyde (2f, Table 5.2, entry 6). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.94 (s, 1H), 7.66 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 2.66 (m, 4H), 1.59 (m, 4H), 1.28 (m, 22H), 0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.6, 148.6, 141.8, 134.7, 130.6, 130.0, 127.7, 33.3, 32.8, 32.2, 31.3, 31.2, 30.0, 29.8, 29.6, 29.5, 22.9, 14.4.

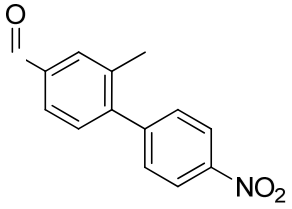


3-(Benzyloxy)-4-(benzyloxymethyl)benzaldehyde (2g, Table 5.2, entry 7). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.95 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H),

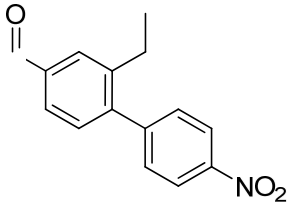
7.39 (m, 11H), 5.14 (s, 2H), 4.72 (s, 2H), 4.65 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 156.6, 138.4, 137.0, 136.6, 135.2, 128.9, 128.7, 128.4, 128.0, 127.6, 125.1, 109.7, 73.3, 70.4, 67.2.



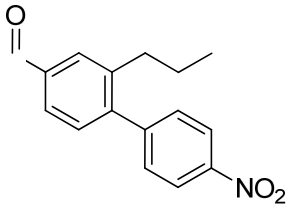
4'-Nitrobiphenyl-4-carbaldehyde (2h, Table 5.3, entry 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.10 (s, 1H), 8.35 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ =191.7, 147.8, 146.0, 144.5, 136.3, 130.5, 128.2, 128.1, 124.3.



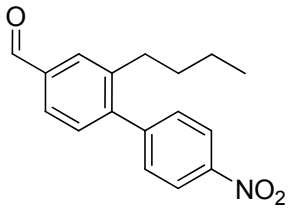
2-Methyl-4'-nitrobiphenyl-4-carbaldehyde (2i, Table 5.3, entry 2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.06 (s, 1H), 8.32 (m, 2H), 7.84 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.53 (m, 2H), 7.41 (d, J = 7.8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.1, 147.6, 145.8, 136.6, 136.4, 132.0, 130.4, 130.1, 127.7, 123.9, 20.5.



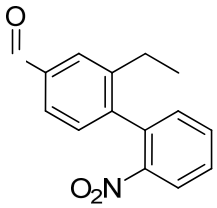
2-Ethyl-4'-nitrobiphenyl-4-carbaldehyde (2j, Table 5.3, entry 3). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.07 (s, 1H), 8.32 (m, 2H), 7.88 (m, 1H), 7.80 (m, 1H), 7.50 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 2.64 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 147.7, 145.6, 142.8, 136.8, 130.6, 130.4, 130.1, 127.6, 123.9, 26.3, 15.6.



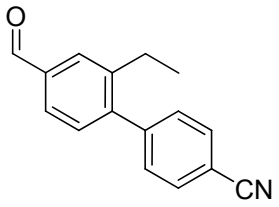
4'-Nitro-2-propylbiphenyl-4-carbaldehyde (2k, Table 5.3, entry 4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.07 (s, 1H), 8.32 (m, 2H), 7.86 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.50 (m, 2H), 7.36 (d, J = 7.8 Hz, 1H), 2.60 (q, J = 7.5 Hz, 2H), 1.53 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 147.8, 147.6, 145.8, 141.3, 136.6, 131.0, 130.6, 130.1, 127.5, 123.8, 35.1, 24.4, 14.1.



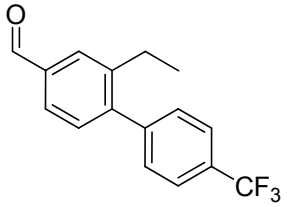
2-Butyl-4'-nitrobiphenyl-4-carbaldehyde (2l, Table 5.3, entry 5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.07 (s, 1H), 8.32 (m, 2H), 7.86 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.50 (m, 2H), 7.36 (d, J = 7.8 Hz, 1H)2.63 (m, 2H), 1.49 (m, 2H), 1.24 (m, 2H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 147.8, 147.6, 145.7, 141.6, 136.6, 131.0, 130.6, 130.1, 127.5, 123.8, 33.5, 32.8, 22.6, 14.0.



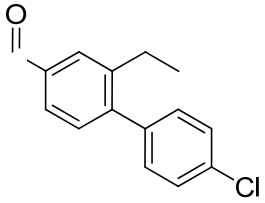
2-Ethyl-2'-nitrobiphenyl-4-carbaldehyde (2m, Table 5.3, entry 6). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.05 (s, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.86 (s, 1H), 7.72 (m, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 2.47 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.4, 148.6, 143.9, 142.8, 136.5, 135.7, 133.2, 132.0, 129.6, 129.5, 129.3, 127.5, 124.8, 26.3, 14.7.



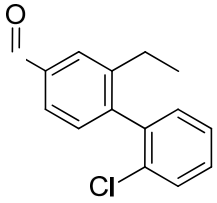
2'-Ethyl-4'-formylbiphenyl-4-carbonitrile (2n, Table 5.3, entry 7). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.06 (s, 1H), 7.87 (s, 1H), 7.77 (m, 3H), 7.45 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 2.63 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 146.0, 145.7, 142.7, 136.6, 132.4, 130.6, 130.3, 129.9, 127.8, 118.9, 111.9, 26.2, 15.5.



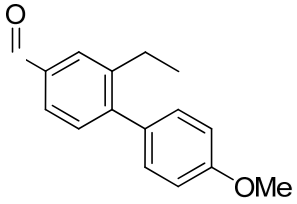
2-Ethyl-4'-(trifluoromethyl)biphenyl-4-carbaldehyde (2o, Table 5.3, entry 8). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.06 (s, 1H), 7.87 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.4, 146.6, 144.6, 142.9, 136.4, 130.8, 130.2, 129.5, 127.5, 125.6, 125.5, 26.3, 15.5.



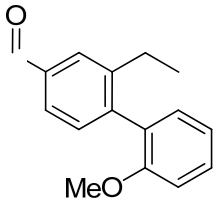
4'-Chloro-2-ethylbiphenyl-4-carbaldehyde (2p, Table 5.3, entry 9). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.04 (s, 1H), 7.83 (s, 1H), 7.73 (m, 1H), 7.40 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.24 (m, 2H), 2.64 (q, J = 8.5 Hz, 2H), 1.14 (t, J = 8.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.4, 146.9, 143.0, 139.4, 136.2, 134.0, 130.9, 130.2, 128.8, 127.5, 26.3, 15.5.



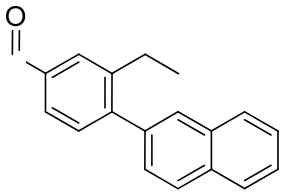
2'-Chloro-2-ethylbiphenyl-4-carbaldehyde (2q, Table 5.3, entry 10). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.06 (s, 1H), 7.85 (s, 1H), 7.76 (m, 1H), 7.49 (m, 1H), 7.30 (m, 3H), 7.22 (m, 1H), 2.50 (m, 2H), 1.12 (t, J = 8.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.5, 145.4, 143.7, 139.5, 136.5, 133.2, 130.9, 129.9, 129.6, 129.5, 127.4, 126.9, 26.3, 14.9.



2-Ethyl-4'-methoxybiphenyl-4-carbaldehyde (2r, Table 5.3, entry 11). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.0 (s, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 3.87 (s, 3H), 2.69 (q, J =7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.6, 159.4, 148.0, 143.1, 135.7, 133.3, 131.2, 130.2, 130.1, 127.4, 114.0, 55.6, 26.3, 15.6.

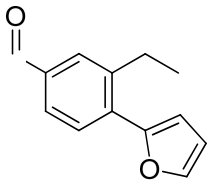


2-Ethyl-2'-methoxybiphenyl-4-carbaldehyde (2s, Table 5.3, entry 12). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.04 (s, 1H), 7.83 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.33 (m, 2H), 7.12 (d, J = 7.5 Hz, 1H), 7.00 (m, 2H), 3.74 (s, 3H), 2.53 (m, 2H), 1.10 (t, J = 8.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.7, 156.6, 145.2, 144.2, 136.0, 131.3, 130.8, 129.8, 129.5, 129.3, 127.3, 120.8, 111.0, 55.7, 26.2, 14.9.

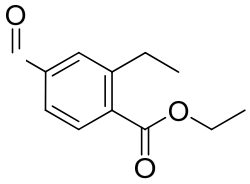


3-Ethyl-4-(naphthalen-2-yl)benzaldehyde (2t, Table 5.3, entry 13). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.07 (s, 1H), 7.88 (m, 4H), 7.78 (m, 2H), 7.53 (m, 2H), 7.45 (m, 2H), 2.71 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.6,

148.2, 143.2, 138.5, 136.0, 133.4, 132.8, 131.3, 130.2, 128.4, 128.0, 127.9, 1275, 127.2, 126.8, 126.6, 26.4, 15.6.



