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Alkynal involved organocatalytic reactions

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ALKYNAL INVOLVED ORGANOCATALYTIC REACTIONS

by

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ABSTRACT

During the past twenty years, vast progress has been achieved in the field of organocatalysis. One of the fruitful areas is iminium catalysis using α, β-unsaturated aldehydes as essential reactants. Enals involved enantioselective reactions (including single-step reactions and cascade/tandem reactions) represent an enormous and fruitful research branch. In contrast, the protocols for the corresponding alkynals, even in single-step conjugate addition reactions, are extremely rare.

Toward this end, my Ph. D research work mainly focuses on the development of alkynal involved organocatalytic reactions and expands the scope of organocatalysis by uncovering new activation modes. Unlike enals, ynals with sp hybridized C≡C bonds are much less studied and the related chemistries are much less understood. Within the context, firstly, we have developed an organocatalytic regio- and stereoselective Michael additions of 1*H*-1, 2, 3-triazole to alkynals which afford the trisubstituted alkenes. It is found that the reaction conditions are critical for the 1- vs 2-isomers. Furthermore, we have discovered several novel asymmetric oxa-Michael-Michael/aldol and aza-Michael-aldol(-aromatization) reaction sequences initiated by the Michael addition to alkynals. Notably, an unprecedented chiral iminium-allenamine cascade is disclosed for the first time. Significantly, these processes serve as efficient and straightforward entries to biologically significant chiral 4*H*-chromenes, polysubstituted quinolines and chiral 1,4-dihydroquinolines with excellent yield and enantioselectivity, as well as broad substrate compatibility. The proposed iminium-allenamine activation mode adds a new domain in the field of organocatalytic enantioselective cascade reactions. Finally, unprecedented organocatalytic 1,6-conjugated addition to yenals, an unmet challenging problem in organic synthesis, also has been realized.

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List of Abbreviations

$[\alpha]_D$	Specific Rotation at Wavelength of Sodium D Line
Ac	Acetyl Acetate
aq.	Aqueous
Ar	Aromatic
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
bp	Boilong Point
t-Bu	*t*-Butyl
Bz	Benzoyl
c	Concentration
Cbz	Benzyloxycarbonyl
$CDCl_3$	Deuterated Chloroform
δ	Chemical Shift
DCE	Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
D_2O	Deuterated Water
EDG	Electron Donating Group

ee	Enantiomeric Excess
equiv.	equivalent
EtOAc	Ethyl Acetate
EWG	Electron Withdrawing Group
g	Gram
h	Hour
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-	Meta-
Me	Methyl
MeCN	Acetonitrile
Mg	Magnesium
mg	Milligram
min.	Minute
mL	Millimole

mp	Melting Point
Ms-	Methanesulfonyl
NMR	Nuclear Magnetic Resonance
o-	Ortho-
p-	Para-
Ph	Phenyl
PG	Protecting Group
ppm	Parts per Million
i-PrOH	Isopropyl Alcohol
rt	Room Temperature
TB(DM)S	*tert*-Butyldimethylsilyl
TBME	*tert*-Butylmethylether
TEA	Triethylamine
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

μL	Microliter

Chapter 1

Development of Organocatalysis

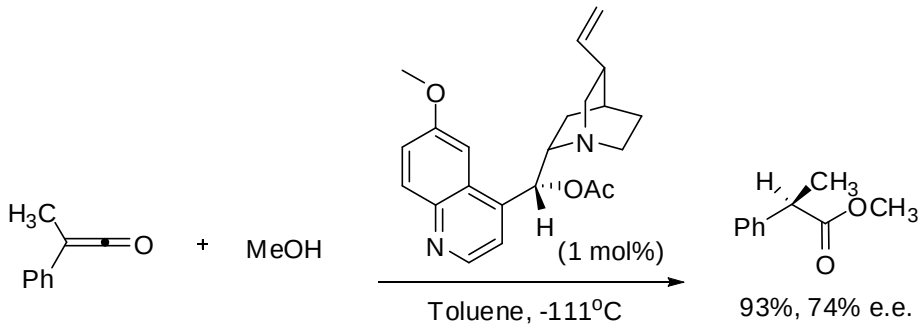
1.1 Introduction

We live in a world that new chemicals, materials and therapeutics come from synthsis, while many chemical processes heavily rely on catalysis. As reported, 90% of all commercially produced chemical products involve catalysts at some stages in the process of their manufacture[1]. Particularly, the application of catalysis to the pharmaceutical industry has steadily increased over the past two decadesdue to the facts that 80% of small-molecule drugs approved by the FDA arechiral and syntheses using conventional asymmetric methods cannot meet the demand[2]. Therefore, the development of new synthesis strategies becomes essential. Notably organocatalysis using pure small organic molecules has been an important player over the past 20 years in organic synthesis[3].

Organocatalysis has a rich history. The first reported asymmetric organocatalytic reaction dated as early as 1912[4]. An enantioselective catalytic addition of HCN to benzaldehyde in the presence of alkaloids quinine and quinidine was realized although the optical activities of the resulting cyanohydrins were less than 10%. Subsequently, in 1960, Pracejus reported that the addition of methanol to phenylmethylketene using *O*-acetylquinine as catalyst again can get (-)-α-phenyl methylpropionate with synthetically

useful levels of enantioselectivity (74% ee)[5] (Scheme 1.1). Further breakthroughs were achieved between 1970s and 1980s. The most famous example is the discovery of the L-proline promoted asymmetric Robinson annulation reaction which is also called Hajos-Parrish-Eder-Sauer-Wiechert reaction[6]. However, the catalytic potential of proline was ignored until 2000, the seminal works were published simultaneously by List, Barbas[7] and MacMillan[8]. Since then, it has grown at an explosive pace over the past decade and the number of publications on the topic of organocatalysis has increased remarkably. Organocatalysis currently seems to be in the state of a ‘‘gold rush’’[9].

Scheme 1.1 Pracejus’ Enantioselective Ester Synthesis Catalyzed by *O*-acetylquinine



Compared with traditional approaches including transition metal catalysis and enzymatic transformations, organocatalysts have several advantages[3b,10]. First, they are relatetively inert toward moisture and oxygen, so experimental operations are simple and no demanding reaction conditions such as inert atmosphere, dry solvents are required in most cases. Second, they are relatively non-toxic and environmentally benign because of the absence of transition metals. This is particularly attractive for the preparation of pharmaceutical products, which do not tolerate toxic metal contamination. The increasing

focuses on the development of environmentally sustainable manufacturing processes also make organocatalysis as one of the most appealing research subjects. Third, organocatalysts are readily available and inexpensive because most of their precursors are directly obtained from naturally occurring optically pure molecules, such as amino acids and alkaloids. Finally, enzymes are usually substrate and reaction specific; however, one kind of organocatalyst usually can catalyze a variety of reactions with broad range of substrate scopes. Although the impact of transition metal catalysis on synthetic chemistry cannot be understated, the advent of organocatalysis indeed has brought the prospect of a complementary mode of catalysis[3b].

1.2 Classification of Organocatalysts

The field of organocatalysis has been a rapidly growing research area which evolved from its infancy through the "gold rush" stage over the last decade[11]. Not only have the scopes and applications of enantioselective organocatalytic reactions been expanded dramatically, but also the fundamental mechanisms and catalytic modes underlying each type of organocatalytic reactions have been deeply comprehended. Obviously, it is relatively straightforward and reliable to apply the established activation modes as a platform to rationally design new enantioselective organocatalytic reactions and discover novel activation modes[3b]. Encouraged by the significant value of catalytic mechanisms, herein, I will briefly summarize them in two categories.

Generally speaking, based on the typical interactions between anorganocatalyst and substrates within the catalytic cycle, the vast majority of organocatalytic transformations can be divided into the two subgroups “covalent organocatalysis” and “non-covalent organocatalysis”. In the former case, covalent adducts are formed between the substrates and the catalyst. Whilst, in the latter case, non-covalent interactions such ashydrogen bonding or the formation of ion pairs play a part in the catalytic process[9]. It is worthy of point out thata bunch of combined catalytic strategies have emerged as a new branch in the field of organocatalyst very recently.

1.2.1 Covalent Organocatalysts

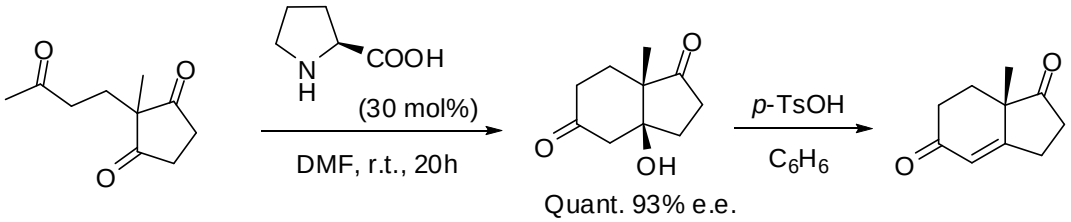
Aminocatalysts are probably the most commonly used organocatalysts in asymmetric transformations[12]. Their properties are closely related with the particular reactivity of the nucleophilic nitrogen, whereby the nitrogen atom condenses with a substrate which is usually a carbonyl compound and give rise either to enamine or iminium intermediates. Besides that, SOMO (Singly Occupied Molecular Orbital) catalysis and dienamine catalysis are also fully investigated very recently. As to other types of covalent catalysts which are not closely related with my Ph. D research work such as planar-chiral heterocycles as nucleophiliccatalysis, *N*-heterocyclic carbine catalyst will not be discussed in my dissertation.

1.2.1.1 Enamine Catalysts

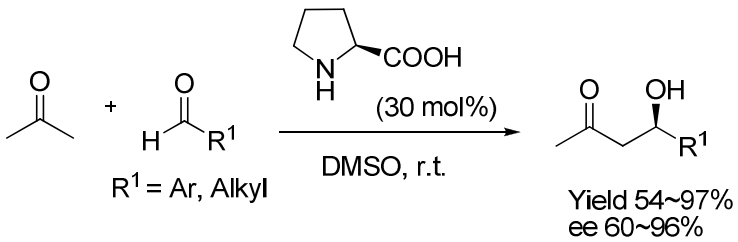
In 1971, the proline-catalyzed intramolecular aldol reaction in the synthesis of the Wieland–Miescher ketone was reported simultaneously by Zoltan Hajos, David Parrish and Rudolf Weichert, Gerhard Sauer, Ulrich Eder (Scheme 1.2)[6]. The wonderful reaction

scenario was recognized by the synthetic community; however, the underlying catalytic mechanistic detail was not explored until more than 30 years later. In 2000, the great potential of activation mode – enamine catalysis was realized by the synthetic community along with the seminal work of intermolecular aldol reaction catalyzed by secondary amine via enamine by List and Barbars research group (Scheme 1.3)[7]. Since then, a number ofnew types of enamine catalysts[13] have been identified and a broad range of asymmetric chemical transformations[13, 14] with aldehydes and ketones via enamine catalysis have been achieved such as Mannich reactions[15~17], Michael addition reactions[18], α-functionalization of carbonyl compounds with a great many of electrophiles, namely, α-amination[19~20], α-oxygenation[21], α-halogenation[22~24], α-sulfenylation[25], α-selenylation[26~27] and intramolecular α-alkylation of aldehydes[28] (Scheme1.4).

Scheme 1.2 Proline Catalyzed Intramolecular Asymmetric Aldol Reaction (Hajos-Parrish-Eder-Sauer-Wiechert Reaction)

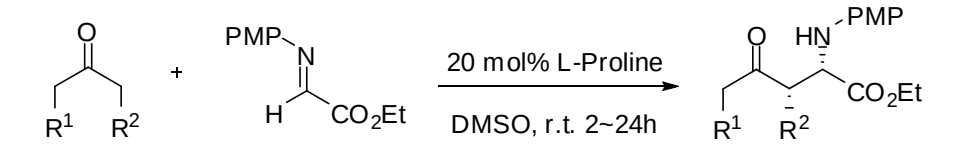


Scheme 1.3 Proline Catalyzed Intermolecular Aldol Reaction



Scheme 1.4 Other Examples of Enantioselective Enamine Catalysis

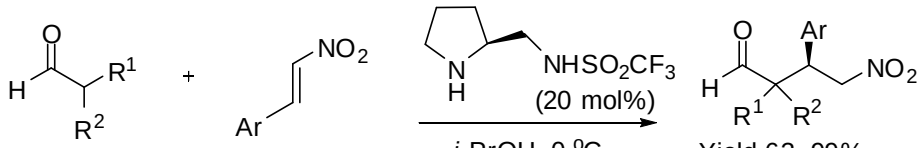
1.



R^1, R^2 = H, Alkyl

Yield 47~86%
ee 61~>99% dr > 19:1

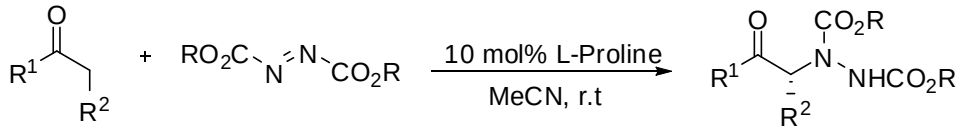
2.



R^1, R^2 = Alkyl

Yield 63~99%
ee 89~99%, dr > 20:1

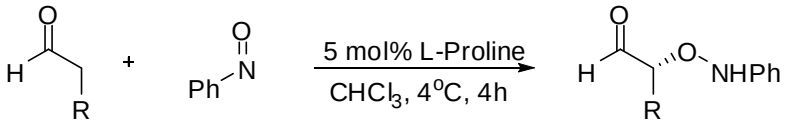
3.



R^1, R^2 = Alkyl R = *t*-Bu, Bn, Et

Yield 67~92%
ee 79~99%

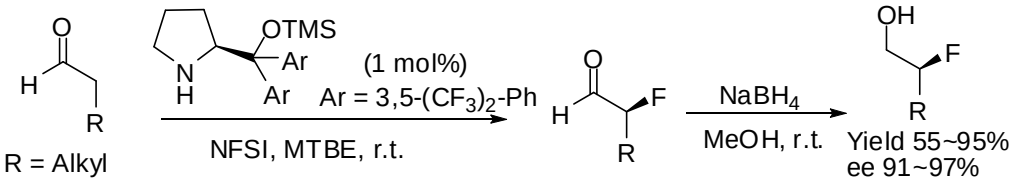
4.



R = Alkyl

Yield 60~95%
ee 97~99%

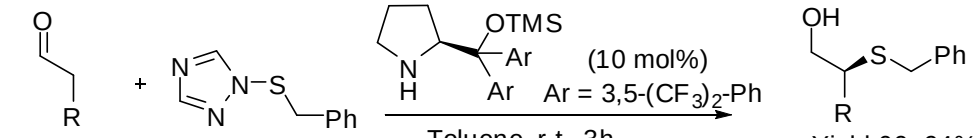
5.



R = Alkyl

Yield 55~95%
ee 91~97%

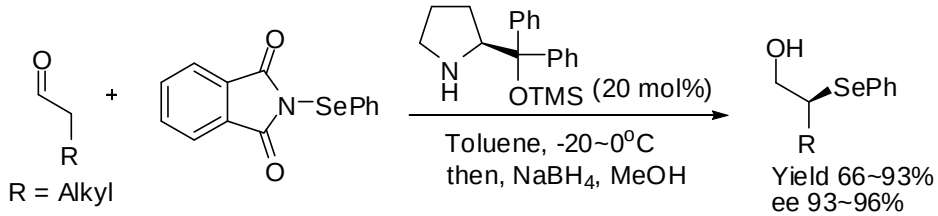
6.



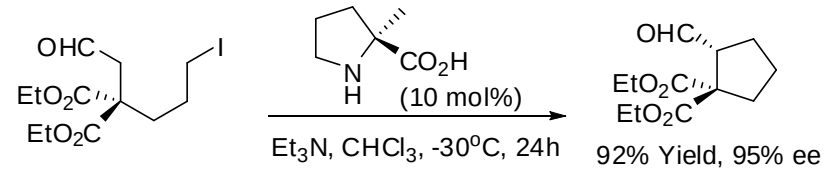
R = Alkyl

Yield 60~94%
ee 95~98%

7.

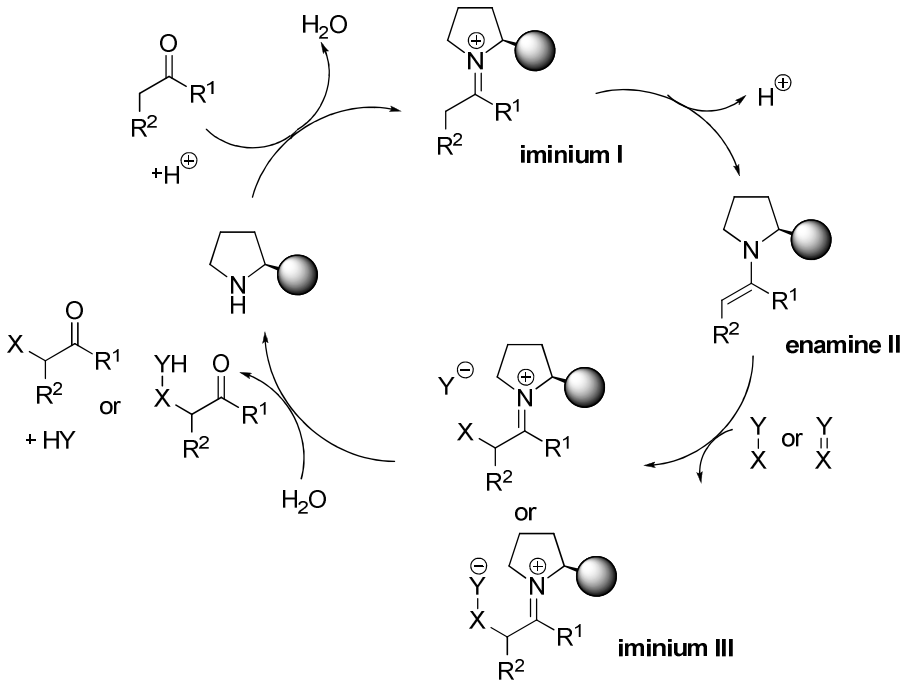


8.



In the enamine catalytic cycle, the LUMO lowering effect results in dramatic increase in C-H acidity of the initial iminium ion **I** (Figure 1.1). Then the active enamine **II** species is reversibly generated. The resulting enamine **II** reacts with the electrophile via nucleophilic substitution or nucleophilic addition to form iminium ion **III** which is then hydrolyzed to afford the desired product[13]. In short, the essence of enamine catalysis is generation of the more nucleophilic enamine species whose HOMO energy is increased.

Figure 1.1 Enamine Catalytic Cycle

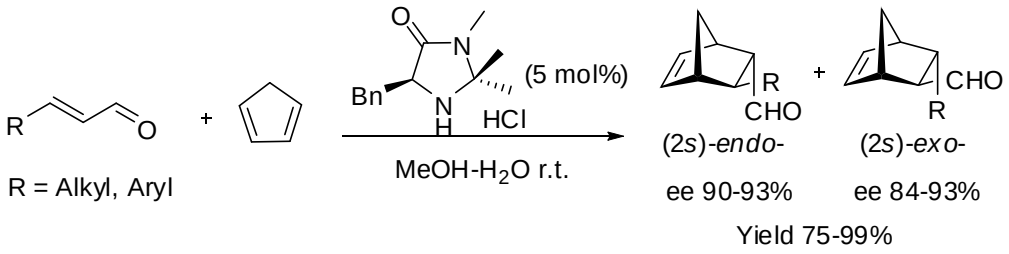


1.2.1.2 Iminium Catalysts

Although the iminium-catalysis strategy had never been documented until 2000, the experimental basis for this organocatalytic concept probably can be stretched back toseveral well-established methodological investigations. One of the well-known examples is the Knoevenagel condensation[29] mediated by primary or secondary amines. In 1931, Blanchard et al. suggested that an iminium ion species reversibly generated by an aldehyde and an amine is involved in the process[30]. In 1953, Crowell and co-worker presented the kinetic evidence for imine/iminium intermediates in the Knoevenagel condensations[31]. The key point for this process is that only the iminium ion is of sufficient electronic deficiency to undergo the following nucleophilic attack which is closely related with LUMO-lowering activation[11b].

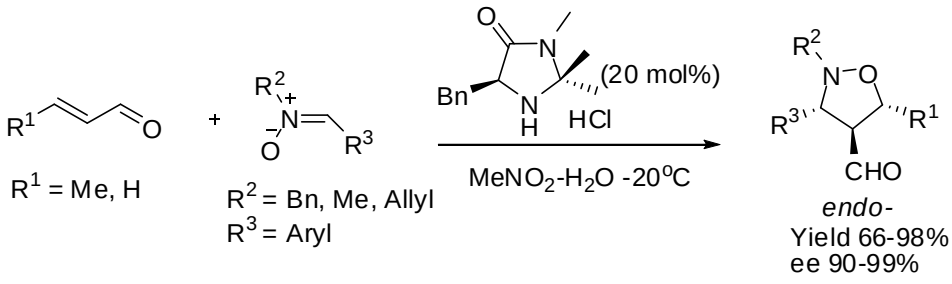
The iminium catalysis concept was first raised by MacMillan for the enantioselective Diels-Alder reaction between enal dienophiles and dienes in the presence of chiral imidazolidinone in 2000 (Scheme 1.5)[32]. Thereafter, the potential of the iminium catalysis was further explored. A myriad of transformations related with enals or enones, for example, [3+2] cycloaddition[33], [4+3]-cycloaddition[34], Friedel-Crafts alkylation[35], Mukaiyama Michael addition[36], Michael addition[37], hydrogenation[38], cyclopropanation[39] and epoxidation[40] have been extensively exploited (Scheme 1.6).

Scheme 1.5 Imidazolidinone Catalyzed Diels–Alder Reaction



Scheme 1.6 Other Examples of Enantioselective Iminium Catalysis

1.



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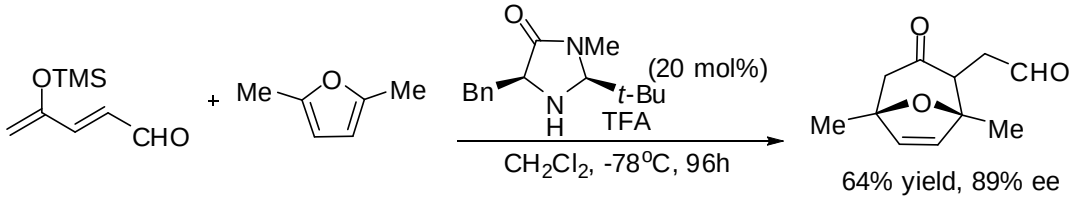
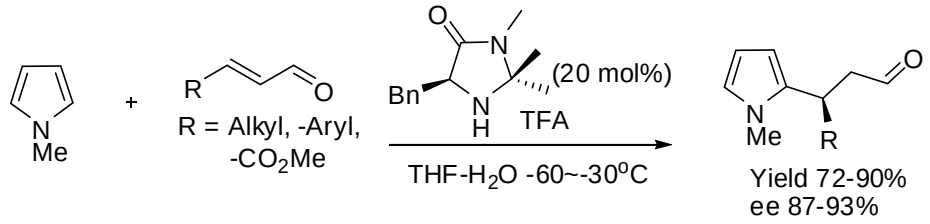
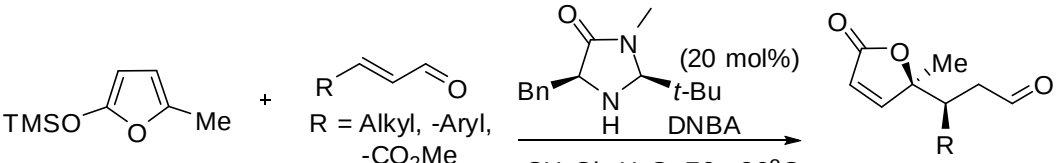


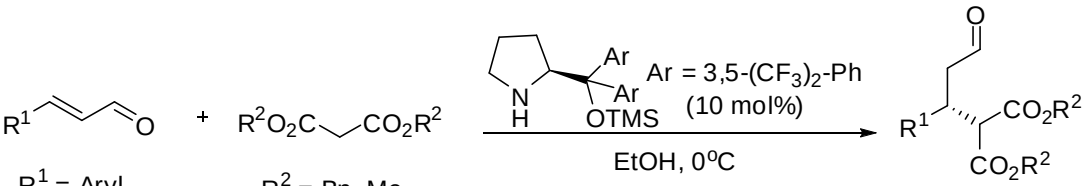
3.


R = Alkyl, -Aryl,
-CO2Me
(20 mol%)
TFA
THF-H2O -60~-30°C
Yield 72-90%
ee 87-93%

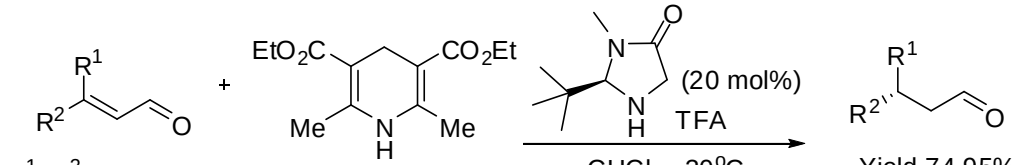
4.


R = Alkyl, -Aryl,
-CO2Me
(20 mol%)
t-Bu
DNBA
CH2Cl2-H2O -70~-20°C
Yield 77-87%
ee 84-99%

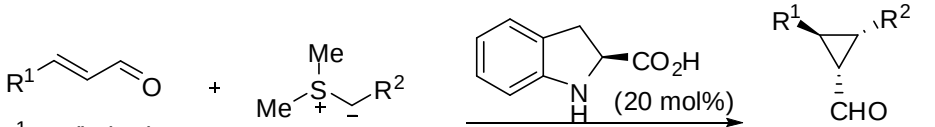
5.