3-Ethyl-4-(furan-2-yl)benzaldehyde (2u, Table 5.3, entry 14). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.00 (s, 1H), 7.79 (m, 3H), 7.58 (s, 1H), 6.71 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 2.94 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.3, 152.5, 143.3, 141.6, 135.5, 131.0, 128.3, 127.6, 112.1, 110.9, 27.5, 14.8.



Ethyl 2-ethyl-4-formylbenzoate (2v, Table 5.3, entry 15). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.06 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.79 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 4.40 (q, J = 7.5 Hz, 2H), 3.03 (q, J = 7.5 Hz, 2H), 1.42 (t, J = 7.5 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.2, 167.4, 146.5, 138.5, 135.7, 131.4, 131.1, 126.9, 61.7, 27.6, 15.9, 14.5.

5.8. Reference

(1) Astruc, D. *Modern Arene Chemistry*; Wiley-VCH, Weinheim, **2002**.

(2) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210-1250.

(3) Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4808-4842.

(4) Thompson, L. A.; Ellman, J. A. *Chem. Re*v. **1996**, *96*, 555-600.

(5) March, J. *Advanced Organic Chemistry,* 4th ed.; Wiley: New York, **1992**; Chapter 11, pp 501-568.

(6) Lenir, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 854-857.

(7) Suwinski, J.; Swierczek, K. *Tetrahedron*, **2001**, *57*, 1639-1662.

(8) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.

(9) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

(10) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.

(11) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(12) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(13) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977.

(14) Newhouse, T.; Baran, P, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362.

(15) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000,** *100,* 2901-2915.

(16) Schore, N. E. *Chem. Rev.* **1988,** *88,* 1081-1119.

(17) Lautens, M.; Klute, W.; Tam, W. Chem. Rev. **1996,** 96, 49-92.

(18) Dotz, K. H.; Stendel, J. Jr. *Chem. Rev.* **2009,** *109,* 3227–3274.

(19) Otterlo, W. A. L.; Koning, C. B. *Chem. Rev.* **2009,** *109,* 3743–3782.

(20) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem. Eur. J.* **2008**, 14*,* 5716-5726.

(21) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2664-2670.

(22) Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.*, **2006**, *8*, 2217-2220.

(23) Hong, B.; Tseng, H.; Chen, S. *Tetrahedron*, **2007**, *63*, 2840-2850.

(24) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003,** *103,* 811-891.

(25) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009,** *109,* 1-48.

(26) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010,** *110,* 5447–5674.

(27) Bartok, M. *Chem. Rev.* **2010,** *110,* 1663–1705.

(28) Wei, Y.; Shi, M. *Acc. Chem. Res.*, **2010**, *43*, 1005-1018.

(29) Marcelli, T.; Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed*. **2006**, *45*, 7496-7504.

(30) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614-4628.

(31) Trost, B. M. *Science* **1991**, *254*, 1471.

(32) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(33) Jensen, K. J.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jorgensen, K. A. *Acc. Chem. Res.*, **2012**, DOI: 10.1021/ar200149w.

(34) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703-4832.

(35) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.*, **2005**, *7*, 4293-4296.

(36) Cabrera, S.; Aleman, J.; BOlze, P.; Bertelsen, S.; Jorgensen, K. A. Angew. Chem. Int. Ed. **2008**, *47*, 121-125.

(37) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem. Int. Ed.*, **2010**, *49*, 9725-9729.

(38) Liu, Y.; Wang, B.; Cao, J.; Chen, L.; Zhang, Y.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.*, **2010**, *132*, 15176-15178.

(39) Song, X.-X.; Song, A.-G.; Zhang, F.; Li, H.-X.; Wang, W. *Nat. Commun.* **2011**, *2*, 524, DOI: 10.1038/ncomms1541.

(40) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

(41) Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas III, C. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1878.

(42) Vesely, J.; Dziedzic, P.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6900.

(43) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.- C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474.

(44) Enders, D.; Yang, X.; Wang, C.; Raabe, G.; Runsik, J. *Chem. Asian J.* **2011**, *6,* 2255.

Chapter 6

Aminocatalytic Diels-Alder-retro-Diels-Alder Cascade Reaction of Alkynals and 2-Pyrones for the One-Pot Construction of Polysubstituted Salicylaldehyde Frameworks

6.1. Introduction to Polysubstituted Salicylaldehydes

Polysubstituted salicylaldehydes are key structural motifs for the construction of synthetically important Salen-ligands[1, 2] and pharmacologically essential natural products,[3-5] such as coumarins, flavones, and mycotoxins. The Reimer-Tiemann reaction, the direct electrophilic *ortho*-formylation of a suitable phenol derivative, is a traditional synthetic approach towards functionalized salicylaldehydes.[6] However, due to the electronic nature of phenolic substrates, when the *ortho*- and *para*-positions with respects to the hydroxyl functionality are not properly blocked, the electrophilic substitution process will furnish poor regioselectivity and chemoselectivity, and thus is restricted from practical application and less demanded by synthetic chemists.[1]

Moreover, the molecular framework of biphenyls is a privileged structure ubiquitously found in pharmaceuticals.[7] Analysis shows that 4.3% of all known drugs consist of the substructure.[7, 8] Due to the versatility in binding interactions of the aromatic moieties with biomolecules, not only do the compounds containing biphenyl framework have various distinct therapeutic properties, such as antiamebic, antifungal,

antihyperchloesteremic, analgesic and uricosuric, they are also known to possess promising potentials as antitumor, antihypertensive, and antiatherosclerotic agents.[7-12]

Recently, Tejedor and coworkers have discovered a microwave-assisted domino rearrangement process in preparation of polysubstituted biphenyl salicylaldehydes.[13] Nevertheless, since a series of pre-arranged complicated substrates is used to foster the intramolecular cycloaddition process under harsh reaction conditions with only moderate yields of desired products, the methodology suffers from the drawback of lack of generality. Herein, we would demonstrate an alternative organocatalytic Diels-Alder-retro-Diels-Alder cascade approach for the direct synthesis of polysubstituted salicylaldehydes containing biphenyl framework.

6.2. Diels-Alder-retro-Diels-Alder process

As for the construction of functionalized six-membered cyclic frameworks, the Diels-Alder reaction is one of the most powerful cycloaddition reactions. Although the synthetic application of Diels-Alder or retro-Diels-Alder reaction have already been respectively documented and reviewed, the strategy of Diels-Alder-retro-Diels-Alder tandem process is seldom systematically summarized or extensively elaborated.

Not only is the cascade methodology widely used in the construction of functionalized synthetic building blocks, such as pyridazines,[14] diaza-polycycles,[15] bipyridine thiamacrocycles,[16] naphtha[2,3-*c*]furan-4(9*H*)-ones[17] and trifluoromethylated olefins,[18] it has already been integrated in the total synthetic route towards nature products including Cycloproparadicicol,[19] Stemoamide,[20, 21] Furanosteroids,[22] *etc*.

Furthermore, the Diels-Alder-retro-Diels-Alder sequence is also a crucial activation mode in asymmetric catalysis, and it has already been employed in the enantioselective synthesis of chiral lactams,[23, 24] chiral allylic alcohols[25] and axially chiral bi-aryl compounds.[26]

6.3. Substrate Design

Recently, we have developed several novel asymmetric oxo-Michael tandemed reactions involving an unprecedented chiral iminium-allenamine cascade using alkynal substrates.[27, 28] Although alkynals were initially designed as a new class of easy-functionalizable oxo-philic Michael acceptor, its potency in direct multiple C-C bonds formation via cycloaddition protocol is attractive and still left uncharted. By employing LUMO-lowering strategy based on iminium activation of alkynals, a suitable diene with matched HOMO energy should be discovered via extensive screens.

After tremendous efforts, the dienes bearing the skeleton of 3-hydroxy-2-pyrone is unprecedentedly found to be readily reactive with various alkynals under the activation of aminocatalysts. 2-Pyrones are usually known as a kind of electron-deficient diene with weak aromatic property, which is relatively inert to participate in Diels-Alder reaction. Although the development of cycloaddition reaction with 2-pyrones as dienes is challenging, the distinct usefulness and synthetic importance of the bicyclic Diels-Alder adduct render the methodology worthy of further exploration.

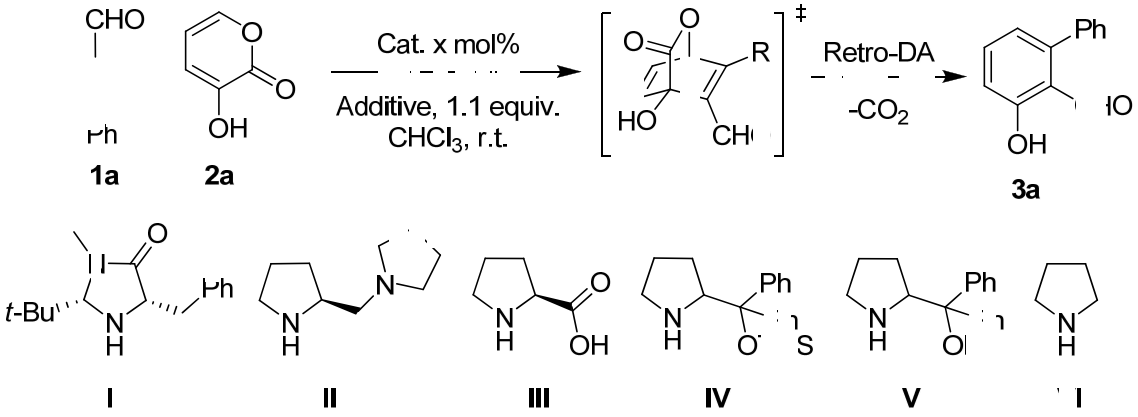
Actually, Deng and coworkers have already discovered asymmetric Diels-Alder reactions of various functionalized alkenes with 2-pyrones.[29, 30] It has been demonstrated

that various cinchona alkaloid-based bifunctional organic ctatlysts are highly effective for enantioselective and diasteroselective catalysis for the cycloaddition process. Additionally, Cho and coworkers have focused on polycarbocycle natural product synthesis via tandem Diels-Alder strategies using modified 2-pyrones.[31-36] Novel efficient synthetic route to galanthamine, aspidosperma alkaloid, pancratistatin, crinine-type alkaloids, and tetracyclolactones have been elaborated by using the tandem Diels-Alder cascade of various modified 2-pyrones as key strategies.

6.4. Optimization of Reaction Conditions

To demonstrate the feasibility of the proposed organocatalytic Diels-Alder reaction, we set up a model reaction between 3-hydroxy-2-pyrone **2a** and alkynal **1a** in the presence of 20 mol% secondary amines in chloroform at room temperature (Table 6.1). Although the [4+2] adduct **3a** was not observed, an aromatized salicylaldehyde derivative was received as final product. The structurally labile bicyclic [4+2] adduct could easily undergo retro-Diels-Alder process by losing a molecule of carbon dioxide. The releasing of ring string of the bridged bicyclic Diels-Alder adduct as well as the aromatization process provided a driving force for the cascade sequence.

Table 6.1. Optimization of secondary amine catalyzed Diels-Alder-retro-Diels-Alder cascade process[a]



entry	cat.	x (mol%)	solvent	additive	time (h)	yield (%)[b]
1	I	20	$CHCl_3$	-	42	0
2	II	20	$CHCl_3$	-	42	33
3	III	20	$CHCl_3$	-	42	39
4	IV	20	$CHCl_3$	-	42	41
5	V	20	$CHCl_3$	-	42	16
6	VI	20	$CHCl_3$	-	42	58
7	VI	20	$CHCl_3$	NaOAc	72	52
8	VI	20	$CHCl_3$	PhCOOH	72	<5
9	VI	20	$CHCl_3$	TEA	8	93
10	VI	20	$CHCl_3$	TEA	12	99
11	VI	10	$CHCl_3$	TEA	12	99
12	VI	5	$CHCl_3$	TEA	12	96
13	VI	2	$CHCl_3$	TEA	60	51

[a]Unless state otherwise, the reaction was carried out with alkynal (0.2 mmol), 3-hydroxy-2-pyrone (0.22 mmol), additive (0.22 mmol), and corresponding amount of catalyst in 2 mL of chloroform for a specified time. [b]Isolated yield.

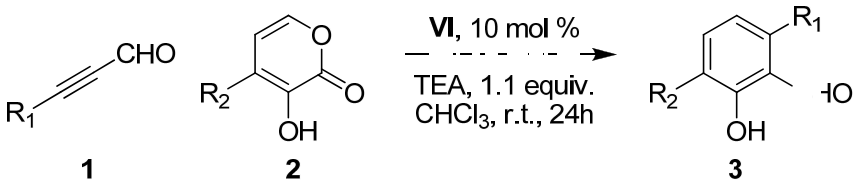
McMillan's 2nd generation catalyst provided no effect of catalysis (Table 6.1, entry 1). Both Barbas' catalyst and *L*-proline could drive the reaction to completion but with moderate yield (entries 2 and 3). While unprotected diphenylprolinol only produce 16% yield (entry 4), diphenylprolinol TMS ether give 41% yield (entry 5). The simple aminocatalyst, pyrrolidine, was found as an optimal catalyst, which provided 58% yield (entry 6). Solvent screening had provided the information that chloroform was the optimal one (data not shown here). When inorganic basic salt, such as sodium acetate, was added to reaction mixture, there was no significant change of yield (entry 7). If organic base was used, a large boost of yield was observed (entry 9). With the presence of triethyl amine as additive, the catalyst loading could be decreased to as low as 5% without significant interference of final yield.

6.5. Expansion of Substrate Scopes

After the optimal reaction conditions have been established, we further extend the substrate scope of the Diels-Alder-retro-Diels-Alder cascade reactions (Table 6.2). As demonstrated, a wide range of alkynals are suitable for the transformation. As for the aromatic alkynals, electronic donating groups would generate a slightly lower yield than alkynals with electronic withdrawing groups on phenyl ring (entries 2-6 v.s. entries 7-13).

The lower electronic density on the alkyne moiety would lower the LUMO energy of the dienophile and thus render a more efficient Diels-Alder transformation. Furthermore, aliphatic alkynals could also produce products in decent yields (entries 15 and 16).

Table 6.2. Substrates scope expansion of the Diels-Alder-retro-Diels-Alder cascade reactions[a]



1 2 3

entry	R_1	R_2	**3**	yield (%)[b]
1	Ph	H	**3a**	99
2	4-Me-Ph	H	**3b**	82
3	3-Me-Ph	H	**3c**	80
4	4-MeO-Ph	H	**3d**	86
5	3-MeO-Ph	H	**3e**	84
6	2-MeO-Ph	H	**3f**	89
7	4-Br-Ph	H	**3g**	91
8	4-Cl-Ph	H	**3h**	99
9	3-Cl-Ph	H	**3i**	98
10	2-Cl-Ph	H	**3j**	98
11	4-F-Ph	H	**3k**	95
12	4-NO_2-Ph	H	**3l**	99
13	4-CN-Ph	H	**3m**	83

14	2-thiophenyl	H	**3n**	83
15	C_5H_{11}	H	**3o**	85
16	THPO-CH_2-	H	**3p**	97
17	Ph	Allyl	**3q**	94
18	4-Cl-Ph	Allyl	**3r**	92
19	4-NO_2-Ph	Allyl	**3s**	90
20	Ph	Cl	**3t**	74
21	Ph	Br	**3u**	64

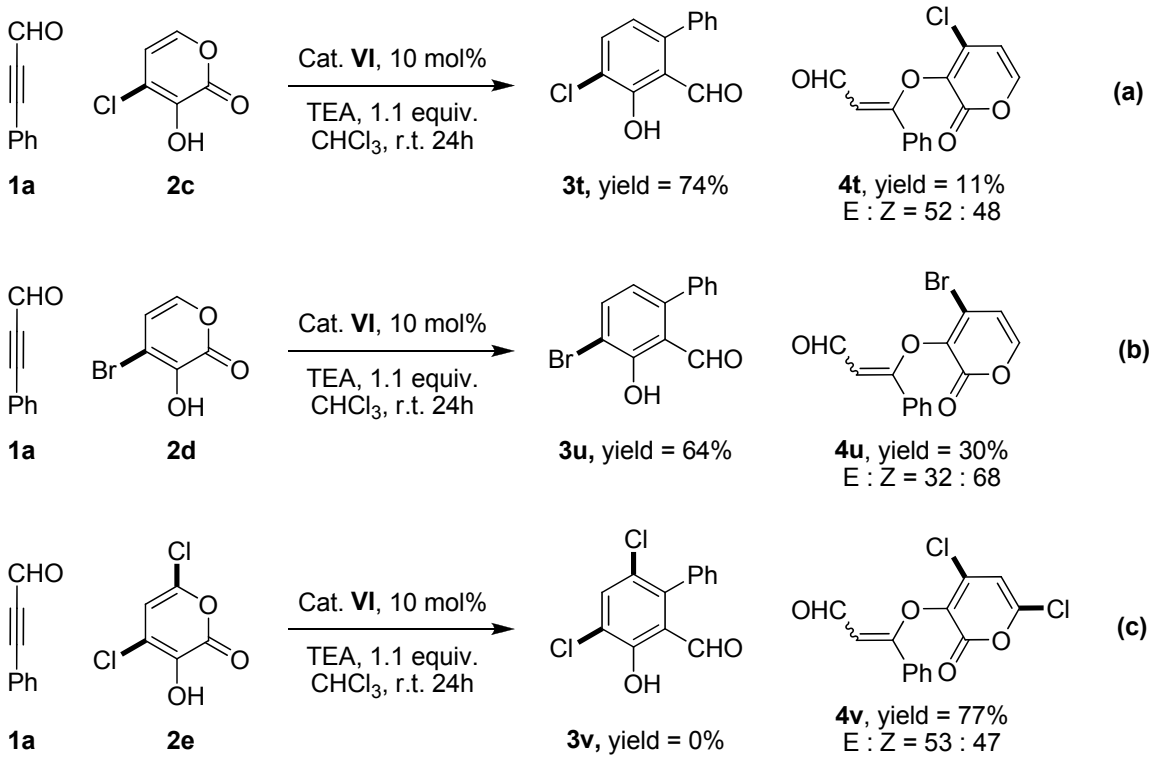
[a]Unless stated otherwise, the reaction was carried out with alkynal (0.2 mmol), 2-pyrone (0.22 mmol), TEA (0.22 mmol), and catalyst **VI** (0.02 mmol) in 2mL chloroform for 24 hours. [b]Isolated yield.