R1 = Aryl
R2 = Bn, Me
Ar = 3,5-(CF3)2-Ph
(10 mol%)
EtOH, 0°C
Yield 31-95%
ee 86-95%

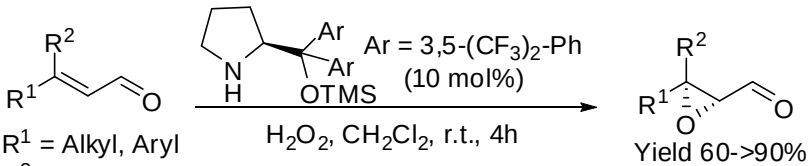
6.


R1, R2 = Alkyl, Aryl
(20 mol%)
TFA
CHCl3, -30°C
Yield 74-95%
ee 90-97%

7.

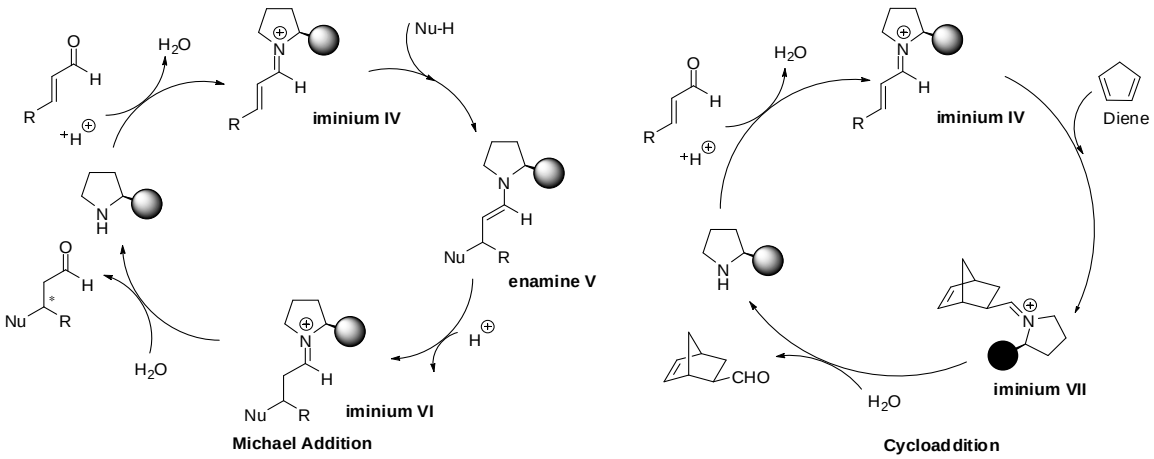

R1 = Alkyl, Ph
R2 = COPh,COt-Bu
(20 mol%)
CHCl3, -10°C
Yield 63-85%
ee 89-96%,
dr 6:1~72:1

8.


R1 = Alkyl, Aryl
R2 = H, Me
Ar = 3,5-(CF3)2-Ph
(10 mol%)
H2O2, CH2Cl2, r.t., 4h
Yield 60->90%
ee 75-98%,
dr 9:1~98:2

These reactions all share the same iminium activation mechanism. In the iminium catalytic cycle, the condensation of enals or enones with chiral amines results in the reversible formation of active iminium ions **IV** whose LUMO energy is lowered[41]. Accordingly, the iminium ions are more electrophilically subjected to attack by a variety of suitable nucleophiles or electron rich dienes. Subsequently, Michael addition results in an enamine **V** followed by iminium **VI** and cycloaddition results in an iminium ion intermediate **VII**. These intermediates (**VI** and **VII**) are then hydrolysed to give the desired product and regenerate chiral amine catalyst (Figure 1.2).

Figure 1.2 Iminium Catalytic Cycle for Michael Addition and Cycloaddition



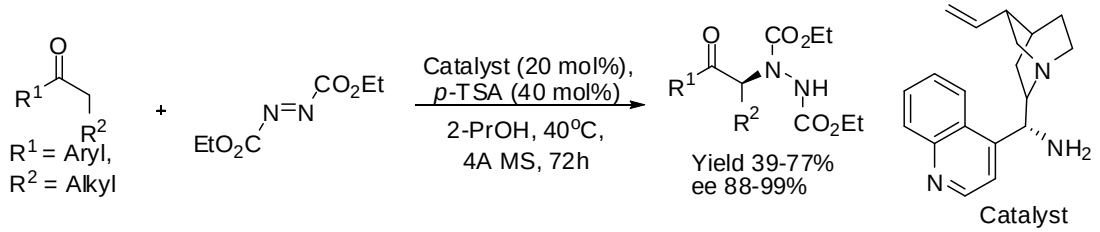
In summary, the HOMO-raising enamine activation and the LUMO-lowering iminium activation are two divergent activation modes in organocatalysis despite the fundamental analogies in the structure of these catalysts and substrates. On the other hand, enamine and iminium catalysis are closely interrelated with each other which can be seen from their catalytic cycles. Enamine catalysis always results in the formation of iminium ion

and iminium catalysis proceeds via the enamine intermediate[12]. The combinations of enamine and iminium catalysis in a cascade reaction leading to the formation of molecules of higher level complexity constitute a second milestone in the field of amine-based organocatalysis[42].

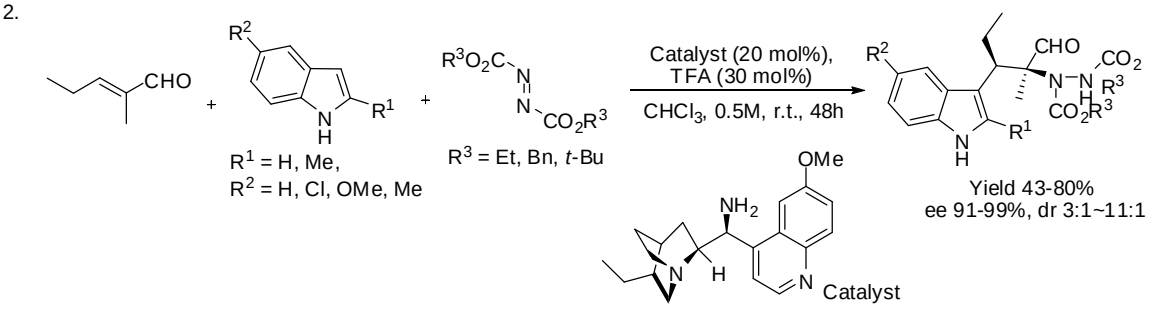
Meanwhile, many new types of chiral amine catalysts have been identified. Remarkably, the diarylprolinol silyl ether catalysts have emerged as highly powerful, potentially general organocatalysts in promoting either enamine catalytic cycle or iminium catalytic cycle[43]. In general, secondary amine is suitable for less hindered carbonyl compounds serving as either enamine or iminium catalysis. However, these catalysts have the inherent difficulties in generating congested covalent intermediates with sterically demanding substrates. Fortunately, the problem was overcome by less hindered primary amine based catalysts which were directly derived from natural cinchona alkaloids[44]. And this strategy has been successfully demonstrated in some cases for activating challenging ketones[45] and α,β-disubstituted enals[46] (Scheme 1.7).

Scheme 1.7 Primary Amine Based Catalyst in Enamine / Iminium Catalysis

1.



2.



1.2.1.3 SOMO Catalysis

In 1992, K. Narasaka and co-workers reported the addition reactions of enamine cation radicals generated in the presence of stoichiometric amount of oxidant ammonium cerium (IV) nitrate (CAN) to olefins (Scheme 1.8)[47]. About 15 years later, the MacMillan research group proposed a novel SOMO (single occupied molecular orbital) organocatalysis concept[48]. SOMO catalysis is based on the idea that single-electron oxidation of a transiently produced, electron-rich enamine selectively generates a three π-electrons radical cation with a single occupied molecular orbital (Figure 1.3). This intermediate readily reacts with a variety of weak nucleophilic carbon-based "SOMOphiles" to afford enantioselectiive α-functionalized carbonyl-containing compounds (Scheme 1.9)[48]. Although SOMO catalysis is one of the most recently discovered activation modes, it has already been extended to many asymmetric transformations[49~51] which are complementary to those via enamine catalysis.

Scheme 1.8 Addition Reaction between Enamine Cation Radical and Olefine

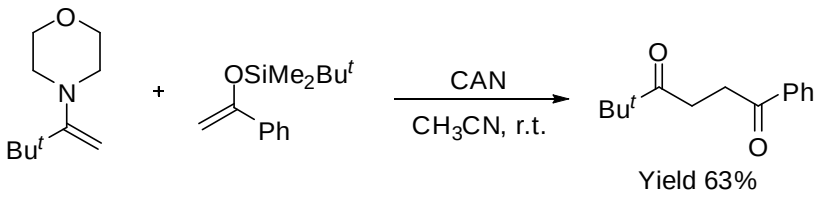
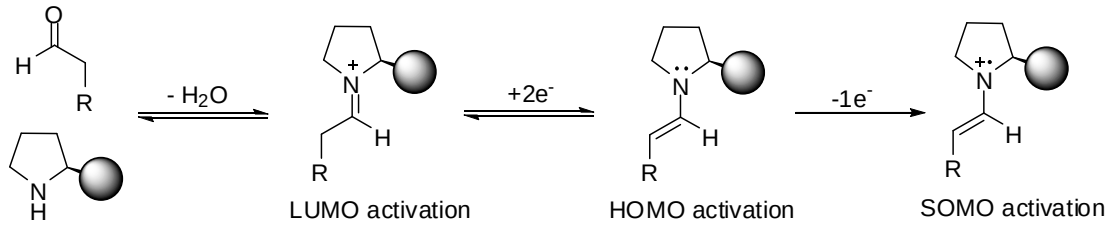
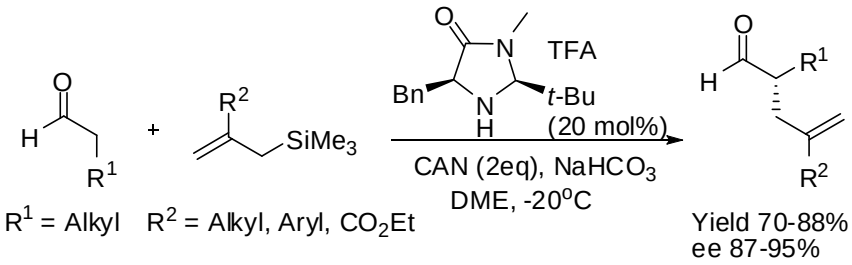


Figure 1.3 SOMO Catalysis via Single-Electron Oxidation of a Transiently Formed Enamine



Scheme 1.9 Representative SOMO Catalysis in Enantioselective α-Allylation of Aldehyde

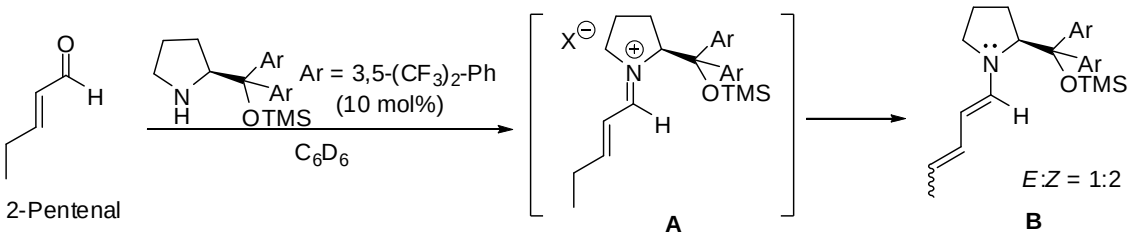


1.2.1.4 Dienamine Catalysis

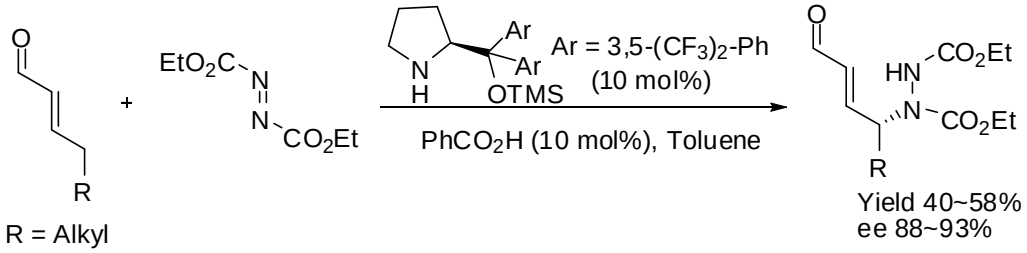
Enamine, iminium and SOMO catalysishave provided us feasible methods for stereoselective functionalization of carbonyl compounds at their α and/or β positions. In 2006, the seminal work about the corresponding γ-functionalization of carbonyl

compounds was reported by Jørgensen and co-workers who launch the unique dienamine organocatalyst[52] concept for the first time. When they undertook ^{1}HNMR spectroscopic investigationsin the attempt to characterize the expected electrophilic iminium-ion intermediate **A** formed by the reaction of 2-pentenal and chiral amine catalyst, contrary to their expectations, electron-rich dienamine species **B** was observed (Scheme 1.10)[52]. Inspired by the observation, Jørgensen demonstrated the first organocatalytic γ-amination of α,β-unsaturated aldehydes with high enantioselectivity by inverting the normal electrophilic alkene into electron-rich diene (Scheme 1.11)[52].

Scheme 1.10 Formation of the Dienamine Intermediate in the Reaction between 2-Pentenal and the Chiral Amine Catalyst



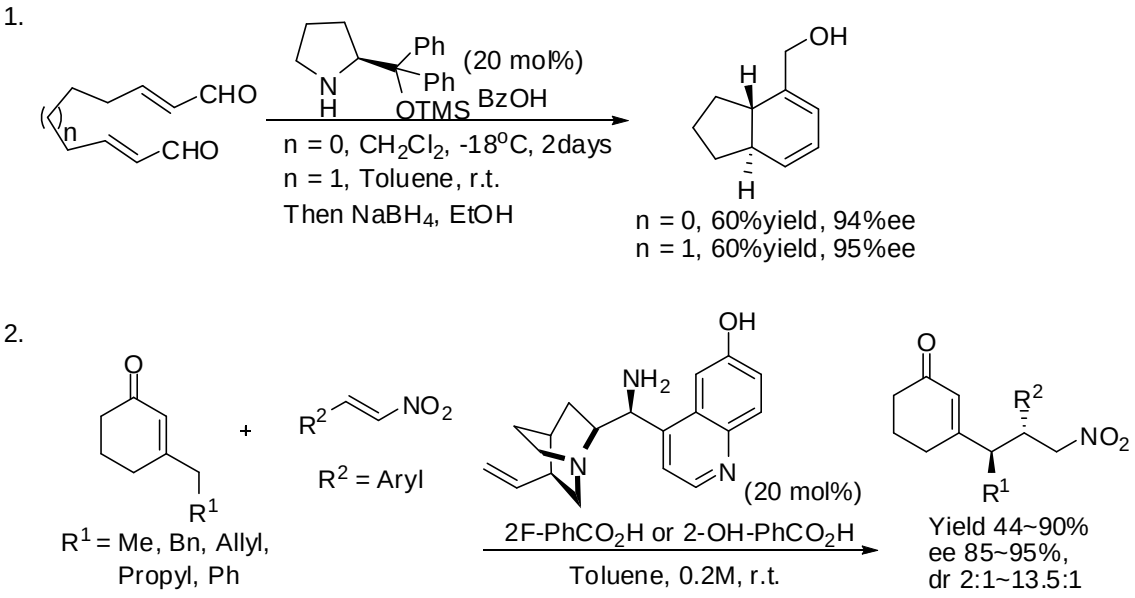
Scheme 1.11 Organocatalytic γ-Amination of α, β-Unsaturated Aldehyde



Since the initial studies, the potential of dienamine catalysis was further exploited. Many dienamine catalytic transformations were designed to expand the scope of γ-

activation such as the intramolecular cyclization of unsaturated dialdehydes[53], primary amine catalyzed vinylogous Michael addition of cyclic enones to nitroalkenes[54] (Scheme 1.12). The common character for the substrate is β-aliphatic-substituted γ-enolizable unsaturated carbonyl compounds.

Scheme 1.12 Other Examples of Dienamine Catalytic Transformations

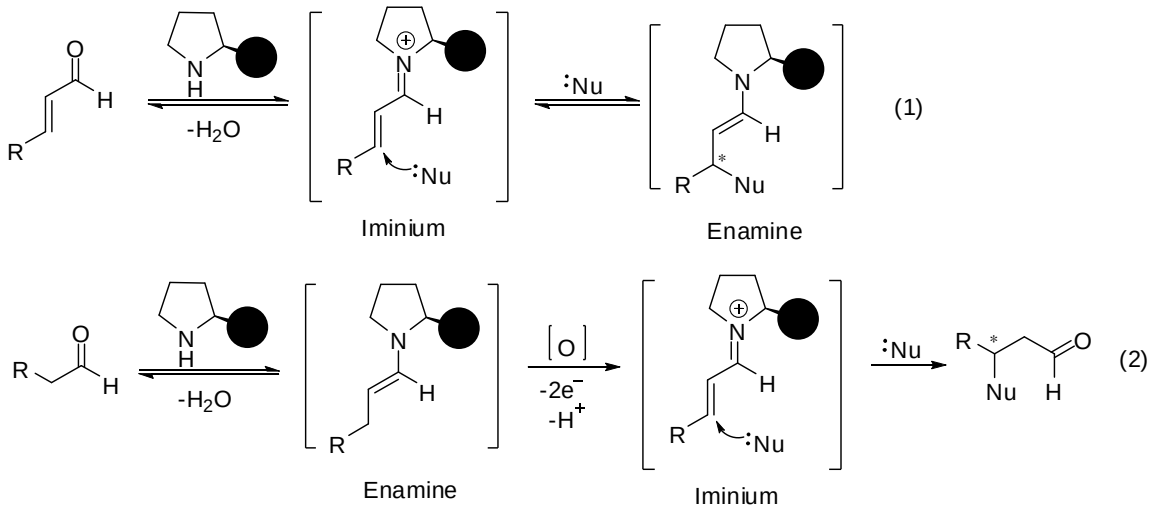


1.2.1.5 Oxidative Enamine Catalysis

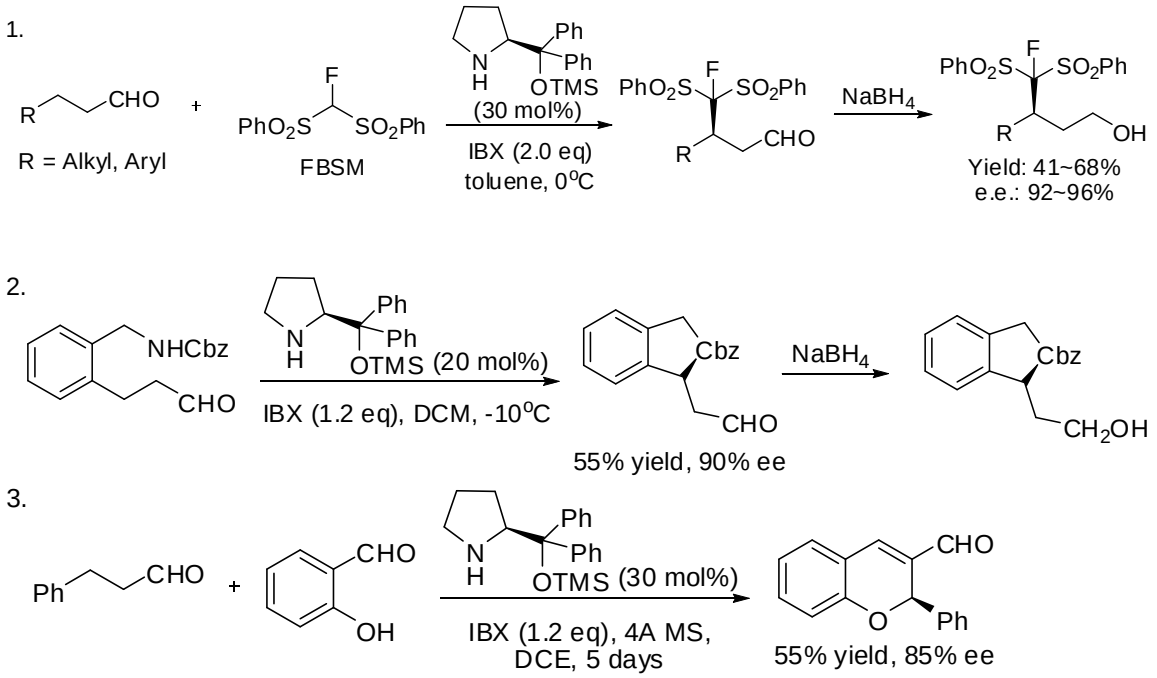
Enamine and SOMO catalysis represent powerful approaches to α-functionalization of aldehydes. In 2011, Wang group reported the seminal work about the direct β-functionalization of simple aldehydes rather than enals in a catalytic enantioselective manner[55]. Although the strategy involving transformation of an iminium ion to an enamine in iminium catalysis has enjoyed tremendous successes (Figure 1.4, eq

(1)), the reverse process in which an enamine is converted to an iminium species has not been explored. Dr. Wang and co-worker reported that the use of *o*-iodoxybenzoic acid (IBX) as an oxidant in the presence of a secondary amine catalyst serves as an effective system for promoting rapid conversion of enamines to iminium ions (Figure 1.4, eq (2))[55]. The preparative power of this process has been demonstrated in the context of direct asymmetric β-functionalization of simple aldehydes. Furthermore, a variety of enantioselective cascade transformations, including triple and quadruple cascades, have been developed for the 'one-pot' synthesis of versatile chiral building blocks and structural frameworks (Scheme 1.13)[55].

Figure 1.4 Aminocatalysis: (1) Iminium Catalysis. (2) Oxidative Enamine Catalysis.



Scheme 1.13 Oxidative Enamine Catalysis in Multiple Cascade Reactions



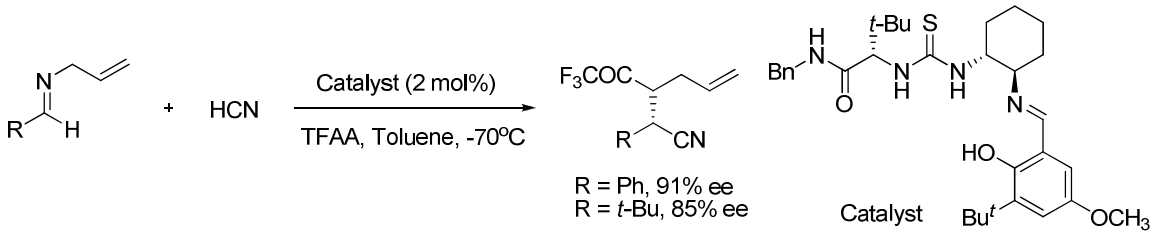
1.2.2 Non-Covalent Organocatalysts

Understanding of the mechanism of enzymatic catalysis identified the key-role for non-covalent interactions[56]. Now, non-covalent interactions-particularly H-bonding has emerged as a widely applicable approach in organocatalysis. Unlike covalent catalysts which rely on strong convalent interactions with substrates, non-covalent catalysts active substrates and stabilize the transition state through well-defined non-covalent interactions.

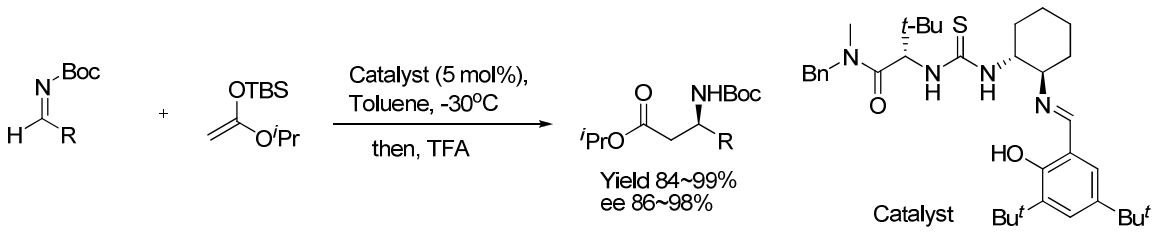
The simultaneous donation of two hydrogen bonds has proven to be a highly successful strategy for electrophile activation because such interactions benefit from increased strength and directionality relative to a single hydrogen bond[57]. In 1998,

Sigman and Jacobsen reported that urea and thiourea derivatives can catalyze enantioselective Strecker reaction (Scheme 1.14)[58]. In 2002, a mechanistic analysis revealed that the thiourea functionality is responsible for catalytic activity and that the imine substrate can interacts with the catalyst via a dual H-bond interaction to the urea protons[59]. Shortly later, Jacobsen's group identified these chiral (thio)urea as highly versatile, effective catalysts for Mannich reaction (Scheme 1.15), launching the generic use of enantioselective hydrogen-bonding catalysis[60]. Along this line, several examples[57, 61] have been presented such as Aza-Baylis--Hillman reaction[62], hydrophosphonylation of imines[63] and Acyl-Pictet Spengler reaction[64] (Scheme 1.16). It should be noted that the Jacobsen (thio)ureas are monofunctional catalysts that work through the sole activation of electrophiles.