The electronic property of diene could be fine tuned via attaching different substituent group on 3-hydroxy-2-pyrone. An electronic donating group, such as allyl group, could raise the HOMO energy of the diene. As a result, 4-allyl-3-hydroxy-2-pyrone could undergo Diels-Alder process smoothly with various alkynals (Table 6.2, entries 17, 18 and 19). On the contrary, an electronic withdrawing group, such as halide, would decrease the reactivity of the diene via lowering the HOMO energy (entries 20 and 21).

In such circumstances, the Diels-Alder process pathway was interfered, and the *O*-Michael addition reaction became a major competitive side reaction (Scheme 6.1). Since the simple cyclic secondary amine, pyrrolidine, could not provide large steric hindrance than other bulkier secondary amines, poor *E/Z* ratio was observed in *O*-

Michael adducts. Additionally, if both 4- and 6- position of the 3-hydroxy-2-pyrone were substituted, the *O*-Michael addition process would overwhelmingly dominate over the Diels-Alder process, and the *O*-Michael adduct was obtained as the only products (equation c).

Scheme 6.1. The competition between Diels-Alder reaction and *O*-Michael addition reaction when electronic deficient dienes used



6.6. Summary

In conclusion, herein we present the first organocatalyzed [4+2] cycloaddition reaction of alkynals with modified 2-pyrones via Diels-Alder-retro-Diels-Alder cascade

process. By releasing carbon dioxide, the bicyclic Diels-Alder adduct was spontaneously collapsed to a class of polysubstituted salicylaldehydes which was difficult to construct using traditional synthetic methods. The operationally friendly one port reaction conditions and high efficiency for overall transformations render the process extremely attractive in the realm of organic synthesis and medicinal chemistry.

6.7. Experimental Section

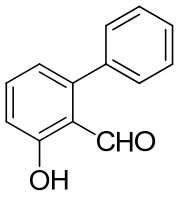
General Information:

All commercially available reagents were used without further purification. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on Whatman silica gel plates with fluorescence F_{254} indicator. And Merck 60 silica gel was used for chromatography. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance 500. When deuteriorated chloroform ($CDCl_3$) was used to dissolve sample, tetramethylsilane (TMS) was used as an internal reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.

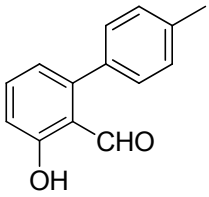
Typical procedure for the synthesis of salicylaldehyde derivatives

Alkynal (0.2 mmol,1 equiv.) and 0.24 mmol of diene (1.2 equiv.) were dissolved in 2 mL of chloroform. 0.22 mmol of triethylamine (1.1 equiv.) and 0.02 mmol of

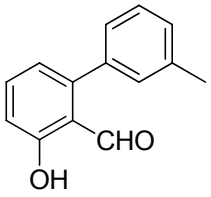
pyrrolidine (10 mol%) were added to the reaction mixture at room temperature. After the alkynal was totally consumed (determined by TLC analysis), the solvent was evaporated and the residue was purified by column chromatography, eluting with a mixture of ethyl acetate and hexane.



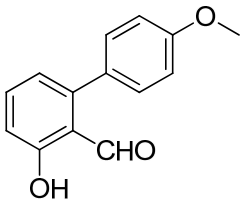
3-Hydroxybiphenyl-2-carbaldehyde (3a). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.90 (s, 1H), 9.84 (s, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.45 (m, 3H), 7.38 (m, 2H), 7.00 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.4, 163.1, 147.8, 137.8, 136.9, 130.4, 128.7, 128.6, 121.8, 118.4, 117.3.



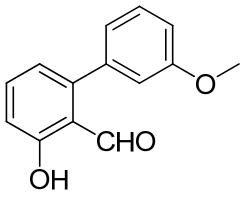
3-Hydroxy-4'-methylbiphenyl-2-carbaldehyde (3b). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.90 (s, 1H), 9.85 (s, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.27 (s, 4H), 6.97 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.6, 163.1, 147.9, 138.6, 136.9, 134.8, 130.3, 129.4, 121.8, 118.4, 117.0, 21.5.



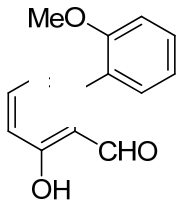
3-Hydroxy-3'-methylbiphenyl-2-carbaldehyde (3c). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.90 (s, 1H), 9.84 (s, 1H), 7.52 (t, J = 8.3 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 7.25 (m, 1H), 7.17 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.6, 163.0, 148.0, 138.5, 137.7, 136.9, 131.1, 129.3, 128.6, 127.5, 121.7, 118.3, 117.1, 21.7.



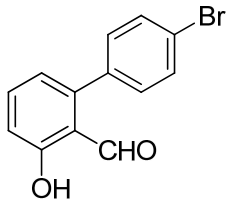
3-Hydroxy-4'-methoxybiphenyl-2-carbaldehyde(3d). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.90 (s, 1H), 9.86 (s, 1H), 7.51 (t, J = 7.5 Hz), 7.29 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.6, 163.2, 160.1, 147.6, 136.9, 131.6, 130.0, 121.8, 118.5, 116.8, 114.3, 55.7.



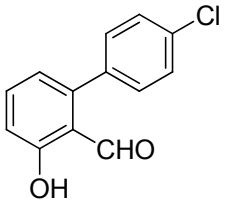
3-Hydroxy-3'-methoxybiphenyl-2-carbaldehyde (3e). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.90 (s, 1H), 9.85 (s, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 6.88-7.02 (m, 5H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.5, 163.0, 159.8, 147.6, 139.1, 136.8, 129.7, 122.9, 121.6, 118.3, 117.3, 116.0, 114.0, 55.7.



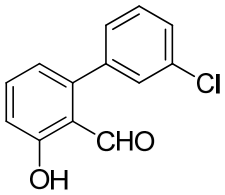
3-Hydroxy-2'-methoxybiphenyl-2-carbaldehyde (3f). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.74 (s, 1H), 9.63 (s, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.41 (td, J = 8.0, 1.5 Hz, 1H), 7.26 (dd, J = 7.5, 1.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.97 (dd, J = 8.0, 2.5 Hz, 2H), 6.80 (d, J = 7.5 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.0, 162.4, 156.7, 143.8, 136.9, 131.7, 130.4, 126.7, 122.2, 121.3, 118.3, 117.4, 111.0, 55.8.



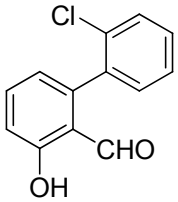
4'-Bromo-3-hydroxybiphenyl-2-carbaldehyde (3g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.89 (s, 1H), 9.82 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.9, 163.2, 146.3, 137.0, 136.6, 132.0, 131.8, 123.1, 121.7, 118.1, 117.7.



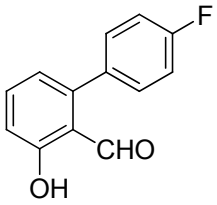
4'-Chloro-3-hydroxybiphenyl-2-carbaldehyde (3h). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.88 (s, 1H), 9.79 (s, 1H), 8.34 (d, J = 8.0 Hz, 2H), 7.57 (m, 3H), 7.08 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.0, 163.4, 148.1, 144.9, 144.4, 137.2, 131.2, 123.9, 121.6, 118.8, 118.0.



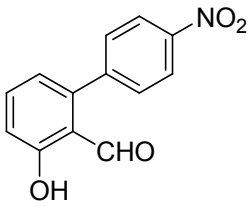
3'-Chloro-3-hydroxybiphenyl-2-carbaldehyde (3i). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.89 (s, 1H), 9.82 (s, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.41 (m, 3H), 7.25 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.9, 163.2, 146.0, 139.5, 137.0, 134.8, 130.2, 129.9, 128.8, 128.6, 121.7, 118.1, 117.9.



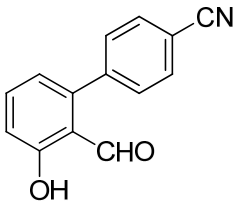
2'-Chloro-3-hydroxybiphenyl-2-carbaldehyde (3j). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.79 (s, 1H), 9.60 (s, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.48 (m, 1H), 7.37 (m, 3H), 7.04 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.8, 162.7, 144.2, 136.9, 136.6, 133.9, 131.9, 130.1, 129.9, 127.2, 121.9, 118.2.



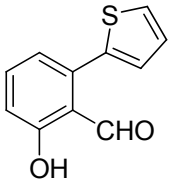
4'-Fluoro-3-hydroxybiphenyl-2-carbaldehyde (3k). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.90 (s, 1H), 9.82 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.35 (m, 2H), 7.16 (m, 2H), 7.00 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.1, 163.2, 146.6, 136.9, 131.9, 131.8, 121.8, 118.4, 117.5, 115.9, 115.7.



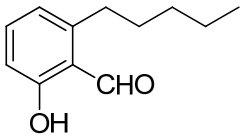
3-Hydroxy-4'-nitrobiphenyl-2-carbaldehyde (3l). ^{1}H NMR ($CDCl_3$,300 MHz): δ = 11.89 (s, 1H), 9.82 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.9, 163.2, 146.3, 136.9, 136.1, 134.9, 131.5, 128.9, 121.7, 118.2, 117.7.