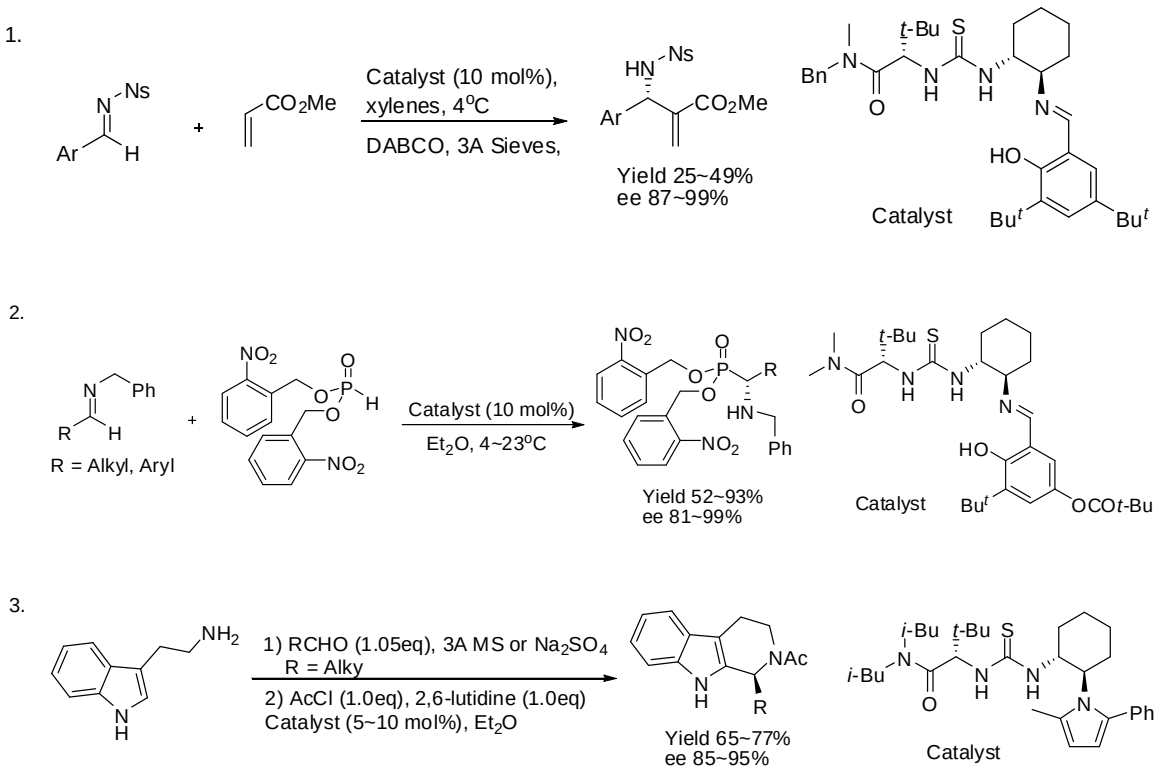
Scheme 1.14 Thiourea-Catalyzed Asymmetric Strecker Reaction



Scheme 1.15 Thiourea-Catalyzed Asymmetric Mannich Reaction

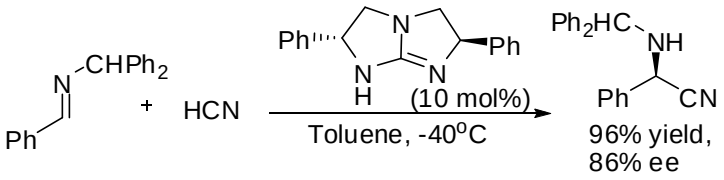


Scheme 1.16 Other Examples of Thiourea Catalyst as Double H-Bonding Catalyst



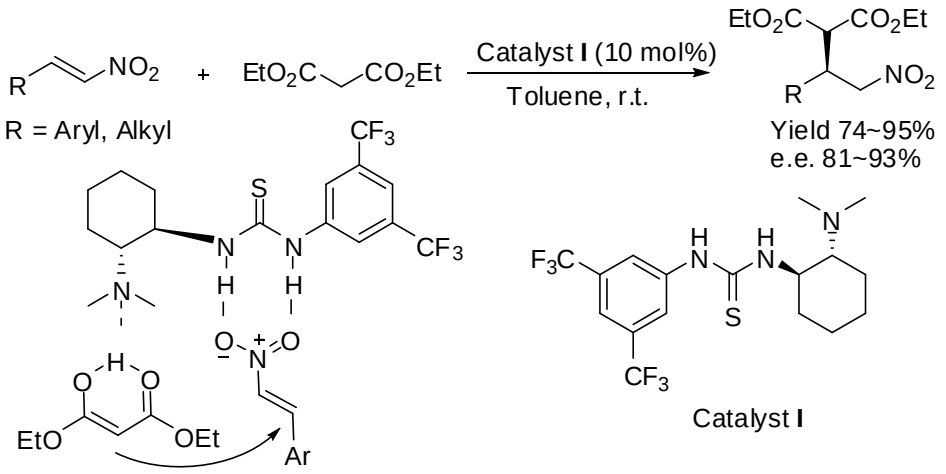
The amino acid arginine possessing a guanidinium functional group, frequently acts as a double H-bond donor in biological systems. Similarly, in synthetic chemistry, guanidinium ion is also capable of participating indouble H-bonding interactions[65]. Pioneering work in this area was reported by Corey and Grogan, who demonstrated that chiral bicyclic guanidine mediates asymmetric Strecker reactions (Scheme 1.17)[66]. The utilizations of chiral guanidines as catalysts in many different kinds of reactions such as Henry reaction[67], Michael reaction[68], Diels–Alder reaction[69], and Mannich reaction[70] havebeen investigated thoroughly in the past few years[65].

Scheme 1.17 Bicyclic Guanidine Catalyst for Asymmetric Strecker Reaction



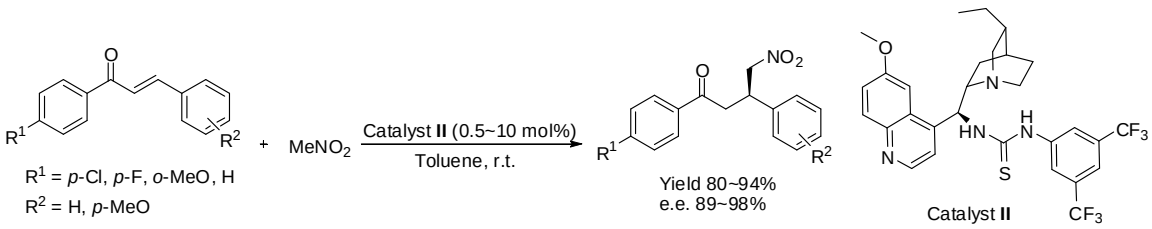
Recently, inspired by enzyme-mediated catalysis, which relies on the synergistic cooperation of a number of functional groups, organic chemists have developed bifunctional organocatalysts which commonly combine the H-bond donors and Brønsted or Lewis base functionalities in a chiral scaffold. Starting with Jacobsen's monofunctional (thio)ureas catalyst, in 2003, Takemoto and co-workers developed novel bifunctional catalyst with the introduction of an additional basic, nucleophile-activating group in the thiourea[71]. As reported, the thiourea catalyst **I** promoted the Michael reaction of malonates tovarious nitroolefins with high enantioselectivities (Scheme 1.18). In the bifunctional catalyst, thiourea moiety activates the Michael acceptor through H-bonding interaction with nitro group and the tertiary amine group serves as Lewis base to activate the nucleophilic enol species simultaneously (Scheme 1.18)[72]. The scope of Takemoto catalyst has also been expanded to transformations using substantially different electrophiles and nucleophiles, such as aza-Henry reaction[73], Mannich reaction[74], cyanosilylation[75], Baylis–Hillman reaction[76] and various Michael additions[77].

Scheme 1.18 Michael Additions of Malonates to Nitroolefins Catalyzed by Takemoto Thiourea Catalyst **I**



The natural products cinchona alkaloids have also been utilized for the creation of a new class of bifunctional organocatalysts by incorporation of thiourea moieties[78]. Pioneering work was reported by Soós and co-workers[79] about Michael addition of nitromethane to chalcones catalyzed by cinchona alkaloid derived bifunctional thioureas catalyst **II** (Scheme 1.19).

Scheme 1.19 Michael Addition of Nitromethane to Chalcones Catalyzed by Cinchona Alkaloid Derived Bifunctional Thioureas Catalyst **II**

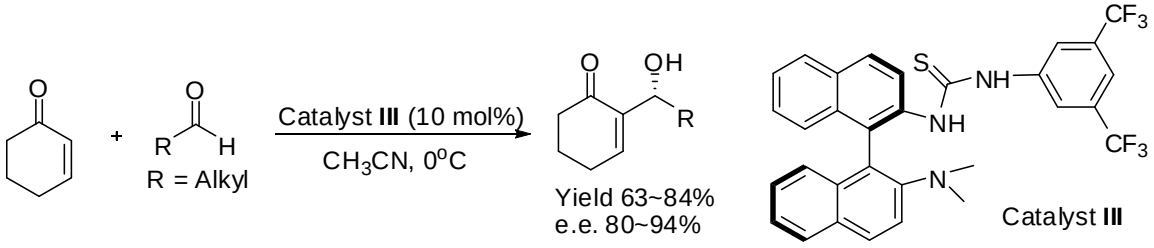


Since then, cinchona alkaloid derived bifunctional thioureas catalysts have been

intensively explored for asymmetric organic transformations. Notable examples include Mannich reaction[80], Diels-Alder reaction[81] and a wide range of Michael addition[82].

Wang and co-workers identified chiral naphthyl-derived bifunctional thiourea catalyst **III**. It has been demonstrated to promote the asymmetric Morita-Baylis-Hillman reactions of cyclohexenone with a varietyof aldehydes to afford highly functionalized, synthetically useful chiral allylic alcohols (Scheme 1.20)[83].

Scheme 1.20 Catalyst **III** Promoted Asymmetric Morita-Baylis-Hillman Reaction



1.3 Summary and Outlook

Over the past ten years, the field of enantioselective organocatalysis has had a significant impact on chemical synthesis and has developed into a practical synthetic paradigm crucial for many applications including drug discovery [3c,9, 11b]. In principle, the most pivotal to the success of organocatalysis in the past decade has been the invention or identification of generic modes of catalyst activation[3b]. Based on them, a myriad of asymmetric reactions have been developed and the number of publications on the topic of organocatalysis has recently increased markedly. Given the significance of new

activation modes, it is desirable for chemists to focus their research efforts on uncovering new modes.

Very recently, another valuable achievement is the combination of different activation modes or catalytic strategies into one single transformation to generate previously unattainable molecules[84]. A number of multicatalysis mechanisms have been identified including cooperative metal-organocatalyst system[85] and organocatalytic photoredox strategy[86]. Although multicatalysis concept is still in its infancy and it has inherent problems such as catalyst compatibility, we believe that it will continue to grow and offer solutions to the challenges; ultimately, it will be recognized as a powerful catalysis strategy.

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Chapter 2

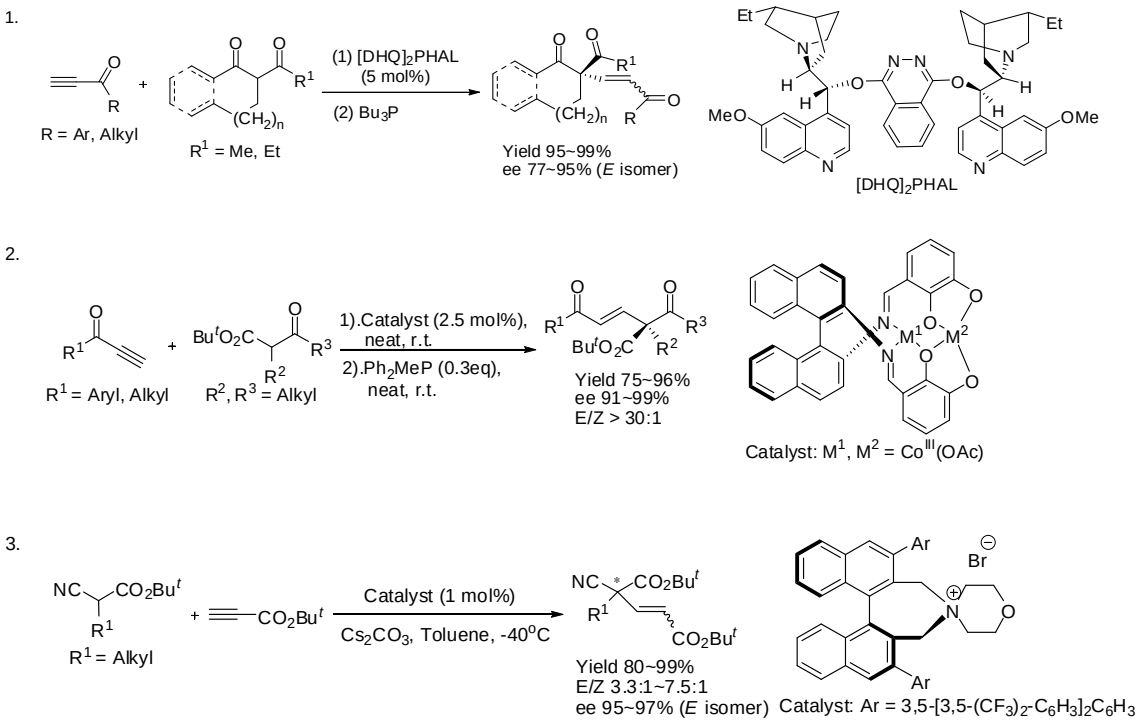
Organocatalytic Regio- and Stereoselective Michael Addition of 1*H*-1, 2, 3-Triazole to Alkynals

2.1 Background and Significance

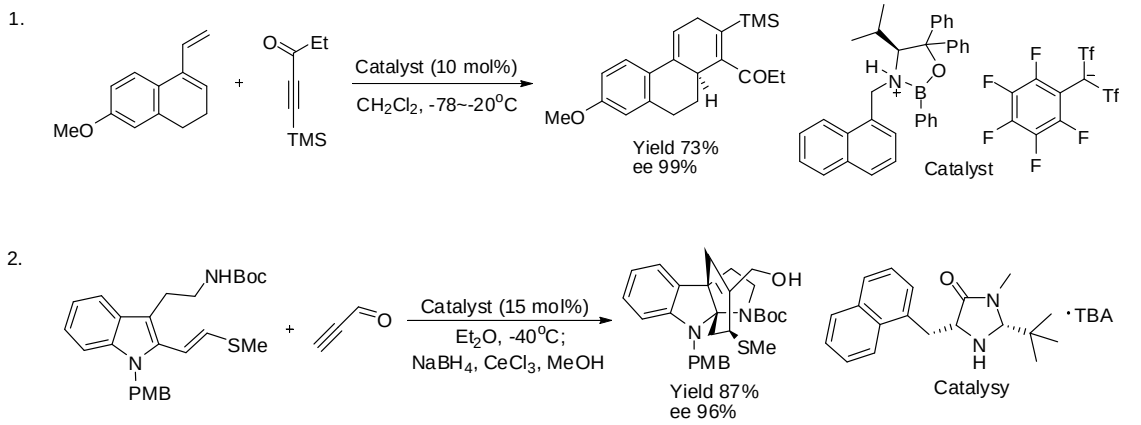
The catalytic Michael addition reactions which efficiently construct C-C and C-heteroatom bonds held persistent interest in the area of asymmetric organocatalysis. Notably, high effective asymmetric organocatalytic additions of various nucleophiles to α, β-unsaturated cyclic and acyclic enals, enones, nitro olefins, vinyl sulfones and vinyl phosphonates have been developed[1]. Among those, Michael additions to enals represent an enormous and fruitful research branch[2]. In contrast, the protocols for conjugate additions to the corresponding alkynals are relatively rare. This is due to the fact that (i) alkynals possess no prochiral center at the β-carbon atom; (ii) alkynals are known to be a challenging class of electrophiles in asymmetric synthesis, and it is expected that they would behave differently to the well-established enals in terms of reactivity and stereo-control, because they adopt different structures and geometry (linear sp hybridized alkynes versus trans sp^2 hybridized olefins). There are only a very small number of reports dealing with Michael additions to alkynones or acetylenic esters which introduce chiral centers by the Michael donors (Scheme 2.1)[3a~3c]. And the examples of substituted alkynals or alkynones act as acetylenic dienophiles in Diels-Alder reactions are sporadic

(Scheme 2.2)[3d~3h].

Scheme 2.1 Examples of Catalytic Asymmetric Michael Additions to Alkynones or Acetylenic Esters



Scheme 2.2 Examples of AcetylenicDienophiles in Asymmetric Diels-Alder Reaction



2.2 Research Design

Motivated by the dearth of applications of alkynals in organocatalysis (versus the widely explored enals), we are pursuing to develop alkynals involved organocatalytic single-step reaction. To the best of our knowledge, in the case of these Michael additions to alkynals or alkynones, the iminium-ion activation mechanism which facilitates the addition of the nucleophile to the β-carbon atom has not been reported although the similar mechanism for activation of enals is already well-established.

In order to successfully develop the conjugate addition to alkynal, we surmise that the key issue is to choose the Michael donor. After a brief screening, we chose to test the Michael addition of 1*H*-1, 2, 3-triazole to alkynals. This is based on the fact that *N*-(1-Alkenyl)azoles are involved in the synthesis of polymers[4] and heteropentalene mesomeric betaines of type B[5]. Moreover, *N*-(1-Alkenyl)azoles have found to display intriguing biological activities[6].

2.3 Introduction

The efficient regio- and stereoselective construction of trisubstituted alkenes is a long standing goal in organic synthesis. Carbonyl olefination such as Wittig[7] and Horner-Wadsworth-Emmons reaction[8] is the most classical strategy. Transition-metal mediated carbometallation of alkynes[9] and cross-coupling reactions[10] has emerged as most widely used methods for formation of trisubstituted alkenes. In all above strategies, regio- and stereocontrol are the two key issues and remain a formidable challenge. Accordingly, we

envisioned to develop a regio- and stereoselective synthetic strategy for trisubstituted alkenes starting from alkynals by employing organocatalyst via an iminium-ion activation mechanism.

2.4 Results and Discussion

At the outset of our investigations, the model reaction between phenyl-propynal **1a** and 1*H*-1, 2, 3-triazole was examined in dichloromethane at room temperature in the presence of 20 mol% organocatalyst (Figure 2.1 and Table 2.1). Several types of secondary amine catalysts **I-VII** (Figure 2.1) were screened because they can activate alkynal via iminium-ion mechanism. It was found that the catalysts tested exhibited significantly different catalytic activity in the event. The diarylprolinol silyl ethers catalyst **I** and **II** promoted the process to achieve 100% conversion in 2 h with good yield (~93%) and good *E/Z* ratio (1:0.19 and 1:0.18 respectively) (Table 2.1, entry 1, 2). It is worthy of point out that the reaction also proceeded with pretty good regioselectivity, affording the *N*-2-alkenyl substituted triazole derivative **2a** as the major product. However, the either moieties had little impact on the *E*/*Z* ratio due to the small Michael donor 1*H*-1, 2, 3-triazole[11]. The reaction proceeded to afford **2a** in 83% yield and a little poor *E*/*Z* ratio (1:0.23) after 60 h using diphenylprolinol **III** as catalyst (Table 2.1, entry 3). Pyrrolidine-based diamine catalyst **IV** was also good promoter for the reaction, resulted in high yield (94%), good *E*/*Z* ratio (1:0.17) and excellent regioselectivity (*N*-2-addition). The stereoselectivity between catalyst **II** and **IV**was nearly the same for the above model reaction (Table 2.1, entry 2, 4). So it was necessary to change the Michael

acceptor phenyl-propynal **1a** to (4-methoxy-phenyl)-propynal **1b** to evaluate which catalyst was more tolerate to versatile substrates. Correspondingly, the *E*/*Z* ratio was 1:0.29 and 1:0.20 when catalyst **II** and **IV** were employed respectively. Poor regioselectivity for Wang's catalyst **VI** was observed (Table 2.1, entry 6). The catalytic activity of L-proline **V** and MacMillan's catalyst **VII** were very poor; the conversion is only 58% and 29% after 60 h respectively. Moreover, catalyst **V** and **VII** afforded *N*-1-alkenyl substituted triazole derivative **3a**. Thereby, the diamine catalyst **IV** was chosen for further optimization reaction condition. Then, the effects of additives on the *E*/*Z* ratio were probed. The *E*/*Z* ratio can be improved slightly by adding 1eq. of NaOAc (Table 2.1, entry 8). It is considered as the result of facilitating the deprotonation of 1*H*-1, 2, 3-triazole. Generally, the relatively strong base such as K_2CO_3 was considered as a detriment to the *E*/*Z* ratio (Table 2.1, entry 9). The steric organic base quinine (Table 2.1, entry 10) and DABCO (Table 2.1, entry 11) cannot achieve better results. Et_3N (Table 2.1, entry 12) is also a poor additive although without sacrificing the yield. In the iminium-ion activation model, $PhCO_2H$ additive usually favors the formation of iminium-ion, as a consequence, improve the reactivity of Michael acceptor. However, in this instance, $PhCO_2H$ (20 mol%) additive can react with phenyl-propynal **1a** completely in 1 h which lead to more complicated reaction system and low yield (Table 2.1, entry 13). The screening of the reaction solvent indicated the use of dichloromethane gave the best results (Table 2.1, entry 14, 15 and 16). At last, we found unexpectedly lowering the reaction temperature to -40ºC, the *E*/*Z* ratio became worse along with the prolonged reaction time (Table 2.1, entry 17). The configuration of the dominant component of

compound **2a** prepared under the optimal condition was determined by X-ray crystallography to be *E* configuration; in other words, the organocatalytic Michael addition process was kinetic controlled process.

Figure 2.1 Secondary Amine Catalysts Screened

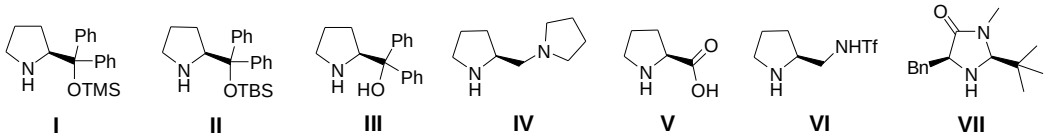
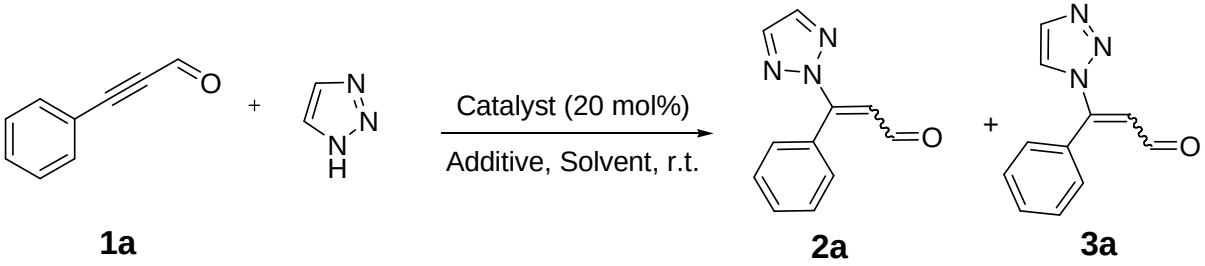


Table 2.1 Optimization Reaction Conditions for the Organocatalytic Regio- and Stereocontrolled Michael Addition of **1a** and 1*H*-1, 2, 3-Triazole to Afford **2a**[a].



Entry	Catalyst	Additive	Solvent	*t* (h)	Yield (%) [b]	*E*/*Z* ratio[c]
1	**I**	None	CH_2Cl_2	2	93	1:0.19
2	**II**	None	CH_2Cl_2	2	93	1:0.18
3	**III**	None	CH_2Cl_2	60	83	1:0.23
4	**IV**	None	CH_2Cl_2	2	94	1:0.17
5	**V**	None	CH_2Cl_2	60	<5	ND[d]
6	**VI**	None	CH_2Cl_2	24	64[e]	1:0.46
7	**VII**	None	CH_2Cl_2	60	<5	ND[d]

8	**IV**	NaOAc	CH_2Cl_2	2	94	1:0.16
9	**IV**	K_2CO_3	CH_2Cl_2	2	92	1:0.24
10	**IV**	quinine	CH_2Cl_2	3	90	1:0.16
11	**IV**	DABCO	CH_2Cl_2	2	85	1:0.26
12	**IV**	Et_3N[f]	CH_2Cl_2	2	92	1:0.26
13	**IV**	PhCOOH[g]	CH_2Cl_2	2	58[e]	1:0.28[e]
14	**IV**	None	DMSO	9	47[e]	1:0.56
15	**IV**	None	toluene	5	93	1:0.23
16	**IV**	None	THF	48	<5	ND[d]
17[h]	**IV**	NaOAc	CH_2Cl_2	48	85	1:0.26

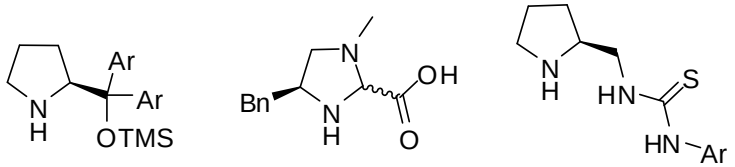
[a] Reaction conditions: unless specified, a mixture of phenyl-propynal **1a** (0.05mmol), 1*H*-1, 2, 3-triazole (0.06mmol), catalyst (0.01mmol) and additive (0.05mmol) in solvent was stirred at r.t. for a specified time. [b] Isolated yields. [c] Determined by ^{1}HNMR of crude reaction solution based on the integral of hydrogen of aldehydes or the integral of hydrogen of alkenes. [d] Not determined.[e] Calculated from ^{1}HNMR of crude reaction solution based on the integral of hydrogen of aldehyde of two regioisomers. [f] 40 mol% Et_3N was employed. [g] 20 mol% PhCOOH was employed. [h] Performed between (4-Methoxy-phenyl)-propynal **1b** and 1*H*-1, 2, 3-triazole at -40ºC.