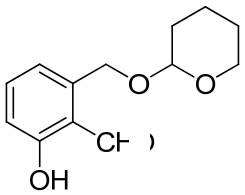
2'-Formyl-3'-hydroxybiphenyl-4-carbonitrile (3m). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.88 (s, 1H), 9.78 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.1, 163.4, 145.3, 142.5, 137.1, 132.5, 131.0, 121.6, 118.6, 117.9, 112.7.



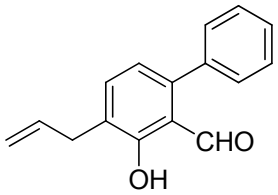
2-Hydroxy-6-(thiophen-2-yl)benzaldehyde (3n). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.92 (s, 1H), 10.07 (s, 1H), 7.48 (m, 2H), 7.14 (m, 1H), 7.09 (m, 1H), 7.01 (m, 2H), ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.2, 163.3, 139.7, 136.9, 129.8, 127.9, 127.7, 122.6, 118.6, 117.8.



2-Hydroxy-6-pentylbenzaldehyde (3o). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.89 (s, 1H), 10.31 (s, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 2.91 (m, 2H), 1.64 (m, 2H), 1.36 (m, 4H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.5, 163.7, 147.8, 137.7, 121.4, 118.1, 116.2, 33.2, 32.1, 31.9, 22.7, 14.2.

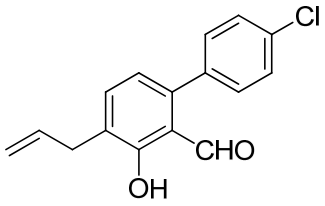


2-Hydroxy-6-((tetrahydro-2H-pyran-2-yloxy)methyl)benzaldehyde (3p). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.94 (s, 1H), 10.39 (s, 1H), 7.45 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.70 (m, 2H), 3.86 (m, 1H), 3.56 (m, 1H), 1.82 (m, 1H), 1.72 (m, 1H), 1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.6, 163.7, 141.6, 137.1, 121.3, 118.8, 118.5, 98.4, 66.4, 62.9, 30.8, 25.6, 19.6.

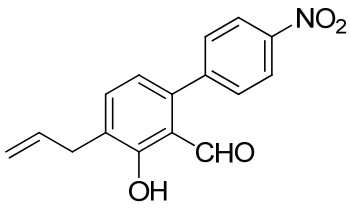


4-Allyl-3-hydroxybiphenyl-2-carbaldehyde (3q). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.82 (s, 1H), 7.43 (m, 4H), 7.33 (m, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.03 (m, 1H), 5.12 (m

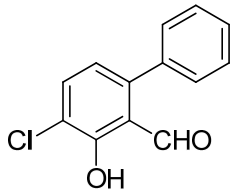
2H), 3.47 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.6, 160.9, 145.8, 137.8, 136.9, 130.4, 128.7, 128.4, 128.3, 121.4, 117.8, 116.6, 33.4.



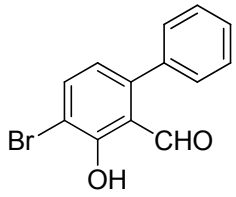
4-Allyl-4'-chloro-3-hydroxybiphenyl-2-carbaldehyde (3r). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.81 (s, 1H), 7.42 (m, 3H), 7.28 (m, 2H), 6.80 (d, J = 7.5 Hz, 1H), 6.01 (m, 1H), 5.13 (m, 2H), 3.47 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.1, 161.1, 144.4, 137.0, 136.3, 136.0, 134.8, 131.6, 128.9, 128.8, 121.3, 117.7, 116.7, 33.4.



4-Allyl-3-hydroxy-4'-nitrobiphenyl-2-carbaldehyde (3s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.79 (s, 1H), 8.33 (m, 2H), 7.56 (m, 2H), 7.47 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.03 (m, 1H), 5.17 (m, 2H), 3.50 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 196.2, 161.3, 148.0, 144.6, 142.9, 137.1, 135.7, 131.2, 130.2, 123.9, 121.3, 117.4, 117.0, 33.5.



4-Chloro-3-hydroxybiphenyl-2-carbaldehyde (3t). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.82 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.47 (m, 3H), 7.36 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 119.9, 81.3, 69.1, 59.4, 56.3, 53.0, 51.6, 44.7, 44.3, 41.6.



4-Bromo-3-hydroxybiphenyl-2-carbaldehyde (3u). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.80 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.49 (m, 3H), 7.38 (m, 2H), 6.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.1, 159.4, 147.2, 139.8, 136.8, 130.2, 129.0, 128.9, 122.6, 118.8, 110.6.

6.8. Reference

(1) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410-421.

(2) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071-3100.

(3) Das, S. G.; Doshi, J. M.; Tian, D.; Addo, S. N.; Srinivasan, B.; Hermanson, D. L.; Xing, C. *J. Med. Chem.* **2009**, *52*, 5937-49.

(4) Yoshida, M.; Fujino, Y.; Saito, K.; Doi, T. *Tetrahedron* **2011**, *67*, 9993-9997.

(5) Brase, S.; Encinas, A.; Keck, J.; Ni, C. F. *Chem. Rev.* **2009**, *109*, 3903-3990.

(6) Wynberg, H. *Chem. Rev.* **1960**, *60*, 169-184.

(7) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930.

(8) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443-3447.

(9) Bemis, G. W.; Murcko, M. A. *Drugs* **1996**, *2623*, 2887-2893.

(10) Henry, K. J.; Wasicak, J.; Tasker, a S.; Cohen, J.; Ewing, P.; Mitten, M.; Larsen, J. J.; Kalvin, D. M.; Swenson, R.; Ng, S. C.; Saeed, B.; Cherian, S.; Sham, H.; Rosenberg, S. H. *J. Med. Chem.* **1999**, *42*, 4844-4852.

(11) Augeri, D. J.; Janowick, D.; Kalvin, D.; Sullivan, G.; Larsen, J.; Dickman, D.; Ding, H.; Cohen, J.; Lee, J.; Warner, R.; Kovar, P.; Cherian, S.; Saeed, B.; Zhang, H.; Tahir, S.; Ng, S.-chung; Sham, H.; Rosenberg, S. H.; Laboratories, A.; Park, A. *Bioorganic & Medicinal Chemistry Letters* **1999**, *9*, 1069-1074.

(12) Mcgaughey, G. B.; Gagne, M.; Rappe, A. K. *Biochemistry* **1998**, *273*, 15458-15463.

(13) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; Ramirez, M.; García-Tellado, F. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2011**, *17*, 3318-3321.

(14) Xie, H.; Zu, L.; Oueis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1923-1926.

(15) Bromley, W. J.; Gibson, M.; Lang, S.; Raw, S. a.; Whitwood, A. C.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 6004-6014.

(16) Ławecka, J.; Karczmarzyk, Z.; Wolińska, E.; Olender, E.; Branowska, D.; Rykowski, A. *Tetrahedron* **2011**, *67*, 3098-3104.

(17) Piggott, M. J.; Wege, D. *Tetrahedron* **2006**, *62*, 3550-3556.

(18) De Matteis, V.; van Delft, F. L.; Jakobi, H.; Lindell, S.; Tiebes, J.; Rutjes, F. P. J. T. *J. Org. Chem.* **2006**, *71*, 7527-7532.

(19) Yang, Z.-Q.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602-9603.

(20) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295-4303.

(21) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409-3410.

(22) Sessions, E. H.; Jacobi, P. A. *Org. Lett.* **2006**, *8*, 4125-4128.

(23) Burgess, K. L.; Lajkiewicz, N. J.; Sanyal, A.; Yan, W.; Snyder, J. K. *Org. Lett.* **2005**, *7*, 31-34.

(24) Burgess, K. L.; Corbett, M. S.; Eugenio, P.; Lajkiewicz, N. J.; Liu, X.; Sanyal, A.; Yan, W.; Yuan, Q.; Snyder, J. K. *Bioorganic & medicinal chemistry* **2005**, *13*, 5299-309.

(25) Jones, S.; Valette, D. *Org. Lett.* **2009**, *11*, 5358-5361.

(26) Liu, Y.; Lu, K.; Dai, M.; Wang, K.; Wu, W.; Chen, J.; Quan, J.; Yang, Z *Org. Lett.* **2007**, *9*, 805-808.

(27) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem. Int. Ed.* **2010**, *49*, 1481-1484.

(28) Liu, C.; Zhang, X.; Wang, R.; Wang, W. *Org. Lett.* **2010**, *12*, 4948-4951.

(29) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364-6365.

(30) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422-2423.

(31) Nguyen, T. T.; Jung, E.; Cho, C. *Org. Lett.* **2010**, *12*, 2012-2014.

(32) Chang, J. H.; Kang, H.; Jung, I.; Cho, C. *Org. Lett.* **2010**, *12*, 2016-2018.

(33) Jung, Y.; Kang, H.; Cho, H.; Cho, C. *Org. Lett.* **2011**, *13*, 5890-5892.

(34) Pang, S.; Min, S.; Lee, H.; Cho, C. *J. Org. Chem.* **2003**, *68*, 10191-10194.

(35) Chung, S.; Seo, J.; Cho, C. *J. Org. Chem.* **2006**, *71*, 6701-6704.