As mentioned above, L-proline **V** and MacMillan's catalyst **VII** afforded *N*-1-alkenyl substituted triazole derivative **3a** althoughthe conversion was low. The results encouraged us to further explore optimal protocol for efficient synthesis of the regioisomer **3a.** An extensive screening of catalysts (Figure 2.1, 2.2), additives and solvents were carried out and some representative results are shown in Table 2.2. Generally speaking, acid additives usually favored the formation of *N*-1-alkenyl substituted triazole derivatives for most secondary amine catalysts. It was found that TFA

additive lead to remarkable reaction rate acceleration together with improvement in the regio- and stereoselectivity. As seen from the results, employing imidazolidine-2-carboxylic acid **IX** as catalyst, TFA as additive and dichloroethane as solvent afforded the best outcome (Table 2.2, entry 8).

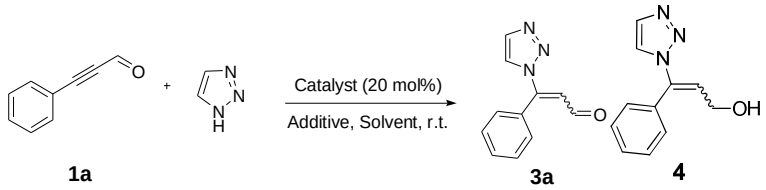
There exit tautomerism for 1*H*-1, 2, 3-triazole (Figure 2.3 and Figure 2.4). In a neutral solution, **1B**-configuration was more stable than **1A**-configuration due to the lone pair/lone pair repulsion of adjacent nitrogen atoms. So the predominant more electron rich species **1B** can be deprotonated, followed by Michael addition to alkynals at *N*-2 position. By contrast, under an acidic condition, **2B** exists as a dominant protonated form, which renders less nulecophilic. Therefore, **2A** serves as a nucleophile for *N*-1addition. It should be noted that the bifunctional catalyst **X** also afforded the *N*-1 addition product exclusively (Table 2.2, entry 11). This might be because the thiourea part of catalyst **X** form H-bonding with two adjacent nitrogen atoms of 1*H*-1, 2, 3-triazole, which rendered them less nucleophilicity. The stereoconfiguration of the major component of the compound **3a** prepared under the optimal condition was determined by X-ray crystallography to be *E* configuration based on enol **4** derived from **3a**. The observed configuration is consistent with the proposed mechanism of the process.

Figure 2.2 Other Secondary Amine Catalysts Screened



VIII **IX** Ar: 3, 5-CF_3-Ph **X**

Table 2.2 Optimization Reaction Conditions for the Organocatalytic Regio- and Stereocontrolled Michael Addition of **1a** and 1*H*-1, 2, 3-Triazole to Afford **3a**[a].



1a **3a** **4**

Entry	Catalyst	Additive	Solvent	*t* (h)	Yield (%) [b]	E/Z ratio[c]
1	**VIII**	HCl	DCM	60	83	1:0.89
2	**II**	TFA	DCM	30	85	1:0.69
3	**VII**	TFA	DCM	7	89	1:0.60
4	**IX**	*p*TsOH•H_2O	DCM	10	84	1:0.49
5	**IX**	TFA	DCM	8	87	1:0.45
6	**IX**	CH_3SO_3H	DCM	10	85	1:0.63
7	**IX**	CF_3SO_3H	DCM	6	91	1:0.53
8	**IX**	TFA	DCE	9	88	1:0.41
9	**IX**	TFA	toluene	10	83	1:0.45
10	**IX**	TFA	MeOH	60	47[d]	1:0.45 [d]
11	**X**	None	DCM	48	90	1:0.83

[a] Reaction conditions: unless specified, a mixture of phenyl-propynal **1a** (0.05mmol), 1*H*-1, 2, 3-triazole (0.058mmol), catalyst (0.01mmol) and additive (0.01mmol) in solvent was stirred at r.t. for a specified time. [b] Isolated yields. [c] Determined by ^{1}HNMR of isolated product based on the integral of hydrogen of aldehydes or the integral of hydrogen of alkenes. [d] Determined by ^{1}HNMR of crude reaction solution.

Figure 2.3 Tautomerism of Neutral 1*H*-1, 2, 3-Triazole

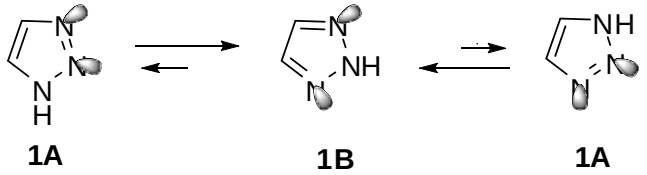
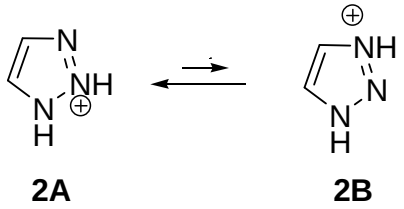


Figure 2.4 Tautomerism of Triazolium Ion

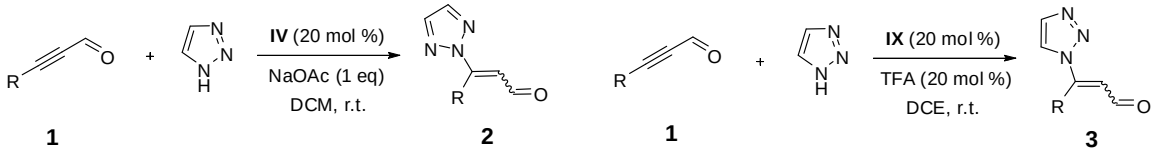


Having established the optimal protocols for the reactions, we proceeded to examine the substrate scope with the results summarized in Table 2.3. In general, the additions of 1*H*-1, 2, 3-triazole to alkynals **1** which afforded compounds **2** proceeded with high yields (75%-96%) and good stereoselectivity (*E*/*Z* ratio ranged from 82:18 to 95:5) within 2 hours. It is notable that alkynals were more active toward the nucleophile 1*H*-1, 2, 3-triazole under the present condition compared with the corresponding enals; for example, cinnamaldehyde gave only low conversions (<20%)[12]. Phenyl-propynal derivatives bearing electron-withdrawing group on the *meta*- and *para*-position of the benzene ring gave slightly poor stereoselectivity (Table 2.3, entry 9-12). The similar stereoselectivity were observed for *meta*- and *para*- position halogen substituted phenyl-propynal (Table 2.3, entry 4-7). Only strong electron-donating group resulted in a little poor stereoselectivity (Table 2.3, entry 2 *vs.* 3). To our surprise, among the substrates we surveyed, *ortho*-fluoro and *meta*-trifluoromethane substituted phenyl-propynal afforded

distinctive stereoselectivity (*E*/*Z* ratio were 95:5 and 91:9 respectively). The aliphatic alkynal also works well with good stereoselectivity although the reaction yield is relatively low (Table 2.3, entry 14).

As for the reactions which synthesized compound **3**, longer reaction time was required. For aromatic alkynals **1**, regardless of electron-donating and electron-withdrawing substitutents on the phenyl ring, participated in the process in moderate yield (79%-90%). However, the *E*/*Z* ratio ranged from 66:34 to 77:23. It is worthy of point out that the reaction proceeded with much better stereoselectivity (*E*/*Z* ratio was 89:11) for aliphatic alkynal (Table 2.3, entry 14).

Table 2.3 Scope of the Organocatalytic Regio- and Stereoselective Michael Addition of 1*H*-1, 2, 3-Triazole to Substituted Phenyl-propynal **1a**-**m** to Afford **2**[a] and **3**[b] Respectively.



1 **2** **1** **3**

Entry	R	2			3		
		t (h)	Yield (%) [c]	*E*/*Z* ratio[d]	*t* (h)	Yield (%) [c]	*E*/*Z* ratio[d]
1	Ph	2	94	86:14	9	88	71:29
2	*p*-$CH_3OC_6H_4$	2	92	84:16	10	89	69:31
3	*p*-$CH_3C_6H_4$	2	89	85:15	10	87	70:30
4	*p*-BrC_6H_4	2	90	85:15	10	88	71:29
5	*p*-ClC_6H_4	2	93	84:16	10	90	70:30

6	*p*-FC_6H_4	2	90	86:14	10	83	68:32
7	*m*-FC_6H_4	2	96	86:14	10	91	77:23
8	*o*-FC_6H_4	2	96	95:5	10	86	73:27
9	*m*-$NO_2C_6H_4$	2	95	82:18	11	89	69:31
10	*p*-$NO_2C_6H_4$	2	88	84:16	10	83	68:32
11	*m*-CNC_6H_4	2	90	83:17	10	79	69:31
12	*p*-CNC_6H_4	2	92	82:18	10	80	66:34
13	*m*-$CF_3C_6H_4$	2	93	91:9	10	82	66:34
14	*n*-C_5H_{11}	2	75	92:8	11	67	89:11

[a] Reaction conditions: unless specified, a mixture of substituted phenyl-propynal **1** (0.08mmol), 1*H*-1, 2, 3-triazole (0.096mmol), catalyst **IV** (0.016mmol) and NaOAc (0.08mmol) in dichloromethane (0.15ml) was stirred at r.t. for 2 h. [b] Reaction conditions: unless specified, a mixture of substituted phenyl-propynal **1** (0.08mmol), 1*H*-1, 2, 3-triazole (0.092mmol), catalyst **IX** (0.016mmol) and trifluoroacetic acid (0.016mmol) in DCE (0.15ml) was stirred at r.t. for a specified time. [c] Isolated yields. [d] Determined by ^{1}HNMR of isolated product based on the integral of hydrogen of aldehydes or the integral of hydrogen of alkenes.

2.5 Conclusions

In summary, we have developed a new strategy for regio- and stereocotrolled synthesis of trisubstituted alkenes by employing appropriate organocatalysts and additives via iminium-ion mechanism starting from alkynals with high efficiency and good stereoselectivity. Under the catalysis of (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine and sodium acetate as additive, the *N*-2 addition product can be achieved in very good yield and the *Z/E* ratio is up to 5:95. Under the catalysis of imidazolidine-2-carboxylic

acid and TFA as additive, the *N*-1 addition product can be obtained in good yield and the *Z/E* ratio is nearly 1:2.

2.6 Supporting Information

General information: (This information is valid for all the experimental parts)

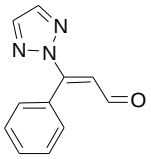
All commercial reagents and solvents were used without further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on Sorbent Technologies silica gel plates with fluorescence F_{254} indicator. And column chromatography was performed using the indicated solvent on Merck 60 silica gel (230-400 mesh).^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 500. ^{1}H NMR data were reported as follows: chemical shifts in ppm using 7.26 signal of $CDCl_3$ and 2.50 signal of DMSO-d_6 as reference respectively, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (*J*), and integration. And ^{13}C NMR data were reported in ppm using 77.0 signal of $CDCl_3$ and 39.50 signal of DMSO-d_6 as reference respectively.

General procedure for Michael addition of 1*H*-1, 2, 3-triazole to substituted phenylpropynal to afford compound 2

To a solution of substituted phenylpropynal (0.08mmol), (*s*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine (2.61ul, 0.016mmol) and sodium acetate (6.56mg, 0.08mmol) in dichloromethane (0.15ml) was added 1*H*-1, 2, 3-triazole (5.56ul, 0.096mmol). The resulting solution was stirred at room temperature for a specified time. Then the reaction

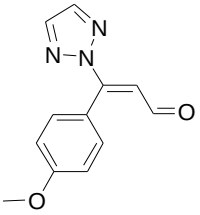
mixture was directly purified by column chromatography, eluted with hexane/EtOAc to afford the desired product.

The following spectra information is related with the major isomer.



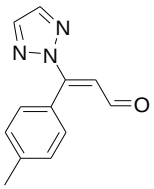
3-Phenyl-3-[1, 2, 3] triazol-2-yl-propenal (2a) (Table 2.3, Entry 1)

The title compound was prepared according to the general procedure, as described above in 94% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.51 (d, J = 8.0 Hz, 1H), 7.87 (s, 2H), 7.59~7.56 (m, 1H), 7.53~7.50 (m, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.1, 155.5, 137.8, 131.1, 129.8, 128.5, 118.7.



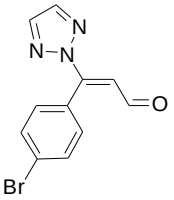
3-(4-Methoxy-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2b) (Table 2.3, Entry 2)

The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.54 (d, J = 7.5 Hz, 1H), 7.87 (s, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.01(d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.2, 161.9, 155.5, 137.7, 132.9, 121.9, 118.5, 114.0, 55.4.



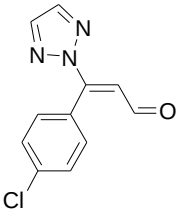
3-*p*-Tolyl-3-[1, 2, 3] triazol-2-yl-propenal (2c) (Table 2.3, Entry 3)

The title compound was prepared according to the general procedure, as described above in 89% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.53 (d, J = 8.0 Hz, 1H), 7.86 (s, 2H), 7.37~7.31 (m, 4H), 7.02 (d, J = 8.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.2, 155.7, 141.6, 137.7, 131.1, 129.2, 126.9, 118.6, 21.5.



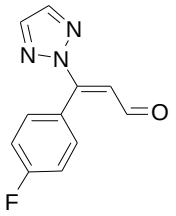
3-(4-Bromo-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2d) (Table 2.3, Entry 4)

The title compound was prepared according to the general procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.51 (d, J = 8.0 Hz, 1H), 7.87 (s, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 154.2, 137.9, 132.5, 131.9, 128.7, 125.9, 118.8.



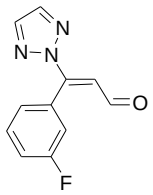
3-(4-Chloro-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2e) (Table 2.3, Entry 5)

The title compound was prepared according to the general procedure, as described above in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.51 (d, J = 8.0 Hz, 1H), 7.87 (s, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.41(d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 154.2, 137.9, 137.2, 132.4, 129.8, 128.9, 118.9.



3-(4-Fluoro-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2f) (Table 2.3, Entry 6)

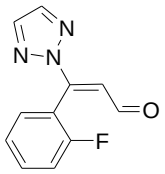
The title compound was prepared according to the general procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.46 (d, J = 8.0 Hz, 1H), 7.82 (s, 2H), 7.43~7.41 (m, 2H), 7.19~7.15 (m, 2H), 7.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.6, 164.3 (J = 251 Hz), 154.3, 137.9, 133.2 (J = 8.6 Hz), 118.9, 115.9 (J = 22 Hz).



3-(3-Fluoro-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2g) (Table 2.3, Entry 7)

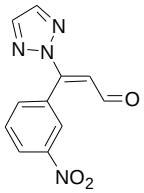
The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.51 (d, J = 8.0 Hz, 1H), 7.87 (s, 2H), 7.52~7.48 (m, 1H), 7.30~7.27 (m, 2H), 7.20~7.18 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H); ^{13}C

NMR ($CDCl_3$, 125 MHz): δ 191.4, 162.3 (J = 247 Hz), 153.8, 137.9, 131.7 (J = 7.8 Hz), 130.2 (J = 8.1 Hz), 127.0, 118.9, 118.2 (J = 21 Hz).



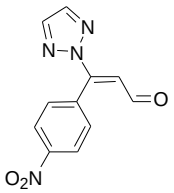
3-(2-Fluoro-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2h) (Table 2.3, Entry 8)

The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (d, J = 8.0 Hz, 1H), 7.89 (s, 2H), 7.60~7.56 (m, 1H), 7.47~7.44 (m, 1H), 7.32~7.29 (m, 1H), 7.25~7.21 (m, 1H), 7.15 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.2, 160.4 (J = 250 Hz), 150.0, 137.8, 133.1 (J = 8.0 Hz), 132.7, 124.2, 119.2, 118.1 (J = 15 Hz), 116.2 (J = 21 Hz).



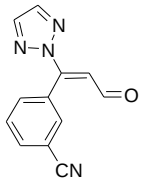
3-(3-Nitro-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2i) (Table 2.3, Entry 9)

The title compound was prepared according to the general procedure, as described above in 95 % yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 8.5 Hz, 1H), 8.36 (s, 1H), 7.89 (s, 2H), 7.82 (d, J = 7.5 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 152.4, 148.2, 138.2, 136.7, 131.4, 129.7, 126.0, 125.6, 119.2.



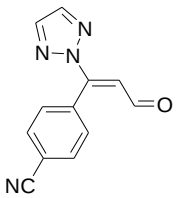
3-(4-Nitro-phenyl)-3-[1, 2, 3] triazol-2-yl-propenal (2j) (Table 2.3, Entry 10)

The title compound was prepared according to the general procedure, as described above in 88 % yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.49 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 9.0 Hz, 2H), 7.89 (s, 2H), 7.68 ((d, J = 8.5 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 152.6, 149.2, 138.2, 136.0, 132.2, 123.7, 119.2.



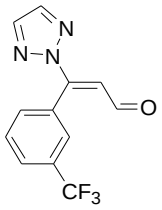
3-(3-Oxo-1-[1, 2, 3] triazol-2-yl-propenyl)-benzonitrile (2k) (Table 2.3, Entry 11)

The title compound was prepared according to the general procedure, as described above in 90 % yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.48 (d, J = 8.0 Hz, 1H), 7.89 (s, 2H), 7.86 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.5, 152.6, 138.2, 135.1, 134.4, 134.2, 131.2, 129.5, 119.2, 117.5, 113.3.



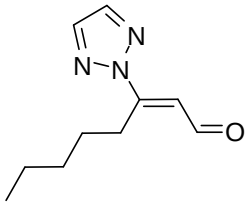
4-(3-Oxo-1-[1, 2, 3] triazol-2-yl-propenyl)-benzonitrile (2l) (Table 2.3, Entry 12)

The title compound was prepared according to the general procedure, as described above in 92 % yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.47 (d, J = 8.0 Hz, 1H), 7.88 (s, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.6, 153.0, 138.2, 132.2, 131.7, 129.2, 119.1, 117.7, 114.9.



3-[1, 2, 3] Triazol-2-yl-3-(3-trifluoromethyl-phenyl)-propenal (2m) (Table 2.3, Entry 13)

The title compound was prepared according to the general procedure, as described above in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.48 (d, J = 8.0 Hz, 1H), 7.89 (s, 2H), 7.84~7.83 (m, 1H), 7.74 (s, 1H), 7.68 (d, J = 4.5 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H).^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.1, 153.6, 138.1, 134.3, 130.7, 129.2, 127.8 (J = 8.8 Hz), 122.2 (J = 50 Hz), 119.1.

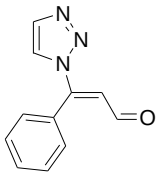


3-(2H-1,2,3-triazol-2-yl)oct-2-enal(2n) (Table 2.3, Entry 14)

The title compound was prepared according to the general procedure, as described above in 75% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ10.09 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 6.0 Hz, 2H), 6.94 (d, J = 7.5 Hz, 1H), 3.30 (t, J= 7.5 Hz, 2H), 1.75~1.68 (m, 2H), 1.43~1.32 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ190.1, 156.8, 137.3, 116.3, 31.4, 29.2, 27.5, 22.3, 13.8.

General procedure for Michael addition of 1*H*-1, 2, 3-triazole to substituted phenylpropynal to afford compound 3

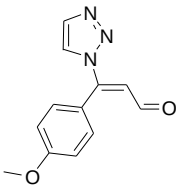
To a solution of substituted phenylpropynal (0.08mmol), imidazolidine-2-carboxylic acid organocatalyst (3.52mg, 0.016mmol) and trifluoroacetic acid (1.23ul, 0.016mmol) in 1, 2-dichloroethane (0.15ml) was added 1*H*-1, 2, 3-triazole (5.33ul, 0.092mmol). The resulting solution was stirred at room temperature for 2 hours. Then the reaction mixture was directly purified by column chromatography, eluted with hexane/EtOAc to give the desired product.



3-Phenyl-3-[1, 2, 3] triazol-1-yl-propenal (3a) (Table 2.3, Entry 1)

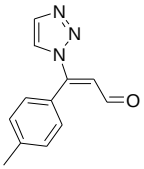
The title compound was prepared according to the general procedure, as described above in 88% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.54 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.57~7.53 (m, 2H), 7.47~7.44 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125

MHz): δ 191.4, 152.3, 134.5, 132.3, 130.6, 129.3, 127.7, 124.1, 120.2.



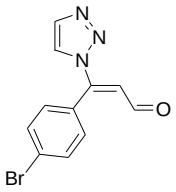
3-(4-Methoxy-phenyl)-3-[1, 2, 3] triazol-1-yl-propenal (3b) (Table 2.3, Entry 2)

The title compound was prepared according to the general procedure, as described above in 89% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.56 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.53 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 7.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.5, 162.5, 152.3, 134.4, 132.4, 126.3, 124.2, 119.8, 114.7, 55.6.



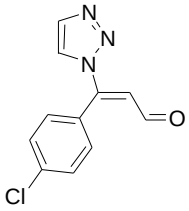
3-p-Tolyl-3-[1, 2, 3] triazol-1-yl-propenal (3c) (Table 2.3, Entry 3)

The title compound was prepared according to the general procedure, as described above in 87% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.55 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 0.5 Hz, 1H), 7.49 (d, J = 1 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 7.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.5, 152.5, 142.6, 134.4, 130.6, 129.9, 127.6, 124.1, 120.0, 21.5.



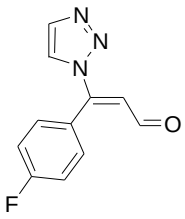
3-(4-Bromo-phenyl)-3-[1, 2, 3] triazol-1-yl-propenal (3d) (Table 2.3, Entry 4)

The title compound was prepared according to the general procedure, as described above in 88% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.55 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.52 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.6, 151.0, 134.6, 132.6, 132.0, 128.9, 126.7, 123.7, 120.4.



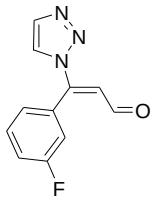
3-(4-Chloro-phenyl)-3-[1, 2, 3] triazol-1-yl-propenal (3e) (Table 2.3, Entry 5)

The title compound was prepared according to the general procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.55 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.7, 151.0, 138.5, 134.7, 131.9, 129.7, 128.8, 123.8, 120.5.



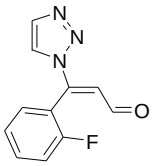
3-(4-Fluoro-phenyl)-3-[1,2,3]triazol-1-yl-propenal (3f) (Table 2.3, Entry 6)

The title compound was prepared according to the general procedure, as described above in 83% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.53 (d, J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.51 (s, 1H), 7.46~7.43 (m, 2H), 7.26~7.22 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.8, 164.7 (J = 253 Hz), 151.2, 134.6, 132.8 (J = 8.8 Hz), 126.1, 123.8, 120.4, 116.7 (J = 22 Hz).



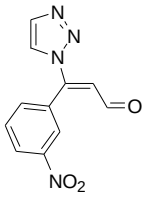
3-(3-Fluoro-phenyl)-3-[1, 2, 3] triazol-1-yl-propenal (3g) (Table 2.3, Entry 7)

The title compound was prepared according to the general procedure, as described above in 91% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.57(d, J = 8.0Hz, 1H), 7.80 (s, 1H), 7.60~7.55 (m, 1H), 7.54 (s, 1H), 7.37~7.34 (m, 1H), 7.30~7.27 (m, 1H), 7.19 (d, J = 8.5Hz, 1H), 7.01 (d, J = 8.0Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.7, 162.7 (J = 249 Hz), 150.6, 134.6 (J = 25Hz), 131.2 (J = 8Hz), 126.5, 123.8, 120.5, 119.0 (J = 21Hz), 117.6 (J = 23Hz).



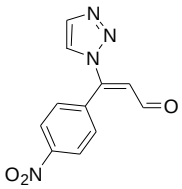
3-(2-Fluoro-phenyl)-3-[1, 2, 3] triazol-1-yl-propenal (3h) (Table 2.3, Entry 8)

The title compound was prepared according to the general procedure, as described above in 86% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.55 (d, J = 7.5 Hz, 1H), 7.80 (s, 1H), 7.68~7.64 (m, 1H), 7.58 (s, 1H), 7.49~7.47 (m, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.32~7.28 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.5, 160.2 (J = 251 Hz), 146.6, 134.6, 133.9 (J = 8.1 Hz), 132.4, 125.0 (J = 15 Hz), 123.1, 120.7, 116.8 (J = 21 Hz).



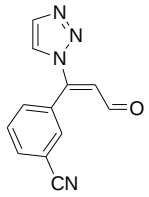
3-(3-Nitro-phenyl)-3-[1, 2, 3] triazol-1-yl-propenal (3i) (Table 2.3, Entry 9)

The title compound was prepared according to the general procedure, as described above in 89% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 7.5 Hz, 1H), 8.34 (s, 1H), 7.84~7.77 (m, 3H), 7.65 (s, 1H), 6.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.6, 149.6, 148.5, 136.2, 133.0, 131.6, 130.5, 126.4, 125.4, 123.4, 120.8.