(36) Tam, N. T.; Chang, J.; Jung, E; Cho, C. *J. Org. Chem.* **2008**, *73*, 6258-6264.

Chapter 7

Enantioselective Diels-Alder Reaction of Alkynals and 3-Hydroxy-2-Pyridones with a C_2 Symmetric Organocatalyst

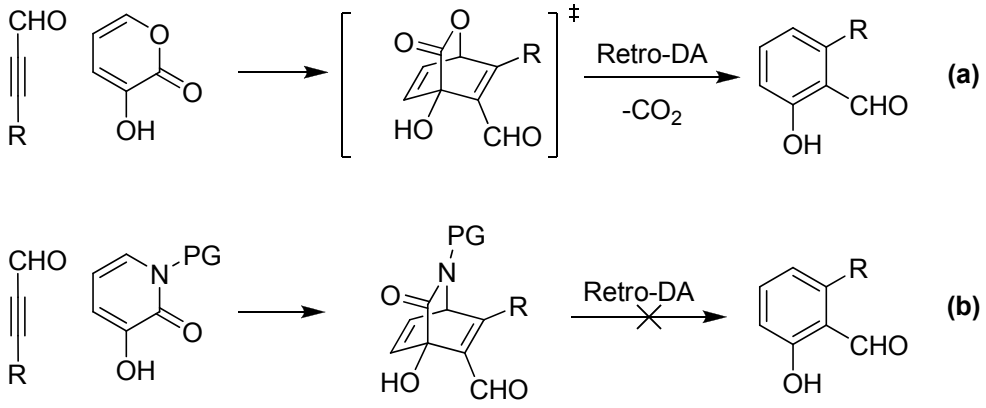
7.1. Introduction

Although Diels-Alder reaction has been extensively scrutinized and broadly applied in organic synthesis, few examples of alkynes as dienophiles in the cycloaddition methodology were documented.[1] The first enantioselective catalytic Diels-Alder reaction of dienes and acetylenic aldehydes had been discovered by Yamamoto and coworkers in 1997.[2] Corey and coworker also brought up the similar strategy in the same year.[3] In both methods, chiral boron catalysts activated the acetylenic aldehydes and provide the asymmetric recognition of the carbonyl face of the acetylenic dienophiles. Hilt and coworkers also developed a regio-selective Diels-Alder reaction of both non-activated and silicon-functionalized alkynes.[4, 5] Cobalt centered metal complexes are also used as efficient catalysts to produce dihydro-aromatic Diels-Alder adducts in good chemo-selectivity. After MacMillan and coworkers had discovered the first enantioselective organocatalytic Diels-Alder reaction as early as in 1999,[6] the same research group has successfully integrated the Diels-Alder reaction of propynal in an enantioselective catalytic cascade sequence to assemble the core structure of (+)-Minfiensine.[7] As a result, a more general methodology of enantioselective organocatalytic Diels-Alder reaction of acetylenic aldehydes is still in urgent need for the further development of modern organic chemistry.

7.2. Substrate Design

Previously, we have discovered an amine catalyzed Diels-Alder-retro-Diels-Alder cascade process of alkynals and 3-hydroxy-2-pyrone (Scheme 7.1, equation a). The [2, 2, 2] bicyclic Diels-Alder adduct was not stable enough to be isolated, and the bicyclic rings could break down and produce the final aromatic salicylaldehydes by releasing a carbon dioxide. In order to strengthen the bicyclic ring system and prevent it from collapsing, the oxygen atom in the ring should be substituted by a protected nitrogen atom (equation b). As a result, the diene designated for the Diels-Alder process should be changed from 3-hydroxy-2-pyrone to *N*-protected 3-hydroxy-2-pyridone accordingly.

Scheme 7.1. Diels-Alder process of acetylenic aldehydes



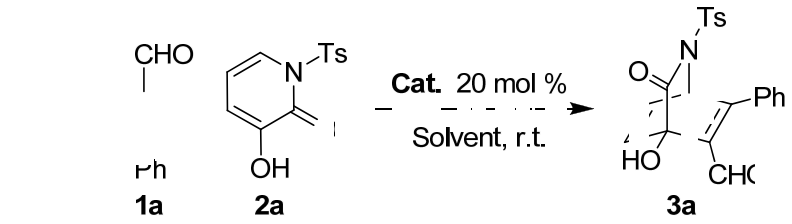
7.3. Optimization of Reaction Conditions

In order to optimize reaction conditions, a model reaction of alkynal **1a** and *N*-protected 3-hydroxy-2-pyridone **2a** was set up for further exploration (Table 7.1).

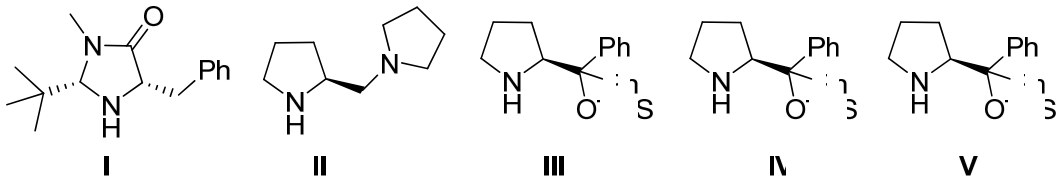
Various aminocatalysts were screened at first (entries 1-9). McMillan's 2nd generation catalyst **I** could not activate alkynal for any transformation, and both reactants were left untouched after two days (entry 1). The expected Diels-Alder adduct **3a** was received when Barbars' catalyst **II** was used, but the catalyst provided no stereoselectivity (entry 2). A series of diphenyl prolinol silyl ethers could drive the Diels-Alder reaction to completion with moderate to good yields and medium enantioselectivities (entries 3-5). Interestingly, increasing the steric hindrance by using larger silane protecting groups, such as from TMS to TES or TBS, decreased the effect of stereo-control of the chiral aminocatalyst, and the enantiomeric excess of the product **3a** decreased from 80% (entry 3) to 78% (entry 4) and 66% (entry 5). To our delight, when a C_2 symmetric aminocatalyst **VI** was chose to mediate the Diels-Alder transformation, excellent stereoselectivity was obtained (entry 6). However, a different class of C_2 symmetric aminocatalyst could not provide similar ability of stereo-control (entries 7-9). Various *N*-protecting groups were also screened, and the toluenesulfonic (Ts) was selected as an optimal one (data not shown here).

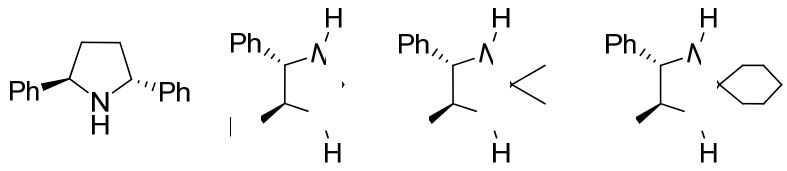
After chiral C_2 symmetric 2, 5-diphenylpyrroildine **VI** was selected as optimal organocatalyst, solvents were screened (entries 10-16). When dichloroethane was used, the Diels-Alder adduct could be obtained with 65% yield and 98% enantiomeric excess (entry 11). Addition of triethylamine could increase the efficiency of the overall transformation (entry 17). And the decrease of the reaction temperature to -20 °C could result in an excellent yield of as high as 95% with the retention of enantioselectivity (entry 18).

Table 7.1. Reaction Condition Optimization of Enantioselective Diels-Alder reaction of Alkynal **1a**[a]



Cat.





entry	cat.	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**I**	$CHCl_3$	48	0	nd[d]
2	**II**	$CHCl_3$	12	47	0
3	**III**	$CHCl_3$	12	73	80
4	**IV**	$CHCl_3$	12	56	78
5	**V**	$CHCl_3$	12	61	66
6	**VI**	$CHCl_3$	12	54	94
7	**VII**	$CHCl_3$	12	41	16
8	**VIII**	$CHCl_3$	12	<5	nd[d]
9	**IX**	$CHCl_3$	12	29	28
10	**VI**	CH_2Cl_2	12	48	95
11	**VI**	DCE	12	65	98

12	**VI**	Toluene	12	51	83
13	**VI**	THF	12	53	94
14	**VI**	Et_2O	12	7	94
15	**VI**	MeOH	12	13	96
16	**VI**	DMF	12	34	90
17[e]	**VI**	DCE	6	66	98
18[e, f]	**VI**	DCE	48	95	97

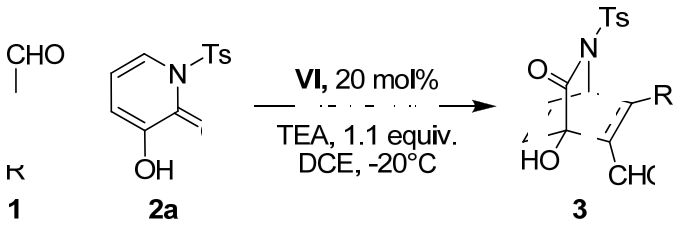
[a]Unless state otherwise, the reaction was carried out with alkynal **1a** (0.2 mmol), 3-hydroxy-2-pyridone **2a** (0.22 mmol), and catalyst (0.04 mmol, 20 mol%) in 2mL solvent for a specified time. [b]Isolated yield. [c]Enantioselective excess determined by chiral HPLC. [d]Not determined. [e]Triethyl amine (0.22 mmol) was added to the reaction mixture before catalyst was added. [f]Reaction mixture was cooled to -20 °C before catalyst was added.