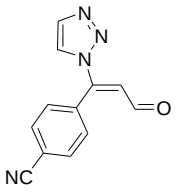
3-(4-Nitro-phenyl)-3-[1,2,3]triazol-1-yl-propenal (3j) (Table 2.3, Entry 10)

The title compound was prepared according to the general procedure, as described above in 83% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.53 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 8.5 Hz, 2H), 7.81 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.62 (s, 1H), 6.96 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 149.7, 135.9, 135.0, 131.8, 128.6, 124.5, 124.3, 120.8.



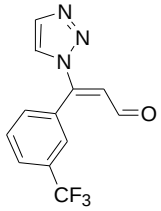
3-(3-Oxo-1-[1, 2, 3] triazol-1-yl-propenyl)-benzonitrile (3k) (Table 2.3, Entry 11)

The title compound was prepared according to the general procedure, as described above in 79% yield. ^{1}H NMR (DMSO-d^6, 500 MHz): δ 9.42 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 1.0 Hz, 1H), 8.21 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 1.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d^6, 125 MHz): δ 191.3, 150.2, 135.5, 134.7, 134.6, 134.5, 131.9, 129.9, 125.1, 119.7, 118.0, 112.0.



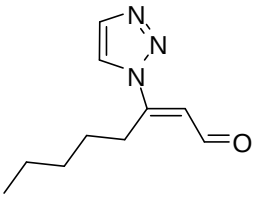
4-(3-Oxo-1-[1, 2, 3] triazol-1-yl-propenyl)-benzonitrile (3l) (Table 2.3, Entry 12)

The title compound was prepared according to the general procedure, as described above in 80% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.52 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.81 (s, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.58 (s, 1H), 6.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 150.0, 134.9, 134.2, 132.8, 131.3, 123.4, 120.7, 117.3, 115.7.



3-[1, 2, 3] Triazol-1-yl-3-(3-trifluoromethyl-phenyl)-propenal (3m) (Table 2.3, Entry 13)

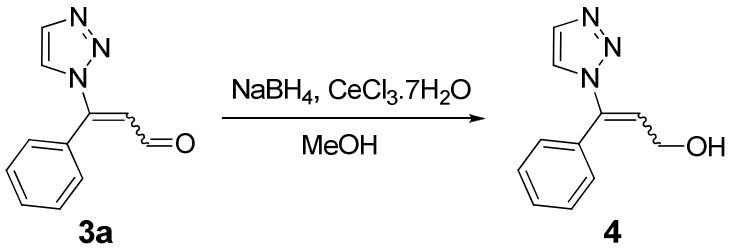
The title compound was prepared according to the general procedure, as described above in 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.52 (d, J = 7.5 Hz, 1H), 7.89 (d, J =7.5 Hz, 1H), 7.80 (s, 1H), 7.72 (s, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.3, 150.5, 134.9, 133.8, 130.8 (J = 9.3 Hz), 130.0, 128.5, 127.2, 124.4, 123.6, 120.7.



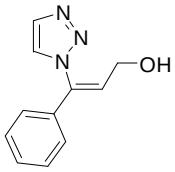
3-(1H-1,2,3-triazol-1-yl)oct-2-enal(3n) (Table 2.3, Entry 14)

The title compound was prepared according to the general procedure, as described above in 67% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ10.11 (d, J = 7.5 Hz, 1H), 7.94 (s, 1H), 7.82 (s, 1H), 6.44 (d, J = 7.5 Hz, 1H), 3.32 (t, J = 8.0 Hz, 2H), 1.71~1.65 (m, 2H), 1.42~1.27 (m, 4H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.5, 154.9, 134.8, 121.5, 117.7, 31.3, 28.8, 28.4, 22.2, 13.8.

Determination of Configuration:



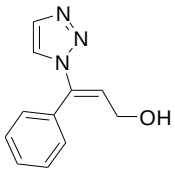
3a **4**



The compound **4** was prepared according to the general procedure:

The obtained compound **3a** (39.8mg, 0.2mmol) in 2ml anhydrous MeOH at 0^{o}C was treated with cerium (III) chloride heptahydrate (89.4mg, 0.24mmol) and sodium borohydride (9.1mg, 0.24mmol). After 1 hour, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (2ml), and extracted with dichloromethane (3 × 20ml). The combined organic layer was then washed once with brine (50ml), dried over anhydrous Na_2SO_4, filtered and concentrated on vacuo. Purification of the residue by column chromatography affords the two isomeric enols in 72% yield totally.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (s, 1H), 7.56 (s, 1H), 7.35 (t, J = 8.0 Hz, 3H), 7.14 (d, J = 7.0 Hz, 2H), 6.40 (t, J = 7.0 Hz, 1H), 4.11 (d, J = 7.0 Hz, 2H), 2.96 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.5, 135.3, 133.7, 129.7, 128.9, 126.6, 126.5, 125.1, 57.9.



The title compound was prepared according to the general procedure, as described above. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 1H), 7.43~7.41 (m, 3H), 7.39 (s, 1H), 7.25 (d, J = 6.0 Hz, 2H), 6.68 (d, J = 7.0 Hz, 1H), 4.30 (d, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.2, 133.5, 132.4, 129.9, 129.3, 128.8, 123.7, 123.6, 58.8.

2.7 Reference

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[11] In fact, in the cases with larger Michael donor, the ether moieties had great influence on the *E*/*Z* ratio. In order to prove this point, we investigated the Michael addition between phenyl-propynal **1a** and 5-phenyl-1*H*-tetrazole in DCM at r.t. in the presence of 20 mol% catalysts **I** and **II**. When changing from less bulkyTMS catalyst **I** to bulky TBS catalyst **II,** the*E*/*Z* ratio can be enhanced significantly from 1:1.08 to 1:0.32.

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Chapter 3

Alkynal Involved Organocatalytic Cascade Reactions

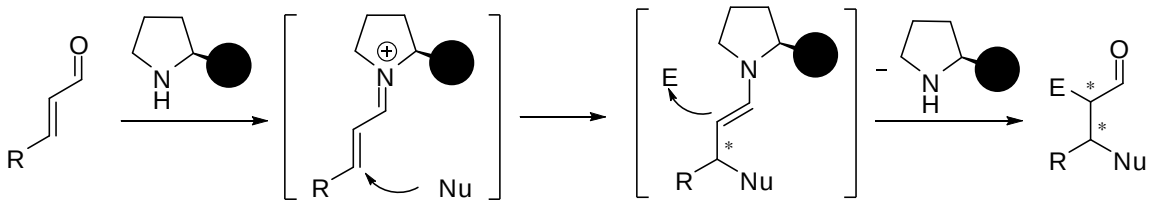
3.1 Background and Significance

Highly efficient constructions of complex organic molecules continue to receive paramount attention in modern synthetic realm. So far, organocatalytic cascade or tandem reactions have grown into one of the most robust and appealing synthetic methodologies which enable rapid assemble versatile biologically relevant compounds containing higher levels of molecular complexity with high enantiomeric purity in an economically and environmentally friendly manner[1]. Of crucial importance is that the remarkable achievements definitely accelerate the development of pharmaceutical industry[2].

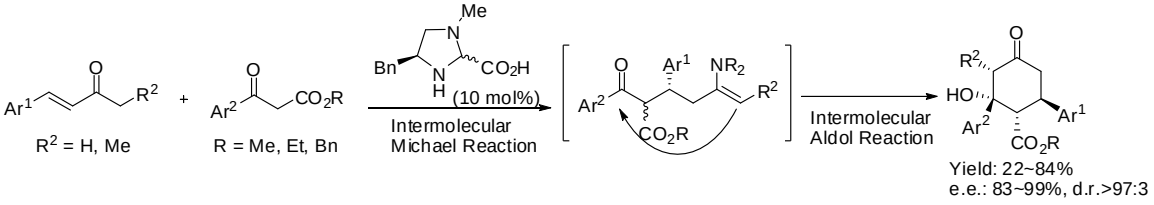
Chiral secondary amines are probably the most successful organocatalyst in organocatalytic asymmetric cascade reactions to date, as secondary amines are capable of both enamine and iminium catalysis[3]. The versatile possibilities of combination of these two catalytic activation modes in one protocol allows for rapid conversion of simple achiral starting materials into complex, highly enantioenriched products although their scope is mainly limited to carbonyl systems[1]. Among them, the iminium-enamine combination has turned out to be very powerful. The enal substrate is first activated through iminium-ion formation, and then facilitates the nucleophilic conjugate addition. The resulting enamine can then undergo a second reaction with an electrophile to afford

the products, which in general contain two new stereocenters (Scheme 3.1). In 2004, Jørgensen and co-workers developed an orgacatalytic Michael-aldol cascade for the assembly of optically active cyclohexanones[4]. Today, numerous examples of this combination can be found in the literature[1a].

Scheme 3.1 the Iminium-Enamine Combination



Scheme 3.2 Orgacatalytic Michael-aldol Cascade for the Assembly of Optically Active Cyclohexanones

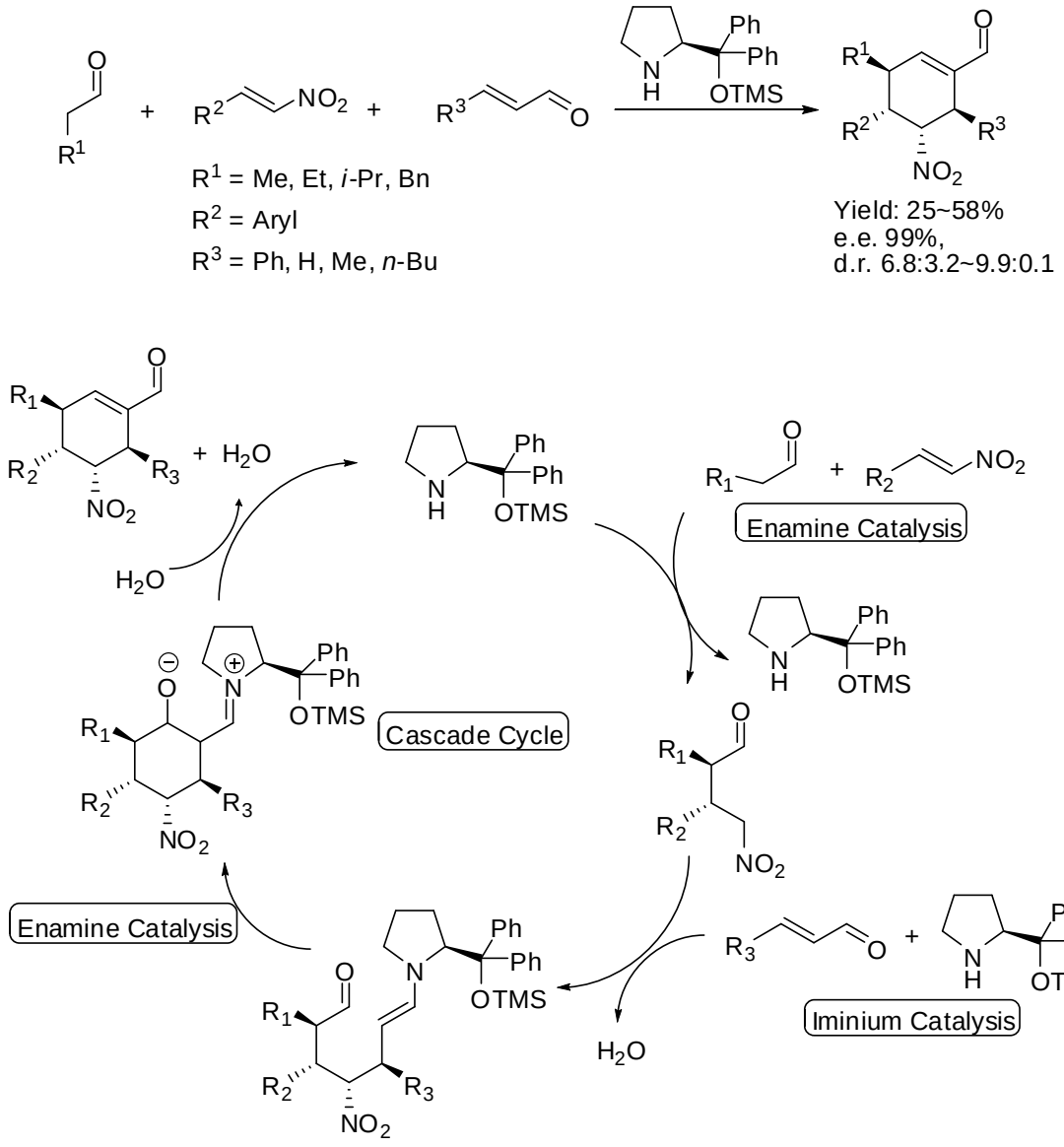


Besides the widely explored iminium-enamine cascade sequence, many other cascade reactions were achieved by simply changing the order of activation modes such as enamine-enamine activation, enamine-iminium activation[1a,1f].

The concept of organocatalytic cascade reaction is also extended to a more complex scenario later. The leading example is reported by Enders and co-workers about the three component triple cascade reaction for the stereocontrolled formation of tetrasubstituted cyclohexene carbaldehyde bearing up to four stereogenic centres[5]. The

reaction proceeds through a Michael-Michael-aldol condensation cascade which can be explained as enamine-iminium-enamine sequence (Scheme 3.3).

Scheme 3.3 Orgacatalytic Michael-Michael-aldol Triple Cascade Reaction



This strategy was substantially extended to quadruple cascade reactions such as Michael-Michael-Michael-aldol condensation reaction which go through an iminium-

enamine-iminium-enamine catalytic cycle. They enable the consecutive formation of four new bonds and provide efficient methods for construction of highly functionalized trisubstituted cyclohexene carbaldehydes[6], spirooxindole motif[7] and marine meroterpene (+)-conicol[8].

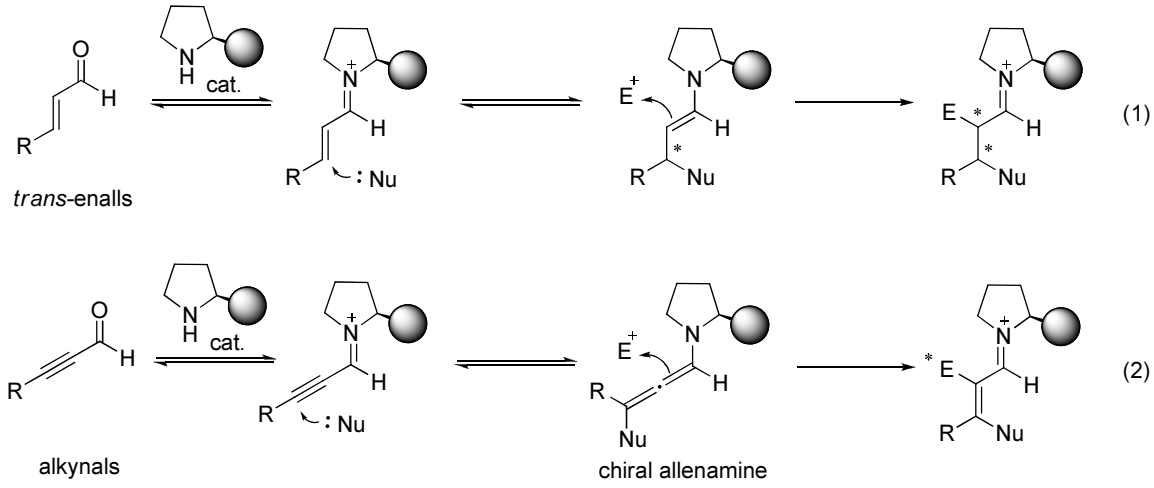
3.2 Research Design

Recently, tremendous efforts have been directed to expand the scope of organocatalyzed cascade reactions triggered by Michael additions to enals which efficiently furnish valuable chiral building blocks via combined iminium-enamine activation strategy[1a] (Figure 3.1, Eq.(1)) to control the enantioselectivity at the β-carbon atom of α, β-unsaturated aldehydes. Importantly, the geometry of the *trans*-enals controls the Michael-initiated cascade reactions to afford high enantio and/or diastereoselectivity. To the best of our knowledge, in contrast to these widely reported iminium-enamine catalyzed systems, the paradigms for organocatalytic cascade/tandem reactions involving conjugate additions to the corresponding alkynals in an asymmetric fashion have not yet been reported so far presumably owing to the fact that the alkynal substrates process no prochiral center at the β-carbon atom. Recently, MacMillan and co-workers reported the use of propynal as the dienophile in an efficient iminium activated [4+2] cycloaddition reaction[9].

To perform an enantioselective cascade reaction on an alkynal substrate, we envision that their use instead of an enal in the initial Michael addition to an iminium ion

formed *in situ* would afford an unprecedented chiral allenamine intermediate (Figure 3.1, Eq. (2))[10~13]. The allenamine formed would then act as the nucleophile in a subsequent enantioselective reaction with an electrophile to produce a new stereogenic center. In this context, the stereochemistry is governed by a poorly understood chiral allenamine[11~13] that is formed *in situ* in the second step of the cascade reaction, whilst in the classic iminium-enamine cascade processes, the enantioselectivity is generally controlled by the initial conjugate addition step.

Figure 3.1 Conventional Iminium-Enamine (1) and Novel Iminium-Allenamine (2) Activation Strategies in Organocatalytic Enantioselective Cascade Reactions.

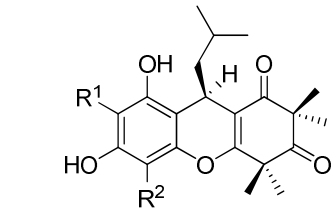


3.3 Iminium–Allenamine Cascade Catalysis: One-Pot Access to Chiral 4*H*-Chromenes by a Highly Enantioselective Michael–Michael Sequence[14]

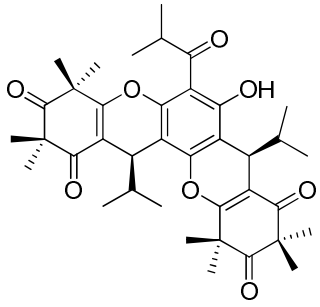
3.3.1 Introduction

4*H*-Chromenes are a core structural feature of an array of fascinating natural products that have intriguing biological activities (Figure 3.2). For example, rhodomyrtone and rhodomyrtosone B show potent antibiotic activities[15], whereas the dimeric 4*H*-chromene acylphloroglucinol, myrtucommulone E, serves as a promising α-glucosidase inhibitor with antibacterial activity[16]. These frameworks have become attractive targets in organic synthesis[17, 18], and despite significant advances having been made, asymmetric methods for their construction are still extremely rare[19].

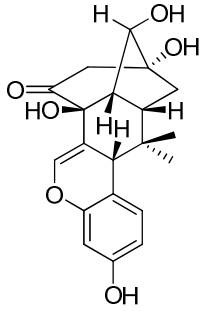
Figure 3.2 Selected Examples of 4*H*-Chromenes as Substructures in Biologically Interesting Natural Products



Rhodomyrtonne: $R^1 = Me_2CHCH_2CO$, $R^2 = H$
Rhodomyrtosone B: $R^1 = H$, $R^2 = Me_2CHCH_2CO$



Myrtucommulone E



Miroestrol

3.3.2 Results and Discussion

Motivated by the above idea and in continuation of our previous research interest in organocatalytic asymmetric cascade reactions for the construction of chromanes or chromenes[20], we ventured into the development of the new double Michael additions between 2-(*E*)-(2-Nitrovinyl)-phenols and alkynals considering the nitroalkenes are among the most reactive Michael acceptors to explore the feasibility of the iminium–allenamine cascade catalysis.

We started our investigations by conducting the model reaction between phenyl-propynal **1a** and 2-(*E*)-(2-Nitrovinyl)-phenol **2a** in dichloromethane at room temperature in the presence of 20 mol% organocatalyst **I** in view of the fact that chiral secondary amine, especially, diarylprolinol silyl ether organocatalysts are capable of both iminium and enamine catalysis in promoting enals cascade reactions[21] (Figure 3.3 and Table 3.1). Encouragingly, the reaction proceeded to completion within 1 h to yield the desired product **3a** in an excellent yield (95%) and in an excellent ee (97%) (Table 3.1, entry 1).

This reaction shows that alkynals are more active than enals. Despite all that good results, we still made a careful optimization. A screen of other diarylprolinol silyl ether analogues **II–IV** revealed that the more bulky TBDMS catalyst **III** gave slightly higher enantioselectivities (Table 3.1, entries 2-4), although diamine **V**, reported by Barbas and Betancort, showed poor enantiocontrol (Table 3.1, entry 5)[22]. Accordingly, catalyst **III** was chosen for further optimization of the reaction conditions. A brief survey of different reaction solvents revealed toluene to be the most suitable for this procedure (Table 3.1, entries 6 and 7). The process displayed low dependence on the base additive (Table 3.1, entry 8). Lowering the reaction temperature to 0 ºC and the catalyst loading to 15 mol% resulted in a higher ee (>99%) and higher yield (97%) without considerably prolonging the reaction time (Table 3.1, entry 9 and 10).

Figure 3.3 Secondary Amine Catalysts Screened

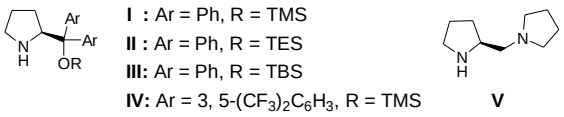
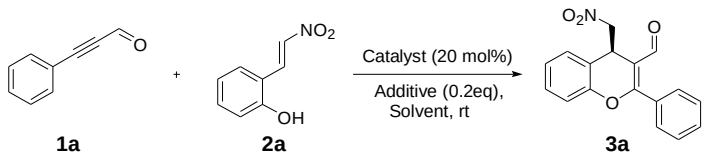


Table 3.1 Optimization Reaction Conditions for the Organocatalytic Asymmetric Cascade Oxa-Michael-Michael Reaction between Phenyl-propynal **1a** and 2-(*E*)-(2-Nitrovinyl)-phenol **2a**[a].



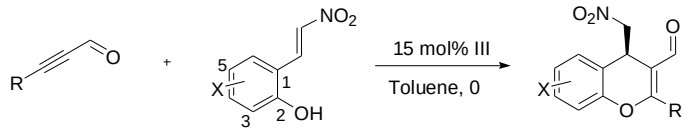
Entry	Catalyst	Additive	Solvent	*t* (h)	Yield (%) [b]	ee (%) [c]
1	**I**	None	CH_2Cl_2	1	95	97
2	**II**	None	CH_2Cl_2	1	93	98
3	**III**	None	CH_2Cl_2	1	92	98
4	**IV**	None	CH_2Cl_2	1	90	96
5	**V**	None	CH_2Cl_2	1	91	66
6	**III**	None	Toluene	1	94	99
7	**III**	None	DCE	1	92	98
8	**III**	NaOAc	Toluene	1	92	99
9	**III**[d]	None	Toluene	5	88	99
10	**III**[e]	None	Toluene	4	97	>99

[a] Reaction conditions: unless specified, a mixture of phenyl-propynal **1a** (0.11mmol), 2-(*E*)-(2-Nitrovinyl)-phenol **2a** (0.10mmol), catalyst (0.02mmol) and additive (0.02mmol) in solvent (0.8ml) was stirred at r.t. for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] 10 mol% of catalyst **III** was applied. [e] Performed at 0°C and 15 mol% of catalyst **III** was applied.

Having established the optimal conditions for this cascade oxa-Michael–Michael reaction, we then investigated the scope of this process. As shown in Table 3.2, the one-pot reaction promoted by organocatalyst **III** serves as a general and atom economical approach to "privileged" chiral 4*H*-chromenes, with formation of two C-C bonds, one new stereogenic center, and the incorporation of two versatile nitro and aldehyde functionalities that are available for further elaboration. Notably, in all cases, the reactions were completed in 4-5 hours, with excellent levels of enantioselectivity (98->99% ee) and in high yields (92-98%). Moreover, a broad substrate scope was observed.

Aromatic alkynals **1** that have electron-donating (Table 3.2, entries 2, 12, and 13) or electron withdrawing substituents (Table 3.2, entries 3-6 and 11) were investigated, and the effects of the substituent on the reaction was found to be very limited. These reactions proceeded very smoothly, affording excellent yields (92-98%) and excellent enantioselectivities (99->99%). A similar trend was observed with the structural variations of substrate **2** (Table 3.2, entries 7-9 and 11-13). Heteroaromatic alkynal thiophen-2-yl-propynal also effectively engaged in the cascade process (Table 3.2, entry 10). Finally, the reaction of the highly sterically hindered aliphatic alkynal also proceeded successfully, in 93% yield and 98% ee (Table 3.2, entry 14). The absolute configuration of product **3g** prepared under the optimal condition was determined to be *R* configuration by using single crystal X-ray diffraction (Figure 3.4).

Table 3.2 Catalyst **III** Promoted Asymmetric Cascade Oxa-Michael-Michael Reactions of Propynal **1** with 2-(*E*)-(2-Nitrovinyl)-phenol **2**[a].



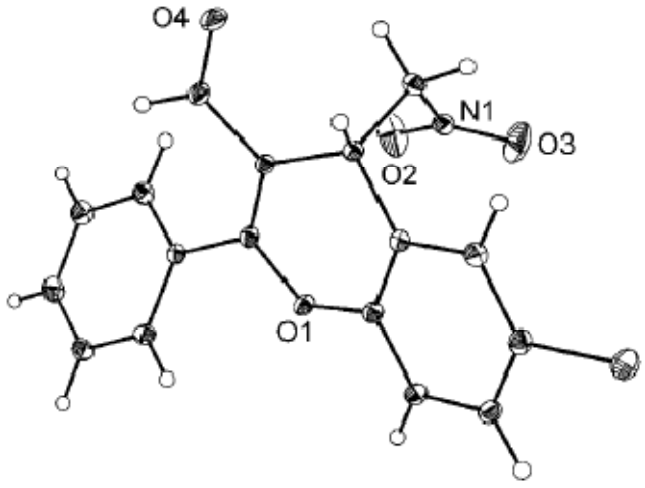
1 **2** **3a~k**

Entry	R	X	*t* (h)	Yield (%) [b]	ee (%) [c]
1	Ph	H	4	97	>99
2	4-$MeOC_6H_4$	H	5	93	99
3	4-ClC_6H_4	H	4	97	99
4	4-BrC_6H_4	H	4	95	99
5	4-$NO_2C_6H_4$	H	4	95	99

6	3-$NO_2C_6H_4$	H	4	93	99
7	Ph	5-Cl	4	92	99
8	Ph	3-MeO	4	95	98
9	Ph	5-MeO	4	97	99
10	Thienyl	H	4	92	99
11	4-BrC_6H_4	5-MeO	4	98	99
12	4-MeC_6H_4	5-Cl	4	94	99
13	4-MeC_6H_4	5-MeO	4	98	99
14	*t*-Bu	H	4	93	98

[a] Reaction conditions: unless specified, a mixture of propynal **1** (0.11mmol), 2-(*E*)-(2-Nitrovinyl)-phenol **2** (0.10mmol), catalyst **III** (0.015mmol) in Toluene (0.8ml) was stirred at 0°C for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or IC).

Figure 3.4 the Single-Crystal X-ray Structure of Compound **3g**, with Ellipsoids Set at 20% Probability



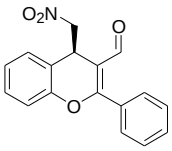
3.3.3 Conclusion

In conclusion, we have developed a novel asymmetric oxa-Michael–Michael reaction involving an unprecedented chiral iminium–allenamine cascade. Ynals are used for the first time in organocatalyzed asymmetric cascade reactions. This process is a viable one-pot approach to synthetically and biologically significant chiral 4*H*-chromenes in high yields and with excellent enantioselectivities. A broad substrate scope has been successfully employed in this reaction, including aromatic and aliphatic alkynals as Michael acceptors, and 2-(*E*)-(2-nitro-vinyl)-phenols as Michael donors/acceptors with significant structural variation. The proposed iminium-allenamine activation mode has potential applications in the development of new organocatalytic enantioselective cascade reactions.

3.3.4 Supporting Information

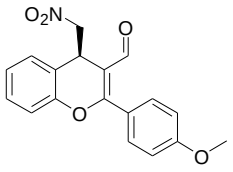
General procedure for Cascade Michael-Michael addition reaction:

To a solution of alkynal (0.11mmol), organocatalyst **III** (5.51mg, 0.015mmol) in toluene (0.8ml) was added 2-(*E*)-(2-Nitrovinyl)-phenol (0.10mmol). The resulting solution was stirred at 0℃ for a specified time. Then the reaction mixture was directly purified by column chromatography, eluted with hexane/EtOAc to afford the desired product.



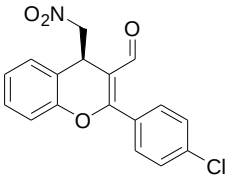
(*R*)-4-Nitromethyl-2-phenyl-4*H*-chromene-3-carbaldehyde (3a) (Table 3.2, Entry 1):

The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.58~7.56 (m, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.34~7.29 (m, 2H), 7.24~7.17 (m, 2H), 4.73~4.69 (m, 2H), 4.66~4.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.2, 169.8, 150.6, 131.7, 130.6, 130.3, 129.3, 128.6, 128.5, 125.9, 119.7, 117.1, 111.5, 79.6, 32.2; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 31.00 min, t_{major} = 21.57 min, ee > 99%; $[\alpha]_D^{27}$= +15.7 (c = 1.0 in $CHCl_3$).



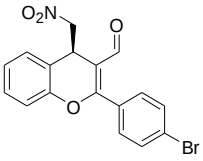
(*R*)-2-(4-Methoxy-phenyl)-4-nitromethyl-4*H*-chromene-3-carbaldehyde (3b) (Table 3.2, Entry 2):

The title compound was prepared according to the general procedure, as described above in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.62 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.36~7.29 (m, 2H), 7.23~7.19 (m, 2H), 7.02 (d, J = 8.5 Hz, 2H), 4.73~4.62 (m, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.1, 169.7, 162.6, 150.7, 132.1, 129.2, 128.5, 125.8, 122.8, 120.1, 117.1, 114.1, 110.7, 79.7, 55.5, 32.3; HPLC (Chiralpak IC, *i*-PrOH/hexane = 30/70, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 104.07 min, t_{major} = 39.79 min, ee = 99%; $[\alpha]_D^{27}$= -16.0 (c = 1.0 in $CHCl_3$).



(*R*)-2-(4-Chloro-phenyl)-4-nitromethyl-4*H*-chromene-3-carbaldehyde (3c) (Table 3.2, Entry 3):

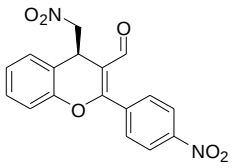
The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.37~7.31 (m, 2H), 7.26~7.18 (m, 2H), 4.76~4.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 168.5, 150.6, 138.2, 131.6, 129.4, 129.1, 128.5, 126.1, 119.6, 117.1, 111.8, 79.6, 32.3; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 34.53 min, t_{major} = 25.80 min, ee = 99%; $[\alpha]_D^{27}$= +14.0 (c = 1.0 in $CHCl_3$).



(*R*)-2-(4-Bromo-phenyl)-4-nitromethyl-4*H*-chromene-3-carbaldehyde (3d) (Table 3.2, Entry 4):

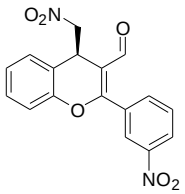
The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.36~7.31 (m, 2H), 7.26~7.23 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H),

4.76~4.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 168.5, 150.5, 132.0, 131.7, 129.5, 129.4, 128.5, 126.6, 126.1, 119.5, 117.1, 111.9, 79.6, 32.3; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 41.68 min, t_{major} = 26.58 min, ee = 99%; $[\alpha]_D^{27}$= -6.9 (c = 0.86 in $CHCl_3$).



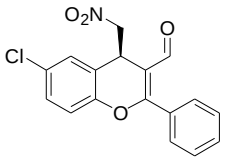
(*R*)-4-Nitromethyl-2-(4-nitro-phenyl)-4*H*-chromene-3-carbaldehyde (3e) (Table 3.2, Entry 5):

The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 8.39 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.39~7.34 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 4.83~4.79 (m, 1H), 4.72~4.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.0, 166.8, 150.4, 149.6, 136.6, 131.3, 129.6, 128.5, 126.4, 123.8, 119.1, 117.2, 113.1, 79.5, 32.3; HPLC (Chiralpak IC, *i*-PrOH/hexane = 40/60, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 112.58 min, t_{major} = 93.90 min, ee = 99%; $[\alpha]_D^{27}$= -5.6 (c = 1.0 in $CHCl_3$).



(*R*)-4-Nitromethyl-2-(3-nitro-phenyl)-4*H*-chromene-3-carbaldehyde (3f) (Table 3.2, Entry 6):

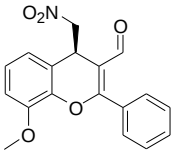
The title compound was prepared according to the general procedure, as described above in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.60 (s 1H), 8.51 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.39~7.33 (m, 2H), 7.27 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 4.83~4.78 (m, 1H), 4.72~4.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.0, 166.7, 150.4, 148.4, 136.2, 132.4, 129.9, 129.6, 128.5, 126.4, 126.2, 124.8, 119.1, 117.2, 112.9, 79.5, 32.3; HPLC (Chiralpak IC, *i*-PrOH/hexane = 40/60, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 110.28 min, t_{major} = 87.38 min, ee = 99%; $[\alpha]_D^{27}$= +42.4 (c = 1.0 in $CHCl_3$).



(*R*)-6-Chloro-4-nitromethyl-2-phenyl-4*H*-chromene-3-carbaldehyde (3g) (Table 3.2, Entry 7):

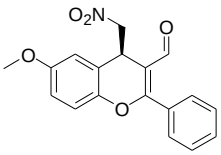
The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 7.62~7.51 (m, 5H), 7.31~7.30 (m, 2H), 7.15~7.13 (m, 1H), 4.79~4.76 (m, 1H), 4.67~4.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.1, 169.6, 149.3, 131.9, 130.9, 130.3, 129.5, 128.7, 128.2, 121.5, 118.6, 111.0, 79.3, 32.2; HPLC (Chiralpak IC, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min,

λ = 254nm): t_{minor} = 27.23 min, t_{major} = 22.94 min, ee = 99%; $[\alpha]_D^{27}$= +68.3 (c = 1.0 in $CHCl_3$).



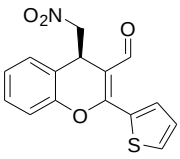
(*R*)-8-Methoxy-4-nitromethyl-2-phenyl-4*H*-chromene-3-carbaldehyde (3h) (Table 3.2, Entry 8):

The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.62 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.60~7.57 (m, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 4.74~4.62 (m, 3H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.2, 169.7, 148.3, 140.4, 131.8, 130.6, 128.7, 125.8, 121.0, 119.6, 111.6, 111.3, 79.6, 56.1, 32.3; HPLC (Chiralpak IC, *i*-PrOH/hexane = 40/60, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 49.63 min, t_{major} = 19.57 min, ee = 98%; $[\alpha]_D^{27}$= +90.2 (c = 1.0 in $CHCl_3$).



(*R*)-6-Methoxy-4-nitromethyl-2-phenyl-4*H*-chromene-3-carbaldehyde (3i) (Table 3.2, Entry 9):

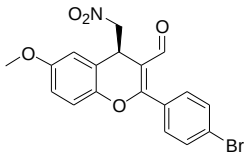
The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 7.62~7.57 (m, 3H), 7.52 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 9.0 Hz, 1H), 6.89~6.86 (m, 1H), 6.79 (s, 1H), 4.74~4.65 (m, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.3, 170.0, 157.3, 144.7, 131.7, 130.8, 130.3, 128.6, 120.6, 118.1, 115.2, 112.4, 110.7, 79.5, 55.7, 32.6; HPLC (Chiralpak IC, *i*-PrOH/hexane = 40/60, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 27.12 min, t_{major} = 21.48 min, ee = 99%; $[\alpha]_D^{27}$= +50.6 (c = 1.0 in $CHCl_3$).



(*R*)-4-Nitromethyl-2-thiophen-2-yl-4*H*-chromene-3-carbaldehyde (3j) (Table 3.2, Entry 10):

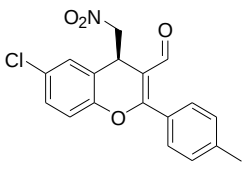
The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.90 (s, 1H), 7.70 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 3.5 Hz, 1H), 7.37~7.34 (m, 1H), 7.30~7.20 (m, 4H), 4.73 (t, J = 5.5 Hz, 1H), 4.64 (d, J = 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.2, 163.0, 150.4, 133.6, 132.2, 131.7, 129.4, 128.5, 127.8, 126.0, 120.0, 117.1, 111.5, 79.5, 32.4; HPLC (Chiralpak IC, *i*-

PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 70.58 min, t_{major} = 31.78 min, ee = 99%; $[\alpha]_D^{27}$= -8.8 (c = 1.0 in $CHCl_3$).



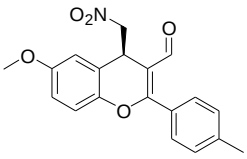
(*R*)-2-(4-Bromo-phenyl)-6-methoxy-4-nitromethyl-4*H*-chromene-3-carbaldehyde (3k) (Table 3.2, Entry 11):

The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.57 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 1H), 6.89~6.86 (m, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 4.76~4.71 (m, 1H), 4.68~4.64 (m, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 168.7, 157.4, 144.6, 132.0, 131.7, 129.7, 126.5, 120.4, 118.1, 115.3, 112.4, 111.0, 79.4, 55.8, 32.6; HPLC (Chiralpak IC, *i*-PrOH/hexane = 40/60, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 31.79 min, t_{major} = 25.25 min, ee = 99%; $[\alpha]_D^{27}$= +20.7 (c = 1.0 in $CHCl_3$).



(*R*)-6-Chloro-4-nitromethyl-2-p-tolyl-4*H*-chromene-3-carbaldehyde (3l) (Table 3.2, Entry 12):

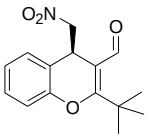
The title compound was prepared according to the general procedure, as described above in 94% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.60 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.34~7.29 (m, 4H), 7.15~7.13 (m, 1H), 4.77~4.72 (m, 1H), 4.66~4.62 (m, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.1, 169.8, 149.3, 142.7, 130.8, 130.3, 129.4, 128.2, 127.4, 121.7, 118.5, 110.6, 79.3, 32.2, 21.6; HPLC (Chiralpak IC, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 30.28 min, t_{major} = 25.69 min, ee = 99%; $[\alpha]_D^{27}$= +36.5 (c = 1.0 in $CHCl_3$).



(*R*)-6-Methoxy-4-nitromethyl-2-p-tolyl-4*H*-chromene-3-carbaldehyde (3m) (Table 3.2, Entry 13):

The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.59 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.5 Hz, 1H), 6.88~6.86 (m, 1H), 6.78 (d, J = 2.5 Hz, 1H), 4.71~4.63 (m, 3H), 3.81 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.3, 170.2, 157.2, 144.8, 142.4, 130.3, 129.3, 127.9, 120.8, 118.1, 115.2, 112.4, 110.4, 79.5, 55.7, 32.6, 21.6; HPLC (Chiralpak IC, *i*-PrOH/hexane = 30/70, flow rate = 0.7 mL/min, λ

= 254nm): t_{minor} = 38.12 min, t_{major} = 29.81 min, ee = 99%; $[\alpha]_D^{27}$= +30.8 (c = 1.0 in $CHCl_3$).



(*R*)-2-tert-Butyl-4-nitromethyl-4*H*-chromene-3-carbaldehyde (3n) (Table 3.2, Entry 14):

The title compound was prepared according to the general procedure, as described above in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.38 (s, 1H), 7.31~7.28 (m, 1H), 7.24~7.22 (m, 1H), 7.19~7.16 (m, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.72~4.70 (m, 1H), 4.49~4.43 (m, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.6, 178.5, 150.6, 129.0, 128.1, 125.7, 120.1, 116.5, 110.4, 79.9, 38.9, 32.5, 31.0; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 30/70, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 14.16 min, t_{major} = 12.08 min, ee = 98%; $[\alpha]_D^{27}$= -44.9 (c = 1.0 in $CHCl_3$).

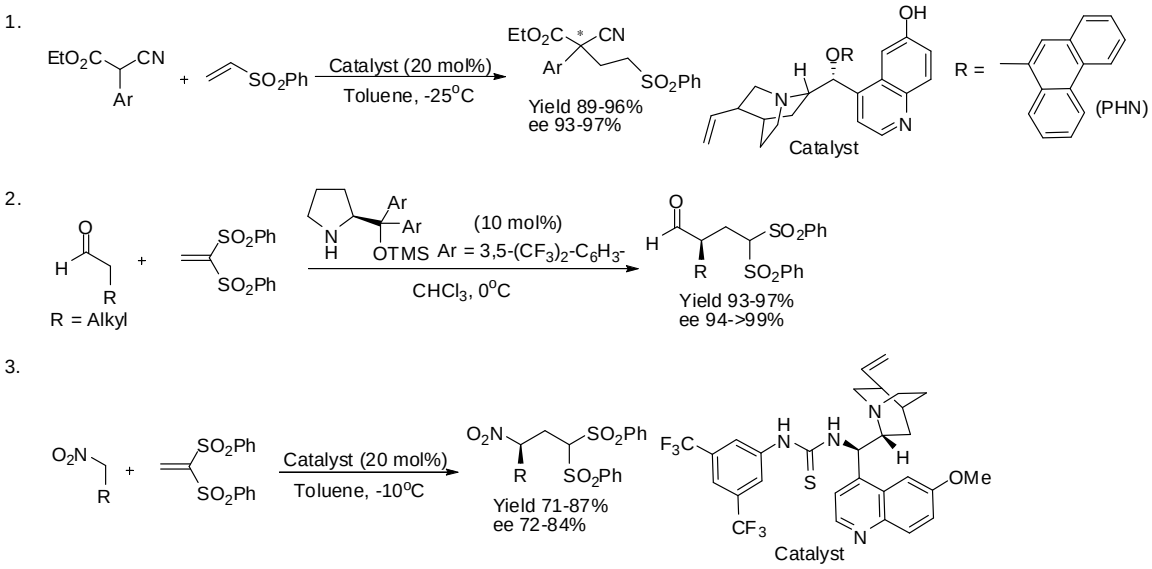
3.4 Development of Organocatalytic Asymmetric Cascade Double Michael Addition Reactions of 2-(2, 2-bis-benzenesulfonyl-vinyl)-phenol to Alkynals

3.4.1 Introduction

Sulfones are widely useful intermediates in synthetic and medicinal chemistry[23] due to the fact that the sulfonyl moiety can be removed by reduction[24] or transformed into

other useful functionalities[25]. In spite of the great chemical versatility of the sulfonyl group, only recently have the sulfones begun to be incorporated systematically into the field of organocatalysis. In particular, the vinyl monosulfones or vinyl bis(sulfones)[26] have been used as very appealing Michael acceptors in organocatalytic enantioselective conjugate additions[27] due to the strong electron-withdrawing nature of the sulfonyl groups (Scheme 3.4).

Scheme 3.4 Selected Examples of Michael Additions to Vinyl Sulfones



Despite all of the aforementioned excellent advances, the employment of vinyl sulfones as one of the Michael acceptors in organocatalytic enantioselective cascade reactions remains an unexplored field and a challenging task. In continuation of our efforts on developing more general and variable strategies for construction of biologically relevant compounds, we envisioned that if the versatile sulfonyl group were incorporated into the compounds formed via enantioselective cascade reactions, a variety of analogues

can be readily available by taking advantage of the chameleonic ability of sulfones. Undoubtedly, the strategy has paramount importance on the rapid development of pharmaceutical industry.

Although the wonderful reaction scenario on the oxa-Michael-Michael sequence of 2-(*E*)-(2-nitrovinyl)-phenols with alkynals using iminium–allenamine cascade catalysis has been recognized by our group recently[14], it is more fascinating to incorporate sulfonyl groups instead of nitro group into the "privileged" chiral 4*H*-chromene motifs in view of the fact that prior to reductive desulfonylation, miscellaneous electrophiles can be readily introduced to efficiently generate a great many of analogues.

3.4.2 Results and Discussion

To fulfill our expectation, we proposed to develop organocatalytic asymmetric cascade reactions between 2-(2, 2-bis-benzenesulfonyl-vinyl)-phenol and alkynalsto synthesize versatile biologically interesting 4*H*-chromene scaffolds.

We started our investigations by conducting the model reaction between phenyl-propynal **1a** and 2-(2, 2-bis-benzenesulfonyl-vinyl)-phenol **4a** in dichloromethane at room temperature in the presence of 20 mol% organocatalyst **IV** (Figure 3.5 and Table 3.3). To our gratification, the initial trial gave encouraging result: the reaction between **1a** and **4a** finished within 2 h to yield the desired product **5a** with a moderate isolated yield (80%) and a moderate ee value (78%) (Table 3.3, entry 1). A brief investigation of reaction medium revealed that dichloromethane is the most suitable solvent for the

process (Table 3.3, entry 1-6). The screening of several other organocatalysts **I-VI** revealed that the bulky TBDMS catalyst **III** gave a slightly higher enantioselectivity and a slightly lower yield (Table 3.3, entry 9). However, the Barbas's catalyst **V** does not show enantioselectivity (Table 3.3, entry 10). The MacMillan catalyst **VI** shows poor enantioselectivity (Table 3.3, entry 11). Thereby, the catalyst **III** and dichloromethane solvent were chosen for further optimization reaction condition. Basic additives screen including both inorganic and organic base indicated that NaOAc additive lead to a slightly increased enantioselectivity (Table 3.3, entry 12-14). Further lowering the reaction temperature to -20ºC and increasing the catalyst loading to 30 mol% resulted in better ee (92%) and yield (78%) (Table 3.3, entry 15).

Figure 3.5 Secondary Amine Catalysts Screened

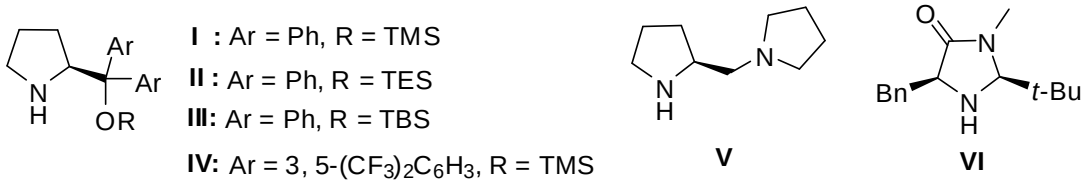
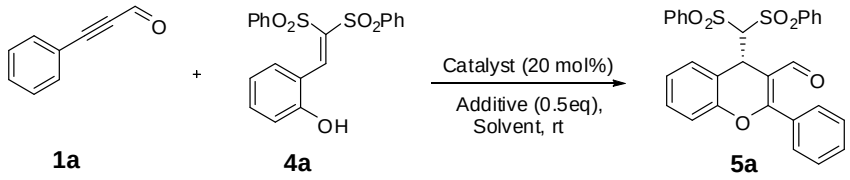


Table 3.3 Optimization Reaction Conditions for the Organocatalytic Asymmetric Cascade Michael-Michael Reaction between Phenyl-propynal **1a** and 2-(2, 2-Bis-benzenesulfonyl-vinyl)-phenol **4a**[a].



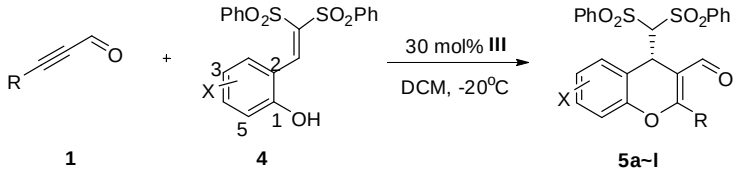
Entry	Catalyst	Additive	Solvent	*t* (h)	Yield (%) [b]	ee (%) [c]
1	**IV**	None	DCM	2	80	78
2	**IV**	None	DCE	2	78	74
3	**IV**	None	Toluene	2	83	60
4	**IV**	None	CH_3CN	23	69	73
5	**IV**	None	Et_2O	6	71	69
6	**IV**	None	MeOH	17	62	78
7	**I**	None	CH_2Cl_2	2	78	82
8	**II**	None	CH_2Cl_2	2	76	83
9	**III**	None	CH_2Cl_2	2	76	85
10	**V**	None	CH_2Cl_2	2	77	0
11	**VI**	None	CH_2Cl_2	20	68	50
12	**III**	NaOAc	DCM	1	77	86
13	**III**	Na_2CO_3	DCM	1	75	79
14	**III**	Et_3N	DCM	1	76	84
15	**III**[d,e]	NaOAc	DCM	48	78	92

[a] Reaction conditions: unless specified, a mixture of phenyl-propynal **1a** (0.055mmol), 2-(2, 2-bis-benzenesulfonyl-vinyl)-phenol **4a** (0.050mmol), catalyst (0.01mmol) and additive (0.025mmol) in solvent (0.4mL) was stirred at r.t. for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak OD-H). [d] Performed at -20ºC. [e] 30 mol% of catalyst **III** was applied.

With the optimal reaction condition in hands, we examined the scope of the cascade oxa-Michael-Michael process with the results summarized in Table 3.4. As shown, the reaction has rather broad applicability. Aromatic alkynal **1**, regardless of neutral substituent (entries 1, 10), electron-donating substituents (entries 2, 3) and electron-withdrawing substituents (entries4-9), participated in the process in

moderate yield (60%~83%) and with excellent enantioselectivities (87%~94%). On the other hand, 2-(2, 2-bis-benzenesulfonyl-vinyl)-phenol bearing electron-withdrawing group is tolerated although relatively low yield is observed (entry 10). Furthermore, low yield and enantioselectivity were observed for heteroaromatic alkynal such as thiophen-2-yl-propynal (entry 11). It is worthy of point out that the highly branched aliphatic alkynal was compatible with this methodology (entry 12). The absolute configuration of **5a** prepared under the optimal condition was determined by X-ray crystallography to be *S* configuration (Figure 3.6).

Table 3.4 Catalyst **III** Promoted Asymmetric Cascade Michael-Michael Reactions of Propynal **1** with 2-(2, 2-Bis-benzenesulfonyl-vinyl)-phenol **4**[a].