7.4. Expansion of Substrate Scopes

After the optimal reaction conditions were determined, further expansion of substrate scope was carried out (Table 7.2). Alkynals with neutral aromatic substituents could provide desired Diels-Alder adducts with almost quantitative yields and excellent enantioselectivities (entries 1 and 2). Similarly, aromatic alkynals with electronic donating groups on phenyl ring could also generate the bicyclic products with decent results (entries 3-7). And the positions of the substituents, such as *para*- (entries 3 and 6), *meta*- (entries 4 and 7) or *ortho*- (entry 5), did not interfere with the activation and stereo-control of substrates. Meanwhile, the Diels-Alder reaction of alkynal substrates with poor electronic withdrawing groups could also proceed smoothly (entries 8 and 9). The

absolute configuration of the bicyclic Diels-Alder adduct **3h** was determined by X-ray crystal structural analysis (Figure 7.1).

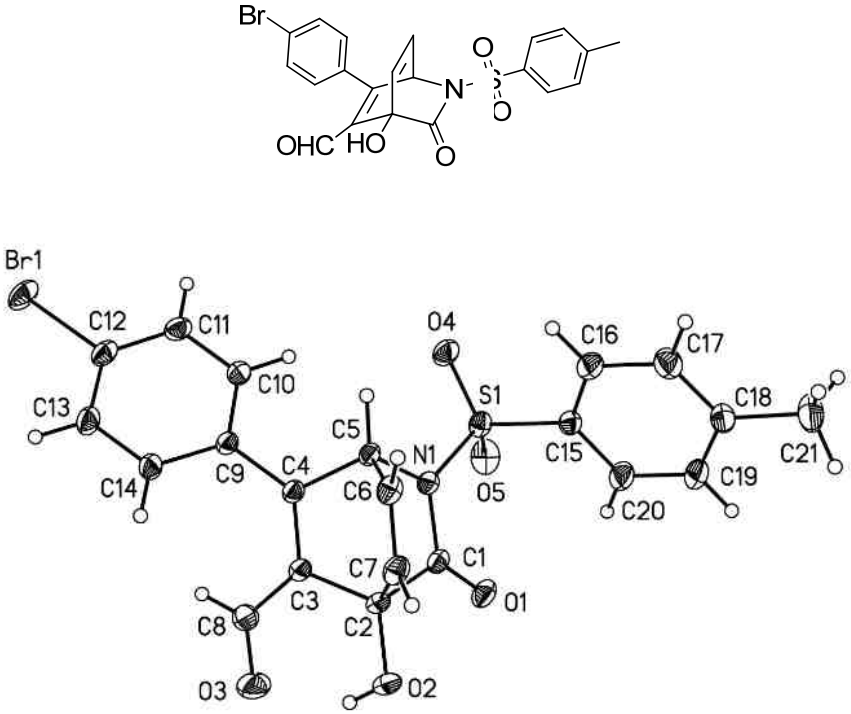
Table 7.2. Substrate Scope Expansion of Enantioselective Diels-Alder reaction of Alkynal **1**[a]



entry	R	time (day)	3	yield (%)[b]	ee (%)[c]
1	Ph	2	**3a**	95	97
2	2-Thiophenyl	2	**3b**	99	99
3	4-MeO-Ph	3	**3c**	92	98
4	3-MeO-Ph	3	**3d**	89	98
5	2-MeO-Ph	3	**3e**	87	98
6	4-Me-Ph	3	**3f**	93	98
7	3-Me-Ph	3	**3g**	94	99
8	4-Br-Ph	2	**3h**	90	99
9	4-Cl-Ph	2	**3i**	90	99

[a]Unless state otherwise, the reaction was carried out with alkynal **1** (0.2 mmol), 3-hydroxy-2-pyridone **2a** (0.22 mmol), triethylamine (0.22 mmol), and catalyst (0.04 mmol, 20 mol%) in 2mL solvent at -20 °C for a specified time. [b]Isolated yield. [c]Enantioselective excess determined by chiral HPLC.

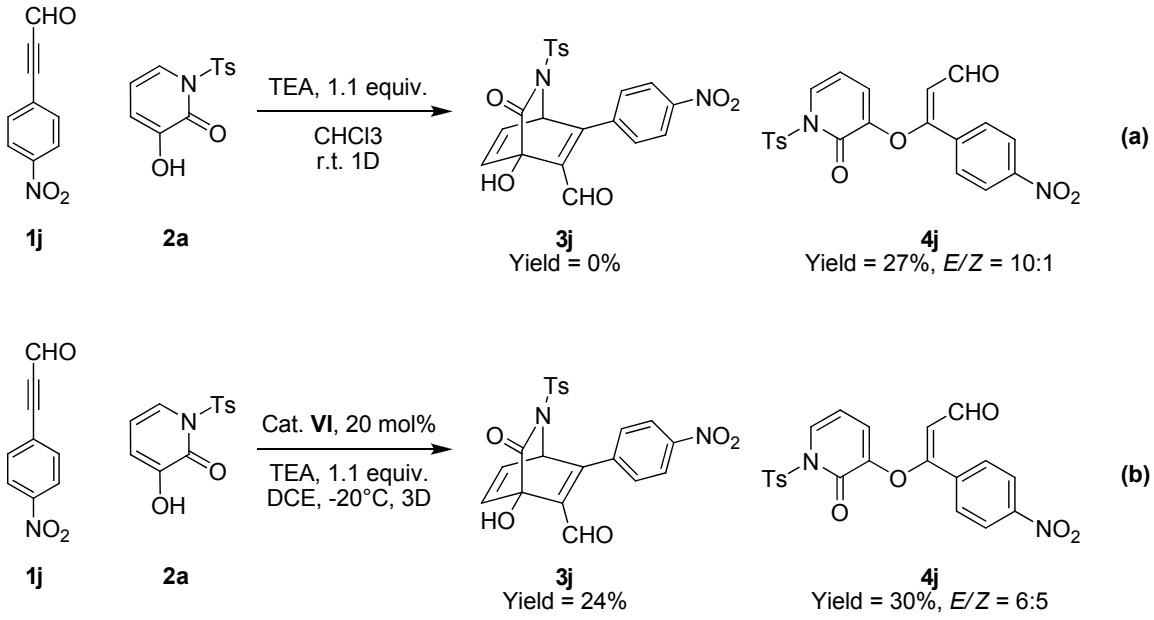
Figure 7.1. Single X-ray crystal structure of **3h** at probability ellipsoids of 20%



Furthermore, when a strong electronic withdrawing group, such as nitro group, was attached on the phenyl ring of aromatic alkynal, a side reaction of oxo-Michael addition would take place (Scheme 7.2). The oxo-Michael addition reaction of 3-hydroxy-2-pyridone to alkynal **1j** could proceed even without the activation of aminocatalyst, and the additive of triethylamine could mediate the background reaction with the yield of 27% of Michael adduct **4j** (Scheme 7.2, equation a). When the C2 symmetric catalyst **VI** was used, both the desired Diels-Alder reaction and the background oxo-Michael addition occurred at the same time (equation b). Moreover, when the 3-hydroxy-2-pyridone diene was substituted, the oxo-Michael addition reaction

would dominate over the Diels-Alder reaction, and only oxo-Michael adduct was received (data not shown here).

Scheme 7.2. The competition between the oxo-Michael addition pathway and the Diels-Alder pathway using alkynal **1j**



7.5. Summary

The enantioselective Diels-Alder reaction of various alkynals with a C_2 symmetric organocatalyst was established. Compared with the cascade process developed in Chapter 6, the decomposition of the bicyclic Diels-Alder adduct via the route of retro-Diels-Alder mechanism was prevented by switch the diene from 3-hydroxy-2-pyrone to *N*-protected 3-hydroxy-2-pyridine. The chiral organocatalyst **VI** with C_2 symmetry was identified as an effective aminocatalyst for acetylenic aldehyde substrates. Additionally, when

alkynals containing strong electronic withdrawing substituent groups were used as dienophiles, the side reaction of oxo-Michael addition could compete with the Diels-Alder reaction.

7.6. Experimental Section

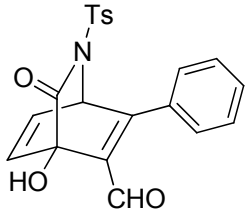
General Information:

All commercially available reagents were used without further purification. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on Whatman silica gel plates with fluorescence F_{254} indicator. And Merck 60 silica gel was used for chromatography. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance 500. When deuteriorated chloroform ($CDCl_3$) was used to dissolve sample, tetramethylsilane (TMS) was used as an internal reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.). Enantiomeric excess was determined by HPLC with a Chiralpak column, compared with racemic isomer.