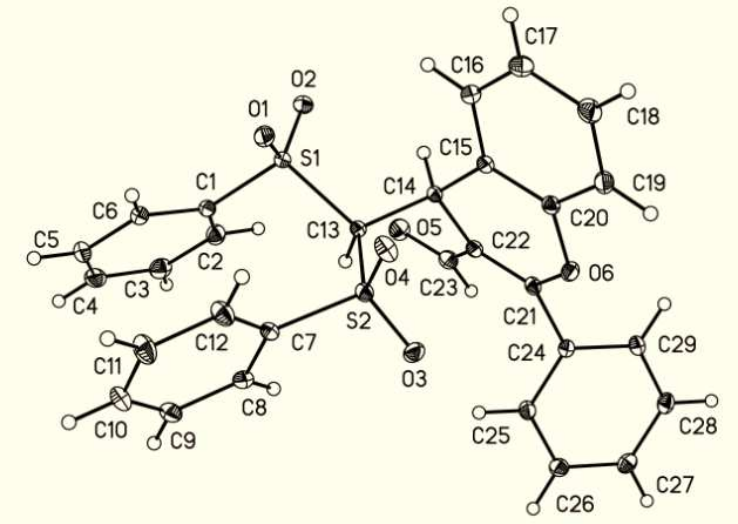


Entry	R	X	*t* (h)	5	Yield (%) [b]	ee (%) [c]
1	Ph	H	48	**5a**	78	92
2 [d]	4-$MeOC_6H_4$	H	70	**5b**	63	89
3	4-MeC_6H_4	H	70	**5c**	68	92
4	4-BrC_6H_4	H	46	**5d**	82	94
5	4-ClC_6H_4	H	46	**5e**	81	92
6	2-FC_6H_4	H	46	**5f**	83	91
7	3-FC_6H_4	H	46	**5g**	78	92
8	3-$CF_3C_6H_4$	H	46	**5h**	80	91
9	3-CNC_6H_4	H	46	**5i**	77	90

10 [d]	Ph	3-Cl	50	**5j**	60	87
11 [d]	Thienyl	H	48	**5k**	65	77
12	*t*-Bu	H	47	**5l**	83	88

[a] Reaction conditions: unless specified, a mixture of propynal **1** (0.055mmol), 2-(2, 2-bis-benzenesulfonyl-vinyl)-phenol **4** (0.050mmol), NaOAc (0.025mmol) and catalyst **III** (0.015mmol) in DCM (1.0ml) was stirred at -20 ºC for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD-H or Chiralpak AS-H). [d] Reaction was performed at -13ºC.

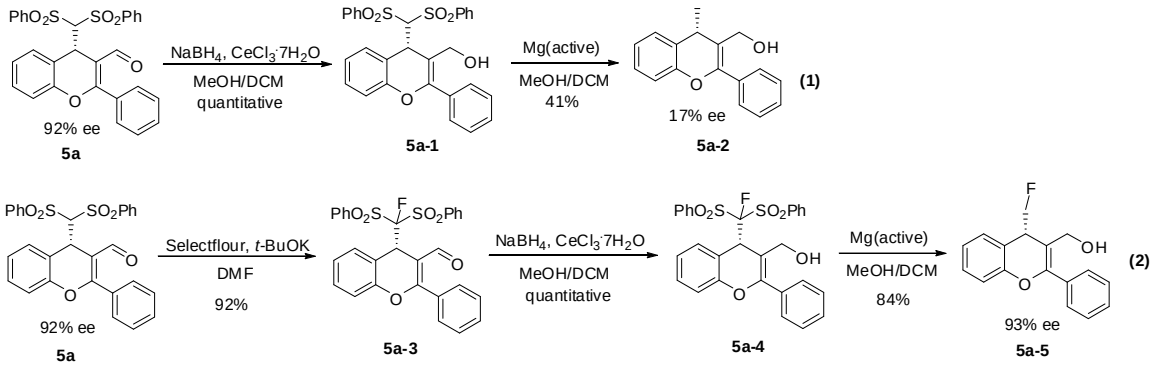
Figure 3.6 the Single-Crystal X-ray Structure of Compound **5a**



To demonstratethe synthetic utility of the obtained enantioenriched 4*H*-chromene motifs **5**, related post-modifications were carried out (Scheme 3.5). In general, the reduction of the aldehyde functionality may be necessary for minimizing the side reactions of the reductive desulfonylation step. Treatment of adduct **5a-1** with magnesium/methanol/dichloromethane gave the desired desulfonated product **5a-2** bearingone chiral methyl group in moderate yield, unfortunately, the enantioselectivity was serious dropped from 92% to 17% (Scheme 3.5, eq (1)). Since fluorine-containing

compounds usually widely exit in pharmaceutical and agrochemical products[28], the efficient and selective incorporation of fluorine-containing moieties into organic compounds to modulate their biological properties has become a powerful strategy in drug design. Considering the significance of fluorine in drug discovery, we incorporated the fluorine atom in compound **5a**, in combination with subsequent reduction and desulfonylation, giving access to optically active monofluoromethylation analogue **5a-5** without erosion of enantioselectivity (Scheme 3.5, eq (2)).

Scheme 3.5 Synthetic Utility of Adduct **5**

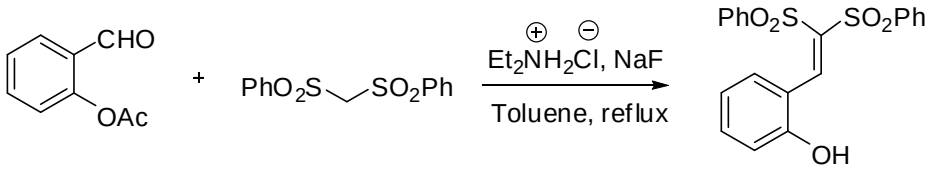


3.4.3 Conclusion

In summary, we have disclosed the first organocatalytic enantioselective oxa-Michael-Michael cascade reaction applying vinyl sulfones as one of the Michael acceptors. This reaction proceeded with moderate yield and excellent enantioselectivity, as well as broad compatability. The described approach together with facile post-modifications represents an efficient strategy to access versatile enantioenriched 4*H*-chromene motifs although further investigations on the utilities of the adduct are needed.

3.4.4 Supporting Information

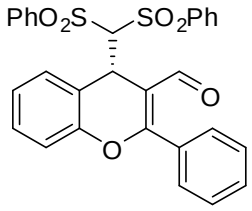
General procedure for the synthesis of 2-(2,2-bis(phenylsulfonyl)vinyl)phenol:



To a solution of 2-acetoxybenzaldehyde (1.11g, 6.75 mmol), Bis(phenylsulfonyl)methane (1g, 3.37 mmol) and sodium fluoride (21.3mg, 0.51 mmol) in toluene (20ml) was added diethylamine hydrochloride (0.74g, 6.75 mmol). The resulting solution was refluxed with Dean-Stark apparatus for 3days. Then evaporate the toluene and the resulting crude solution was purified directly by running column chromatography to give the product with 45% isolated yield.

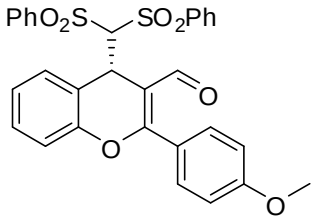
General procedure for Cascade Oxa-Michael-Michael addition reaction (Table 3.4):

To a solution of alkynal **1** (0.055 mmol), organocatalyst **III** (5.51mg, 0.015 mmol) and sodium acetate (2.05mg, 0.025 mmol) in dichloromethane (0.8ml) was added 2-(2,2-bis(phenylsulfonyl)vinyl)phenol **4** (0.05 mmol). The resulting solution was stirred at -20^{o}C for a specific time. Then the reaction mixture was directly purified by column chromatography, eluted with hexane/EtOAc to afford the desired product.



(*S*)-4-(bis(phenylsulfonyl)methyl)-2-phenyl-4*H*-chromene-3-carbaldehyde (5a) (Table 3.4, Entry 1):

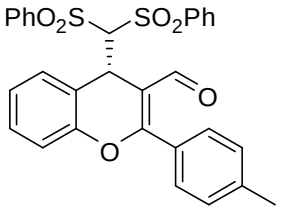
The title compound was prepared according to the general procedure, as described above in 78% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.56 (s, 1H), 8.10~8.09 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.71~7.55 (m, 10H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.31~7.24 (m, 3H), 7.16~7.10 (m, 2H), 5.82 (s, 1H), 5.46 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.0, 170.7, 151.0, 140.5, 138.6, 134.0, 133.8, 131.7, 130.9, 130.8, 130.6, 129.7, 129.5, 129.1, 128.55, 128.50, 128.3, 125.6, 117.1, 116.8, 112.5, 85.5, 31.7. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 29.19 min, t_{major} = 23.12 min, ee = 92%; $[\alpha]_D^{25}$= -80.6 (c = 1.0 in $CHCl_3$).



(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(4-methoxyphenyl)-4*H*-chromene-3-carbaldehyde (5b) (Table 3.4, Entry 2):

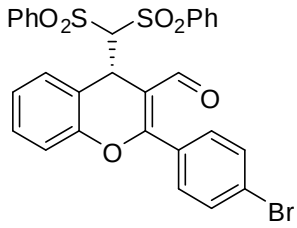
The title compound was prepared according to the general procedure, as described above in 63% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.51 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 4H), 7.55 (t, *J* = 8.0 Hz,

2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.24~7.18 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 5.74 (s, 1H), 5.41 (s, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.8, 170.6, 162.5, 150.9, 140.6, 138.6, 134.0, 133.8, 132.4, 130.7, 129.7, 129.4, 129.1, 128.6, 128.3, 125.5, 123.0, 117.1, 117.0, 114.0, 111.6, 85.7, 55.5, 31.8. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 60.09 min, t_{major} = 28.98 min, ee = 89%; $[\alpha]_D^{25}$= -28.1 (c = 1.0 in $CHCl_3$).



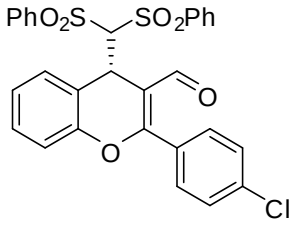
(*S*)-4-(bis(phenylsulfonyl)methyl)-2-p-tolyl-4*H*-chromene-3-carbaldehyde (5c) (Table 3.4, Entry 3):

The title compound was prepared according to the general procedure, as described above in 68% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.51 (s, 1H), 8.06~8.05 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.5Hz, 1H), 7.61~7.59 (m, 2H), 7.57~7.53 (m, 4H), 7.42 (t, *J* = 7.5Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.24~7.19 (m, 3H), 7.09~7.05 (m, 2H), 5.75 (s, 1H), 5.41 (d, *J* = 1.5 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.0, 170.9, 151.0, 142.4, 140.5, 138.6, 134.0, 133.8, 130.8, 130.6, 129.7, 129.5, 129.3, 129.1, 128.6, 128.3, 128.0, 125.5, 117.1, 116.8, 112.1, 85.6, 31.7, 21.6. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 37.56 min, t_{major} = 20.30 min, ee = 92%; $[\alpha]_D^{25}$= -22.9 (c = 1.0 in $CHCl_3$).



(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(4-bromophenyl)-4*H*-chromene-3-carbaldehyde (5d) (Table 3.4, Entry 4):

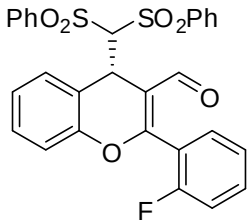
The title compound was prepared according to the general procedure, as described above in 82% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (s, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 7.5 Hz, 1H), 7.67~7.63 (m, 3H), 7.59 (d, J = 8.5 Hz, 2H), 7.56~7.52 (m, 4H), 7.43 (t, J = 7.5 Hz, 1H), 7.23~7.19 (m, 3H), 7.09~7.05 (m, 2H), 5.75 (s, 1H), 5.37 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 169.5, 150.9, 140.5, 138.6, 134.0, 133.9, 132.0, 131.9, 130.8, 129.7, 129.6, 129.1, 128.5, 128.4, 126.5, 125.8, 117.1, 116.7, 112.9, 85.5, 31.7. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 72.60 min, t_{major} = 25.63 min, ee = 94%; $[\alpha]_D^{26}$= -45.0 (c = 1.0 in $CHCl_3$).



(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(4-chlorophenyl)-4*H*-chromene-3-carbaldehyde (5e) (Table 3.4, Entry 5):

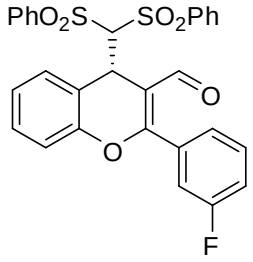
The title compound was prepared according to the general procedure, as described above in 81% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.79

(d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.61~7.58 (m, 4H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.27~7.24 (m, 1H), 7.21 (t, *J* = 8.0 Hz, 2H), 7.10~7.05 (m, 2H), 5.76 (s, 1H), 5.37 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 169.4, 150.9, 140.4, 138.5, 138.1, 134.0, 133.9, 131.8, 130.8, 129.7, 129.6, 129.3, 129.1, 128.9, 128.43, 128.35, 125.8, 117.1, 116.7, 112.8, 85.4, 31.7. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 63.73 min, t_{major} = 24.12 min, ee = 92%; $[\alpha]_D^{26}$= -55.5 (c = 1.0 in $CHCl_3$).



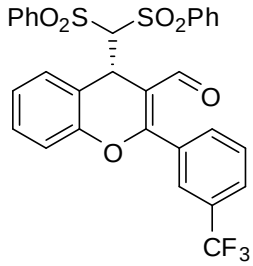
(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(2-fluorophenyl)-4*H*-chromene-3-carbaldehyde (5f) (Table 3.4, Entry 6):

The title compound was prepared according to the general procedure, as described above in 83% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.42 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.66~7.61 (m, 4H), 7.57~7.50 (m, 3H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.27~7.21 (m, 3H), 7.10~7.07 (m, 2H), 5.73 (s, 1H), 5.31 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.4, 161.5, 159.4, 151.2, 140.2, 138.8, 134.1, 133.9, 133.4, 133.3, 132.7, 130.8, 129.7, 129.1, 128.5, 128.4, 125.7, 124.4, 119.2, 119.1, 117.2, 116.5, 116.3, 114.2, 85.4, 31.7. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 29.83 min, t_{major} = 21.14 min, ee = 91%; $[\alpha]_D^{26}$= -70.0 (c = 1.0 in $CHCl_3$).



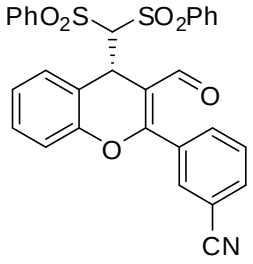
(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(3-fluorophenyl)-4*H*-chromene-3-carbaldehyde (5g) (Table 3.4, Entry 7):

The title compound was prepared according to the general procedure, as described above in 78% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.53 (s, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 2H), 7.50~7.47 (m, 1H), 7.45~7.42 (m, 2H), 7.37 (d, J = 7.5 Hz, 1H), 7.30~7.25 (m, 2H), 7.21 (t, J = 8.0 Hz, 2H), 7.11~7.06 (m, 2H), 5.76 (s, 1H), 5.37 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.5, 169.0, 163.4, 161.4, 150.9, 140.4, 138.5, 134.0, 133.9, 132.82, 132.76, 130.7, 130.3, 130.2, 129.7, 129.1, 128.41, 128.38, 126.6, 125.8, 118.8, 118.7, 117.4, 117.2, 117.1, 116.6, 113.0, 85.4, 31.6. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 37.31 min, t_{major} = 22.88 min, ee = 92%; $[\alpha]_D^{26}$= -47.5 (c = 1.0 in $CHCl_3$).



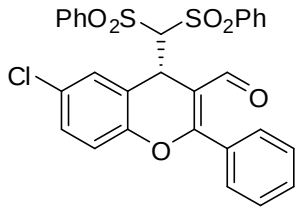
(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(3-(trifluoromethyl)phenyl)-4*H*-chromene-3-carbaldehyde (5h) (Table 3.4, Entry 8):

The title compound was prepared according to the general procedure, as described above in 80% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.48 (s, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.87~7.84 (m, 3H), 7.80 (d, J = 7.5 Hz, 1H), 7.68~7.64 (m, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 8.0 Hz, 2H), 7.13 (d, J = 8.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 5.79 (s, 1H), 5.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.2, 168.8, 150.9, 140.4, 138.5, 134.1, 134.0, 131.7, 131.5, 131.2, 130.8, 129.7, 129.3, 129.1, 128.4, 128.3, 126.9, 125.9, 117.2, 116.6, 113.4, 85.4, 31.6. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 25.84 min, t_{major} = 19.40 min, ee = 91%; $[\alpha]_D^{27}$= -79.1 (c = 1.0 in $CHCl_3$).



(*S*)-3-(4-(bis(phenylsulfonyl)methyl)-3-formyl-4*H*-chromen-2-yl)benzonitrile (5i) (Table 3.4, Entry 9):

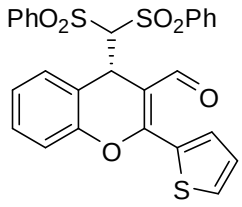
The title compound was prepared according to the general procedure, as described above in 77% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.47 (s, 1H), 7.97~7.94 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.68~7.62 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J*= 8.0 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.24~7.21 (m, 2H), 7.13~7.09 (m, 2H), 5.78 (s, 1H), 5.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 168.0, 150.8, 140.3, 138.4, 134.8, 134.7, 134.1, 134.0, 133.7, 132.3, 130.8, 129.8, 129.7, 129.6, 129.1, 128.4, 128.3, 126.1, 117.6, 117.1, 116.5, 113.7, 113.3, 85.2, 31.6.HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 99.49 min, t_{major} = 58.73 min, ee = 90%; $[\alpha]_D^{27}$= -82.6 (c = 1.0 in $CHCl_3$).



(*S*)-4-(bis(phenylsulfonyl)methyl)-6-chloro-2-phenyl-4*H*-chromene-3-carbaldehyde (5j) (Table 3.4, Entry 10):

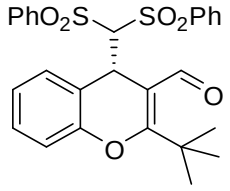
The title compound was prepared according to the general procedure, as described above in 60% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.78 (s, 1H), 7.65~7.63 (m, 5H), 7.60~7.47 (m, 6H), 7.28~7.25 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 1H), 5.69 (s, 1H), 5.38 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.8, 170.4, 149.6, 140.2, 138.5, 134.1, 131.9, 130.7, 130.6, 130.5, 129.7, 129.4, 129.2, 128.9, 128.6, 128.5, 128.4, 118.4, 112.1, 85.3, 31.6. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 51.19 min, t_{major} =

21.46 min, ee = 87%; $[\alpha]_D^{27}$= -110.4 (c = 1.0 in $CHCl_3$).



(*S*)-4-(bis(phenylsulfonyl)methyl)-2-(thiophen-2-yl)-4*H*-chromene-3-carbaldehyde (5k) (Table 3.4, Entry 11):

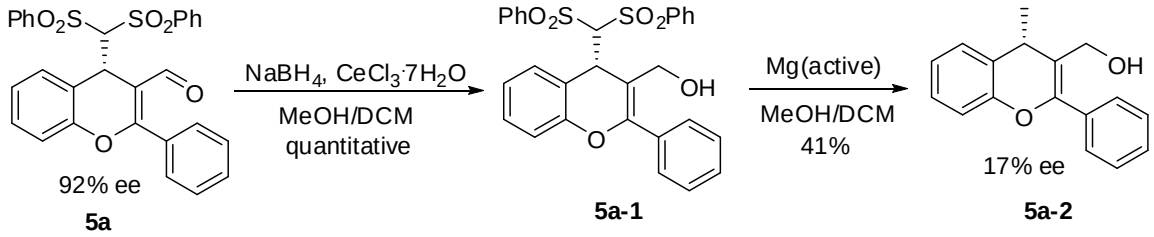
The title compound was prepared according to the general procedure, as described above in 65% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.78 (s, 1H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.69~7.68 (m, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.59~7.54 (m, 4H), 7.47~7.46 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.18~7.16 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 5.37 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.0, 164.0, 150.7, 140.4, 138.8, 134.2, 134.1, 133.9, 131.8, 130.7, 129.5, 129.4, 129.1, 128.9, 128.6, 128.4, 127.6, 125.7, 117.1, 116.8, 112.3, 85.5, 31.9. HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 20/80, flow rate = 0.7 mL/min, λ = 254nm): t_{minor} = 49.19 min, t_{major} = 30.01 min, ee = 77%; $[\alpha]_D^{27}$= -42.3 (c = 1.0 in $CHCl_3$).



(*S*)-4-(bis(phenylsulfonyl)methyl)-2-tert-butyl-4*H*-chromene-3-carbaldehyde (5l)

(Table 3.4, Entry 12):

The title compound was prepared according to the general procedure, as described above in 83% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.3 (s, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.49~7.43 (m, 3H), 7.27~7.21 (m, 3H), 7.09~7.05 (m, 2H), 5.68 (s, 1H), 5.05 (d, J = 1.0 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.2, 180.1, 150.9, 140.4, 139.0, 133.83, 133.75, 130.3, 129.6, 129.3, 129.0, 128.3, 125.5, 116.9, 116.7, 110.9, 86.1, 38.9, 32.0, 31.1.HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 14.66 min, t_{major} = 18.88 min, ee = 88%; $[\alpha]_D^{27}$= -83.0 (c = 1.0 in $CHCl_3$).

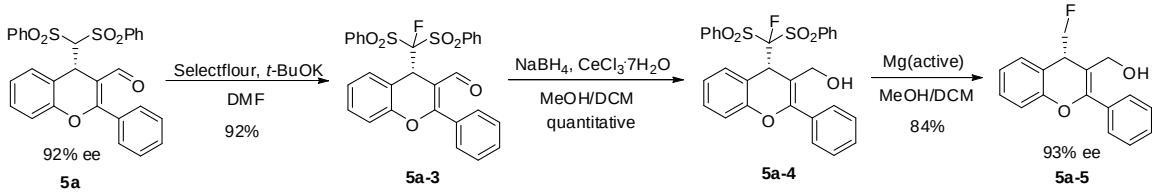


(*S*)-(4-methyl-2-phenyl-4*H*-chromen-3-yl)methanol (5a-2)

A round-bottom flask is charged with 100 mg **5a** (0.188 mmol, 92 % e.e.) in methanol (5 ml) and dichloromethane (1 ml). To the well-stirred solution at 0°C is added $CeCl_3{\cdot}7H_2O$ (140.4 mg, 0.377 mmol), then sodium borohydride (14.3 mg, 0.377 mmol). The reaction mixture is stirred at 0°C for 1h and monitored by TLC. After the reaction finish, 20 ml of saturated ammonium chloride aqueous solution is added at 0°C to quench the reaction. Evaporating solvent and the resulting residue is dissolved in dichloromethane. Then it is transferred to a separatory funnel. The aqueous phase is separated and extracted with dichloromethane (3x10ml). The organic layers are combined and washed with brine,

dried with $MgSO_4$, filtered, and concentrated. The crude product is purified by column chromatography to give the alcohol **5a-1** in quantitative yield.

Compound **5a-1** (100 mg, 0.188 mmol) was dissolved in 5 mL MeOH. Activated Mg (prepared from Mg and $BrCH_2CH_2Br$ in Et_2O) (90 mg, 3.76 mmol) was added to this solution and the mixture was stirred at room temperature for 2 h. HCl (25 mL, 1 mol/L) was added and extracted with EtOAc for three times. The combined organic layers were then washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was then purified by column chromatography to give 19.4 mg the desired product **5a-2** in 41% yield and 17% e.e. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (d, J = 7.5 Hz, 2H), 7.42~7.41 (m, 3H), 7.21~7.16 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.32~4.25 (m, 2H), 3.80~3.76 (m, 1H), 1.46 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.4, 148.8, 134.2, 128.9, 128.2, 128.1, 127.2, 127.0, 123.6, 116.1, 113.9, 61.6, 31.4, 24.4.



(*S*)-(4-(fluoromethyl)-2-phenyl-4*H*-chromen-3-yl)methanol (5a-5)

A round-bottom flask is charged with 100 mg **5a** (0.188 mmol, 92 % e.e.) in anhydrous DMF (3 ml). To the well-stirred solution is added *t*-BuOK (63.4 mg, 0.564 mmol) in one portion, then stir at r.t. for 20 min. Selectflour (200.3 mg, 0.564 mmol) in 2 ml anhydrous DMF is added dropwise. The reaction mixture is stirred at r.t. for 8h and monitored by TLC. After the reaction finish, water and EtOAc are added to extract the reaction solution.

The aqueous layer is separated and extracted with EtOAC for three times. The combined organic layers were then washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was then purified by column chromatography to give the desired product **5a-3** in 92% yield. The compound **5a-4** and **5a-5** are prepared according to the general procedure described for **5a-1** and **5a-2**.

For compound **5a-5**, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60~7.59 (m, 2H), 7.44~7.43 (m, 3H), 7.29~7.25 (m, 2H), 7.14~7.09 (m, 2H), 4.66~4.48 (m, 2H), 4.34 (d, J = 12 Hz, 1H), 4.23 (d, J = 12 Hz, 1H), 4.01~3.95 (m, 1H), 1.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.2, 151.6, 133.7, 129.4, 129.0, 128.8, 128.3, 128.2, 123.8, 120.8, 120.7, 116.3, 108.8, 87.5, 86.1, 62.6, 39.8, 39.6. HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate = 0.5 mL/min, λ = 254nm): t_{minor} = 15.28 min, t_{major} = 11.38 min, ee = 93%; $[\alpha]_D^{28}$= -13.7 (c = 1.0 in $CHCl_3$).