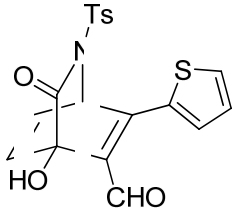
Typical procedure for the synthesis of

0.2 mmol of alkynal (1 equiv.) and 0.24 mmol of diene (1.1 equiv.) were dissolved in 2 mL of DCE (dichloroethane) and were cooled to $-20^{0}C$. Following with

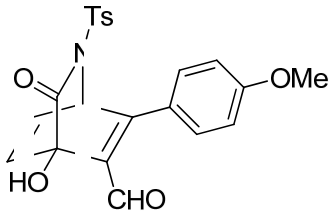
0.22 mmol of triethylamine (1.1 equiv.), 0.02 mmol of catalyst **VI** (20% mol) was added to the reaction mixture at -20 ^{0}C. After the alkynal was totally consumed (determined by TLC analysis), the solvent was evaporated and the residue was purified by column chromatography eluting with a mixture of diethyl ether and dichloromethane within 20 min at room temperature. The product solution was carefully evaporated at -20 ^{0}C within 60 min.



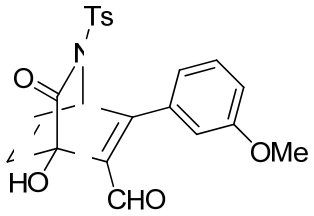
(1R,4R)-4-hydroxy-3-oxo-7-phenyl-2-p-tolyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3a). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.67 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.56 (m, 5H), 7.28 (d, J = 8.0 Hz, 2H), 6.79 (dd, J = 7.0 1.5 Hz, 1H), 6.64 (t, J = 6.5 Hz, 1H), 6.31 (s, 1H), 6.24 (d, J = 6.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 183.4, 161.2, 154.7, 138.5, 136.4, 127.4, 124.6, 124.5, 122.6, 122.2, 122.1, 121.1, 120.9, 78.5, 52.2, 22.6; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 38.13 min, t_{minor} = 55.59 min, ee = 97%.



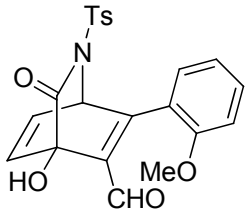
(1R,4R)-4-hydroxy-3-oxo-7-(thiophen-2-yl)-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3b). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.03 (s, 1H), 7.75 (m, 4H), 7.26 (m, 3H), 6.80 (dd, J = 6.5 1.5 Hz, 1H), 6.67 (t, J = 6.5 Hz, 1H), 6.38 (dd, J = 6.5 1.5 Hz, 1H), 6.14 (s, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 189.8, 168.6, 152.2, 145.9, 143.7, 134.5, 134.4, 133.4, 132.9, 129.9, 129.3, 128.3, 85.4, 59.5, 21.9; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 60.39 min, t_{minor} = 70.30 min, ee = 99%.



(1R,4R)-4-hydroxy-7-(4-methoxyphenyl)-3-oxo-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3c). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.63 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 6.5 Hz, 1H), 6.62 (t, J = 6.5 Hz, 1H), 6.53 (s, 1H), 6.24 (d, J = 6.5 Hz, 1H), 3.90 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.9, 168.6, 162.9, 162.2, 145.8, 143.7, 134.7, 133.9, 131.6, 129.9, 129.3, 128.2, 124.2, 115.1, 85.8, 59.2, 55.9, 21.9; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 41.41 min, t_{minor} = 61.13 min, ee = 98%.

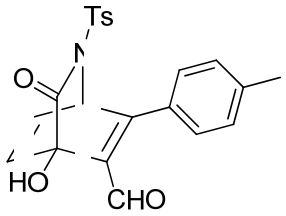


(1R,4R)-4-hydroxy-7-(3-methoxyphenyl)-3-oxo-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3d). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.69 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 3H), 6.78 (d, J = 6.0 Hz, 1H), 6.63 (t, J = 6.0 Hz, 1H), 6.37 (s, 1H), 6.22 (d, J = 6.0 Hz, 1H), 3.88 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.9, 168.5, 161.9, 160.3, 145.9, 143.7, 136.4, 134.7, 133.2, 130.6, 129.5, 128.2, 121.9, 117.7, 114.5, 85.9, 59.5, 55.6, 21.9; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 34.65 min, t_{minor} = 50.34 min, ee = 98%.

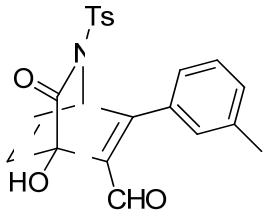


(1R,4R)-4-hydroxy-7-(2-methoxyphenyl)-3-oxo-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3e). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.54 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.51 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 6.99 (m, 3H), 6.74 (m, 1H), 6.70 (m, 1H), 6.27 (s, 1H), 6.21 (m, 1H), 3.95 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.8, 168.9, 161.9, 158.0, 145.6, 142.9, 137.5, 135.1, 133.1, 132.1 130.7, 129.8, 128.4, 120.9, 120.7, 111.7, 85.5, 59.3, 55.9, 21.9; HPLC (Chiralpack AS-H, *i*-

PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 31.86 min, t_{minor} = 44.55 min, ee = 98%.

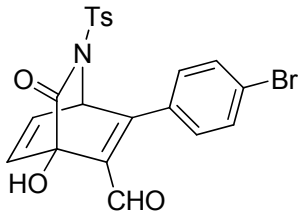


(1R,4R)-4-hydroxy-3-oxo-7-p-tolyl-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3f). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.65 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.77 (dd, J = 6.5 1.5 Hz, 1H), 6.63 (t, J = 6.5 Hz, 1H), 6.43 (s, 1H), 6.23 (dd, J = 6.5 1.5 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.9, 168.6, 162.4, 145.8, 143.7, 142.8, 135.3, 134.7, 130.3, 129.9, 129.6, 129.4, 129.0, 128.2, 85.8, 76.9, 59.4, 21.9, 21.8; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 34.57 min, t_{minor} = 49.45 min, ee = 98%.

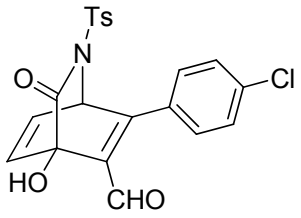


(1R,4R)-4-hydroxy-3-oxo-7-m-tolyl-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3g). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.65 (s, 1H), 7.82 (d, J = 8.5 Hz,

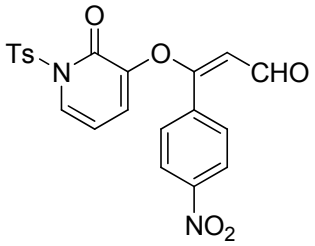
2H), 7.39 (m, 2H), 7.28 (m, 4H), 6.77 (dd, J = 6.5 1.5 Hz, 1H), 6.63 (t, J = 6.5 Hz, 1H), 6.38 (s, 1H), 6.22 (dd, J = 6.5 1.5 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 191.0, 168.6, 162.4, 145.9, 143.6, 139.5, 136.0, 134.8, 132.7, 131.9, 130.0, 129.9, 129.5, 129.4, 128.2, 126.7, 85.9, 76.9, 59.5, 21.9, 21.6; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 27.81 min, t_{minor} = 43.72 min, ee = 99%.



(1R,4R)-7-(4-bromophenyl)-4-hydroxy-3-oxo-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3h). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.66 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 6.0 Hz, 1H), 6.63 (t, J = 6.0 Hz, 1H), 6.18 (m, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.2, 168.4, 160.3, 146.1, 143.7, 136.9, 134.6, 132.9, 130.9, 130.1, 129.4, 128.2, 126.7, 85.9, 59.3, 53.7, 21.9; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 35.35 min, t_{minor} = 44.73 min, ee = 98%.



(1R,4R)-7-(4-chlorophenyl)-4-hydroxy-3-oxo-2-tosyl-2-azabicyclo[2.2.2]octa-5,7-diene-8-carbaldehyde (3i). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.67 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 6.0 Hz, 1H), 6.63 (t, J = 6.0 Hz, 1H), 6.16 (d, J = 6.0 Hz, 1H), 6.12 (s, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.1, 168.4, 160.1, 146.1, 143.8, 138.4, 137.0, 134.7, 130.7, 130.5, 130.1, 129.9, 129.4, 128.3, 85.9, 59.5, 21.9; HPLC (Chiralpack AS-H, *i*-PrOH/Hexane = 40/60, flow rate = 0.6 mL/min, λ = 254 nm): t_{major} = 32.09 min, t_{minor} = 38.36 min, ee = 99%.



(E)-3-(4-nitrophenyl)-3-(2-oxo-1-tosyl-1,2-dihydropyridin-3-yloxy)acrylaldehyde (4j). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.39 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.0 Hz, 2H), 8.10 (dd, J = 7.5 1.8 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.27 (dd, J = 7.5 1.8 Hz, 1H), 6.33 (t, J = 7.5 Hz, 1H), 5.48 (d, J = 7.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 190.8, 171.7, 155.0, 149.6, 147.3,

144.3, 137.7, 132.9, 131.7, 130.9, 130.2, 130.1, 130.0, 129.8, 128.5, 126.7, 124.0, 123.7, 110.9, 104.8, 22.1.

7.7. Reference

(1) Kobayashi, S.; Jorgensen, K. A. (Eds.); Hayashi, Y. *Cycloaddition Reactions in Organic Synthesis*, **2001**, *Chapter 1*, Wiley-VCH Verlag GmbH.

(2) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H.; Ohashi, S.; Inagaki, S. *J. Org. Chem.* **1997,** *62,* 3026-3027.

(3) Corey, E. J.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 5755-5758.

(4) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 5204-5206.

(5) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773-776.

(6) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 4243-4244.

(7) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606-13607.