3.5 "One-Pot" Access to 4*H*-Chromenes with Formation of a Chiral Quaternary Stereogenic Center by a Highly Enantioselective Iminium-allenamine Involved Oxa-Michael Aldol Cascade[29]

3.5.1 Introduction

Quaternary stereogenic centers are essential structural unit in many biologically active natural products and pharmaceuticals[30]. The catalytic enantioselective construction of complex molecules containing quaternary stereocenters still pose a demanding

challenge for synthetic organic chemists although significant improvements have been achieved in this area[31]. Notably, organocatalytic formation of quaternary stereocenters[30e,31g] with impressive levels of stereocontrol has received special attention over the past decade by virtue of relative simple and mild catalytic system. Among the developed organocatalytic methods suitable for this purpose, the chiral functionalized tertiary alcohols[32] which are known to be important building blocks of bioactive natural products and drugs are commonly obtained by the direct aldol reactions of prochiral ketones[33].

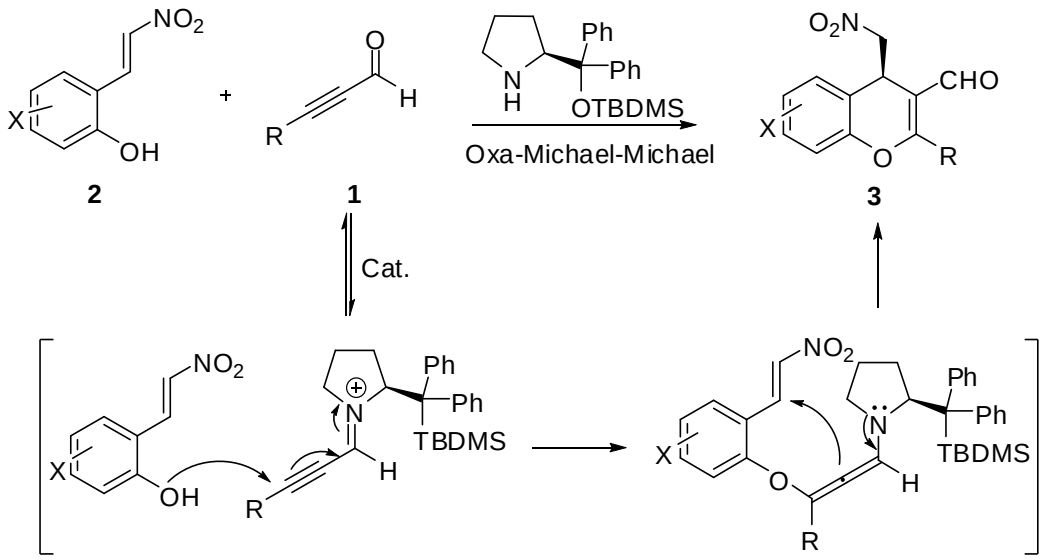
4*H*-chromenes are an important class of core structures featured in a number of naturally occurringand biologically active molecules[17, 34]. The ability to access the complex members of the chiral 4*H*-chromene family in an enantioselective and cascade manner allows chemists to explore their potential biological properties. Therefore, the development of catalytic asymmetric strategies for the efficient construction of structurally diverse chiral 4*H*-chromenes is highly valuable to the fields of organic synthesis and chemical biology/medicinal chemistry.

Toward this end, our group has recently reported the enantioselective cascade oxa-Michael Michael reactions of ynals involving an unprecedented iminium-allenamine activation mode (Scheme 3.6, eq 1)[14]. Despite the extensively investigated iminium-enamine strategy with cascade sequences[1a], the respective iminium-allenamine chemistry is much less appreciated. Expanding the scope of the chemistry will not only add a new domain in organocatalysis but also, more importantly, afford new potentially useful platforms for the facile assembly of important molecular scaffolds. We questioned

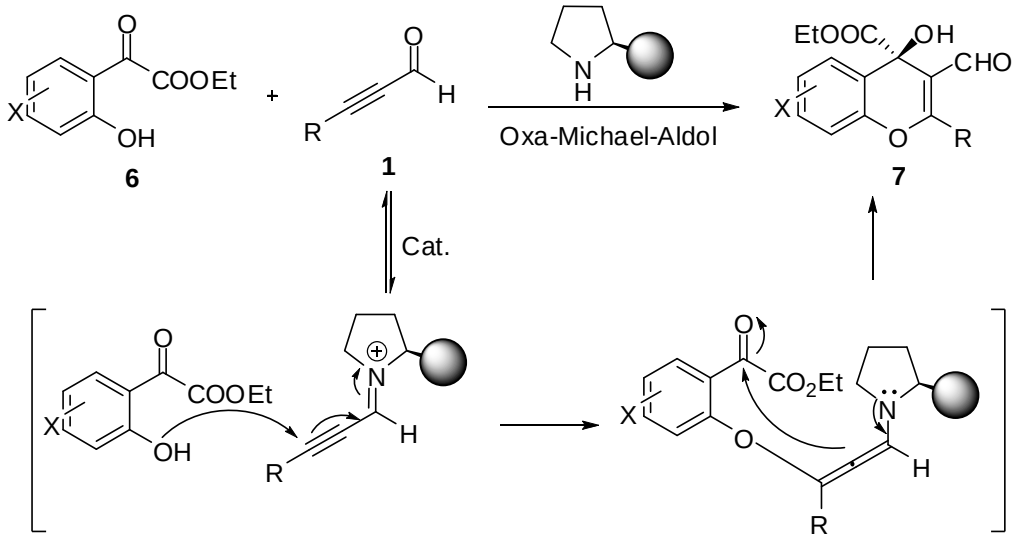
whether the conceptually novel tactic could be extended to an oxa-Michael aldol cascade sequence, which would generate the structurally diverse 4*H*-chromenes with installation of new functionalities. Herein, we wish to reportthe results which have led to an asymmetric iminium-allenamine approach to chiral 4*H*-chromenes bearing chiral-hydroxy carboxylate functionality in high yields (84~99%) and with excellent enantioselectivities (93~>99% ee) for a wide range of substrates (Scheme 3.6, eq 2). A powerful “one-pot” oxa-Michael aldol cascade reaction between (2-hydroxy-phenyl)-2-oxoacetates and ynals is realized for the first time. Furthermore, a quaternary stereogenic center involving formation of versatile α-hydroxy carboxylate motif, a still synthetically unmet issue in organic synthesis, is created highly enantioselectively.

Scheme 3.6 Alkynals Participating in Enantioselective Cascade Oxa-Michael-Michael and Aldol Reactions Promoted by a Chiral Secondary Amine Involving a Novel Iminium-allenamine Activation Mode

Oxa-Michael-Michael Cascade (Eq. 1)



Oxa-Michael-Aldol Cascade (Eq. 2)

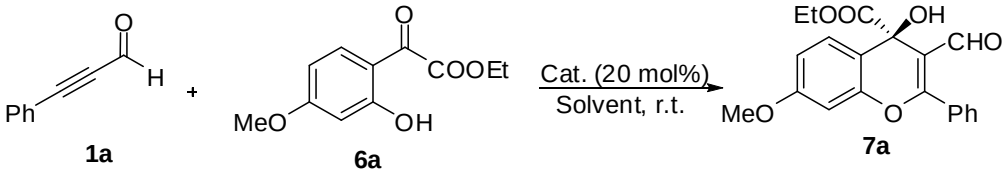


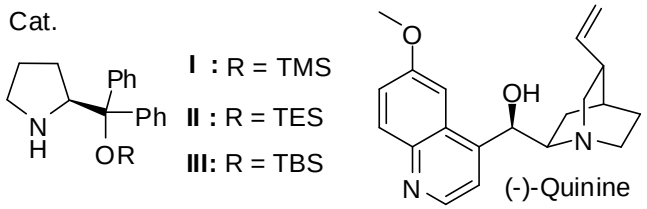
3.5.2 Results and Discussion

Initial efforts on the proposed organocatalytic enantioselective oxa-Michael-aldol cascade reaction of simple salicylaldehyde or -ketone with phenyl ynal in the presence of

20 mol % (*S*)-diphenylpyrrolinol TMS ether **I** in toluene were frustrated by the failure of delivering the desired products as a result of very poor reaction yield. These studies underscored the completely different reaction behavior between ynals and enals since we have shown that enals can efficiently engage in the Michael aldol cascade process with salicylaldehydes[20b]. We turned our attention to the more reactive ketone ester **6a** (Scheme 3.6 and Table 3.5)[33]. To our delight, the oxa-Michael-aldol cascade sequence proceeded smoothly to give the desired product **7a** in an excellent yield (97%) and with excellent enantiomeric excess (ee) (97%) under the same reaction conditions in toluene at r.t. in the presence of 20 mol % catalyst **I** within 3 h (Table 3.5, entry 1), albeit the highly steric ketoester substrate employed. Notably, the process provides an efficient entry to useful chiral α-hydroxycarboxylates with formation of a quaternary stereogenic center in a cascade fashion. The screening of other diarylprolinol silyl ether analogues **II**-**III** revealed that the bulky TBDMS catalyst **III** gave a slightly higher enantioselectivity (Table 3.5, entries 2~3). Quinine alone was not effective for this transformation (Table 3.5, entry 4). Therefore, the catalyst **III** was defined as the optimal promoter for this process. A survey of solvents led to choose toluene as the reaction medium for the process (Table 3.5, entries 5~7). Better e.e. (99%) was observed when decreasing the reaction temperature to -15~-10 °C and lowering the catalyst loading to 15 mol% (Table 3.5, entry 8).

Table 3.5 Development and Optimization of Reaction Conditions of an Organocatalytic Enantioselective Cascade Oxa-Michael-aldol Cascade Reaction[a]



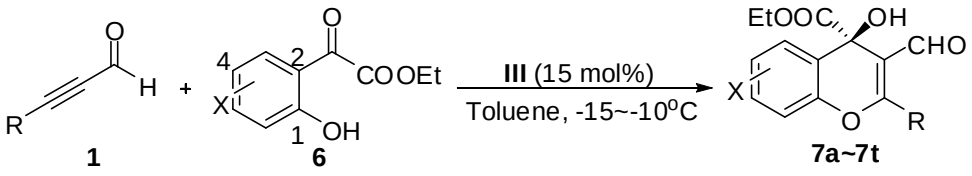


Entry	Catalyst	Solvent	*t* (h)	Yield (%) [b]	ee (%) [c]
1	**I**	Toluene	3	97	97
2	**II**	Toluene	3	98	98
3	**III**	Toluene	3	98	98
4	**(-)-quinine**	THF	2	<5	ND[d]
5	**III**	Xylene	3	96	98
6	**III**	CH_2Cl_2	3	99	97
7	**III**	$Cl(CH_2)_2Cl$	3	94	96
8[e]	**III**	Toluene	6	98	99

[a] Reaction conditions: unless specified, a mixture of phenyl-propynal **1a** (0.080 mmol), ethyl 2-(2-hydroxy-4-methoxyphenyl)-2-oxoacetate **6a** (0.080 mmol), and catalyst (0.016 mmol) in solvent (0.5 mL) was stirred at r.t. for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel AD). [d] Not determined. [e] Performed at -15~-10 °C, and 15 mol % of catalyst **III** was applied.

With the optimal conditions in hand, the scope of the cascade oxa-Michael-aldol reaction was investigated. Remarkably, as shown in Table 3.6, the cascade process exhibits a broad substrate tolerance, and a quaternary stereogenic center is generated highly enantioselectively in all cases. A full range of aromatic ynals **1**, including electron-neutral (entries 1~5), -donating (entries 6 and 7), and -withdrawing substituents (entries 8~15), as well as heterocyclic examples (entries 16 and 17), can participate in the cascade reactions in excellent yields (84%~99%) and with excellent enantioselectivities (93~>99%). It is noteworthy that the substrate scope can also be expanded to highly steric demanding aliphatic alkynal, providing the desired productin 91% yield and 98% ee (entry 18). Moreover, alkyl alkynals (R=CH_2CH_2Ph and *n*-C_5H_{11}, entries 19 and 20, respectively) were also probed for the cascade process. It was found that they efficiently participated in the reaction with excellent enantioselectivities (97 and 99% e.e., respectively), although the reaction occurred slower (60 h) than aryl ones and higher catalyst loading (25 mol %) was needed as a result of their poorer reactivity. The variation in ethyl 2-(2-hydroxyphenyl)-2-oxoacetate components **6** was also possible, as demonstrated by the aromatic structures carrying electron-donating (entries 1, 3, 4, 6 10, and 12~18), -neutral (entries 2 and 11), and -withdrawing (entry 5) groups. It is observed that with respect to substrate **6e** having electron-with drawing Cl (entry 5) poor e.e. was observed. However, we found that quinine as co-catalyst was essential to ensure high enantioselectivity presumably due to its interaction with the ketone moiety in the ketoester. The absolute configurationof **7h** was determined to be *R* configuration by X-ray crystallographic analysis (Figure 3.7).

Table 3.6 Catalyst **III** Promoted Enantioselective Cascade Oxa-Michael-aldol Reactions of Alkynals **1** with Ethyl 2-(2-Hydroxyphenyl)-2-oxoacetates **6**[a]

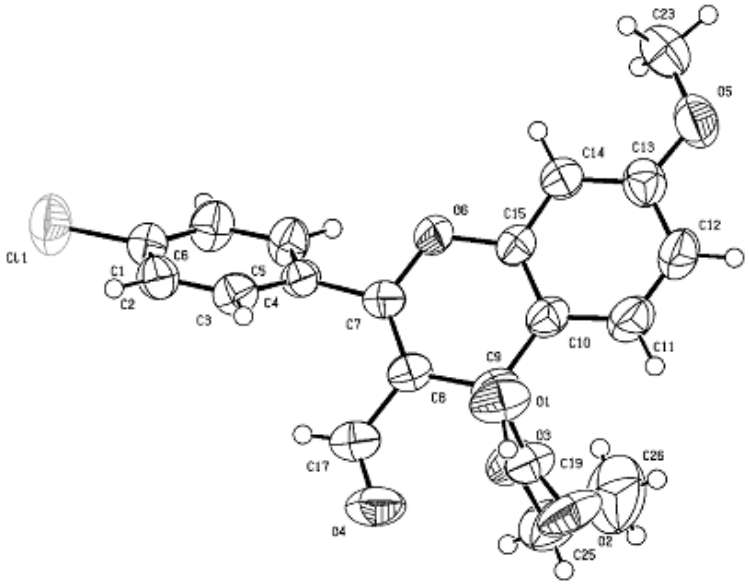


Entry	R	X	*t* (h)	Yield (%) [b]	ee (%) [c]
1	Ph	5-MeO	6	98	99
2	Ph	H	8	97	99
3	Ph	4-MeO	8	84	96
4	Ph	4-Me	9	93	98
5[d]	Ph	4-Cl	6	99	93
6	4-$MeOC_6H_4$	5-MeO	6	99	99
7	4-MeC_6H_4	5-MeO	6	99	99
8	4-ClC_6H_4	5-MeO	6	97	99
9	4-BrC_6H_4	5-MeO	6	99	99
10	4-BrC_6H_4	4-Me	10	92	98
11	4-BrC_6H_4	H	9	98	98
12	4-FC_6H_4	5-MeO	6	99	>99
13	3-FC_6H_4	4-Me	9	93	98
14	4-$NO_2C_6H_4$	5-MeO	6	98	99
15	3-$NO_2C_6H_4$	5-MeO	6	98	99
16	2-thienyl	5-MeO	10	92	99
17	2-furanyl	5-MeO	10	97	96
18	*t*-Bu	5-MeO	10	91	98

19[e]	$PhCH_2CH_2$	4-Me	60	69	97
20[e]	n-C_5H_{11}	4-Me	60	75	99

[a] Reaction conditions: unless specified, see footnote *a* in Table 3.5 and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel AD or Chiralpak IC). [d] 15 mol % of **I** and 10 mol % of (-)-Quinine were used. [e] 25 mol % of **III** was used.

Figure 3.7 X-ray Structure of **7h**



3.5.3 Conclusion

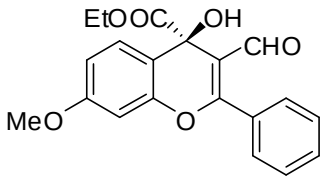
In conclusion, we have described a new protocol for asymmetric organocatalysis through the first iminium-allenamine engaged oxa-Michael-aldol cascade reaction. In addition to the potential of this powerful "one-pot" approachto the catalytic generation of chiral 4*H*-chromenes bearing a quaternary stereogenic center, it is a rare example of a highly enantioselective cascade reaction with ynals. The operationally friendly reaction conditions and high efficiency (cascade, high yields and e.e., and readily available achiral

starting materials) render the process particularly attractivein the practice of organic synthesis and medicinal chemistry. Chiral 4*H*-chromene products with a versatile α-hydroxycarboxylate moiety are valuable structures for the synthesis of biologically active molecules.

3.5.4 Supporting Information

General procedure for Cascade Michael-Aldol addition reaction:

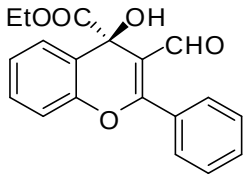
To a solution of alkynal **1** (0.08mmol), organocatalyst **III** (4.41mg, 0.012 mmol) in toluene (1.0 mL) was added ethyl 2-(2-hydroxyphenyl)-2-oxoacetate **6** (0.08 mmol). The resulting solution was stirred at -15~-10 °C for a specified time. Then the reaction mixture was directly purified by column chromatography, eluted with hexane/EtOAc to afford the desired product.



(*R*)-Ethyl3-formy-4-hydroxy-7-methoxy-2-phenyl-4*H*-chromene-4-carboxylate (7a) (Table 3.5, entry 1).

The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.56 (s, 1H) ,7.51~7.65 (m, 5H), 7.45 (d, *J* =

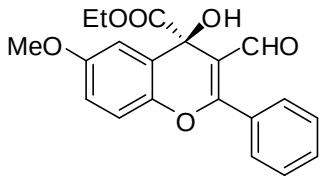
9.0 Hz,1H), 6.82 (dd, *J* = 9.0, 2.4 Hz,1H), 6.72 (d, *J*=2.4 Hz,1H), 4.76 (s,1H), 4.13~4.29 (m, *J* = 7.2 Hz,2H), 3.81 (s,3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}CNMR(CDCl3, 75 MHz): δ 191.6, 173.3, 166.8, 160.8, 150.0, 131.4, 130.7, 130.1, 128.6, 128.1, 116.2, 113.6, 113.2, 101.3, 68.0, 62.6, 55.5, 13.9; HPLC (Chiralcel AD, *i*-PrOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 48.86 min, t_{major} = 51.31 min, ee = 99%; $[\alpha]_D^{25}$ = -2 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): $C_{20}H_{18}O_6$+Na, calcd: 377.0996, found: 377.0989; IR ($CHCl_3$, cm^{-1}): 3478, 2978, 2935, 2860, 1738, 1663, 1635, 1506, 1334, 1306, 1236, 1197, 1173, 1114, 1067, 1032, 887, 775, 701.



(*R*)-Ethyl 3-formyl-4-hydroxy-2-phenyl-4*H*-chromene-4-carboxylate (7b) (Table 3.5, entry 2).

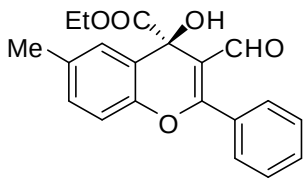
The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.57 (s,1H), 7.22~7.67 (m,9H), 4.85 (s,1H), 4.14~4.31 (m, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ191.6, 173.2, 167.0, 149.1, 131.5, 130.7, 130.2, 130.1, 128.6, 127.2, 125.8, 121.4, 117.2, 116.0, 68.2, 62.8, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 44.92 min, t_{major} = 46.69 min, ee = 99%; $[\alpha]_D^{25}$ = -5 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): $C_{19}H_{16}O_5$+Na, calcd: 347.0890, found: 347.0895; IR ($CHCl_3$,

cm^{-1}): 3483, 2981, 2932, 2860, 1740, 1664, 1578, 1396, 1334, 1239, 1219, 1192, 1118, 1071, 1039, 890, S3 838, 765, 702.



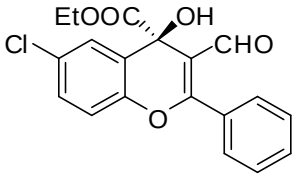
(*R*)-Ethyl 3-formy-4-hydroxy-6-methoxy-2-phenyl-4*H*-chromene-4-carboxylate (7c) (Table 3.5, entry 3).

The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.56 (s,1H), 7.51~7.66 (m,5H), 7.16 (d, J = 9.0 Hz,1H), 7.01 (d, J = 3.0 Hz, 1H), 6.95 (dd, J = 9.0, 3.0 Hz, 1H), 4.87 (s,1H), 4.14~4.31 (m, J = 7.2 Hz, 2H), 3.81 (s,3H), 1.19 (t, J = 7.2Hz, 3H); ^{13}CNMR($CDCl_3$, 75 MHz): δ 191.8, 173.2, 167.1, 157.2, 143.3, 131.4, 130.8, 130.2, 128.6, 121.8, 118.4, 113.6, 117.6, 115.1, 109.6, 68.7, 62.8, 55.8, 14.0; HPLC (Chiralcel AD, EtOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 25.17 min, t_{major} = 31.75 min, ee = 96%; $[\alpha]_D^{25}$ = -18 (c = 1.0 in $CHCl_3$); HRMS (ESI): $C_{20}H_{18}O_6$+Na, calcd: 377.0996, found: 377.0991; IR ($CHCl_3$, cm^{-1}): 3473, 2980, 2923, 2855, 1738, 1654, 1619, 1331, 1303, 1235, 1198, 1153, 1098, 1060, 1038, 817, 773, 753, 700, 664.



(*R*)-Ethyl 3-formy-4-hydroxy-6-methyl-2-phenyl-4*H*-chromene-4-carboxylate (7d) (Table 3.5, entry 4).

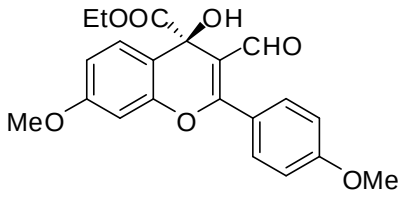
The title compound was prepared according to the general procedure, as describedabove in 93% yield. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 9.55 (s, 1H), 7.65~7.63 (m, 2H), 7.60~7.57 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.34 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 4.82 (s, 1H), 4.32~4.26 (m, 1H), 4.19~4.12 (m, 1H), 2.35 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}CNMR ($CDCl_3$, 125 MHz): δ 191.7, 173.3, 167.0, 147.1, 135.6, 131.3, 131.0, 130.8, 130.1, 128.6, 127.1, 120.9, 116.9, 115.8, 68.3, 62.7, 20.9, 13.9; HPLC (Chiralpak IC, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 57.56 min, t_{major} = 44.41 min, ee = 98%; $[\alpha]_D^{20}$= -45.6 (*c* = 1.0 in $CHCl_3$).



(*R*)-Ethyl 6-chloro-3-formy-4-hydroxy-2-phenyl-4*H*-chromene-4-carboxylate (7e) (Table 3.5, entry 5).

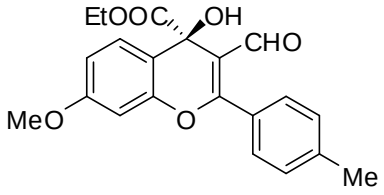
The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): *δ* 9.56 (s, 1H),7.51~7.66 (m, 6H), 7.34 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 4.87 (s,1H), 4.13~4.36 (m, *J*=7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): *δ* 191.4, 172.7, 166.6, 147.6, 131.6, 130.8, 130.4, 130.3, 130.2, 128.7, 127.1, 122.9, 118.7, 115.6, 68.1, 63.0, 13.9; HPLC

(Chiralcel AD, EtOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 20.54 min, t_{major} = 22.93 min, ee = 93%; $[\alpha]_D^{25}$ = -49 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): $C_{19}H_{15}O_5Cl$+Na, calcd: 381.0500, found: 381.0499; IR ($CHCl_3$, cm^{-1}): 3475, 2980, 2925, 2858, 1741, 1662, 1632, 1478, 1331, 1238, 1184, 1094, 1069, 1037, 890, 771, 701.



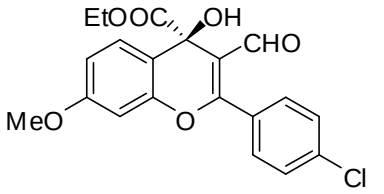
(*R*)-Ethyl 3-formy-4-hydroxy-7-methoxy-2-(4-methoxy-phenyl)-4*H*-chromene-4-carboxylate (7f) (Table 3.5, entry 6).

The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.57 (s,1H),7.59 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.04 (dd, *J* = 6.6, 1.8 Hz, 2H), 6.81 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.72 (d, *J* = 2.7 Hz, 1H), 4.76 (s,1H), 4.12~4.28 (m, *J* = 7.2 Hz, 2H), 3.89 (s,3H), 3.81 (s,3H), 1.17(t, *J* = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 191.6, 173.4, 166.7, 162.1, 160.8,150.0, 131.8, 128.0, 122.8, 115.7, 114.6, 113.7, 113.0, 101.3, 68.2, 62.5, 55.5, 55.4, 21.5, 13.9; HPLC (Chiralcel AD, *i*-PrOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 116.37 min, t_{major} = 97.17 min, ee = 99%; $[\alpha]_D^{25}$ = +1 (*c* = 1.0 in $CHCl_3$); HRMS (ESI):$C_{21}H_{20}O_7$+Na, calcd: 407.1101, found: 407.1110; IR ($CHCl_3$, cm^{-1}): 3469, 2958, 2926, 2850, 1738, 1632, 1607, 1508, 1333, 1292, 1254, 1197, 1174, 1116, 1066, 1032, 889, 834.



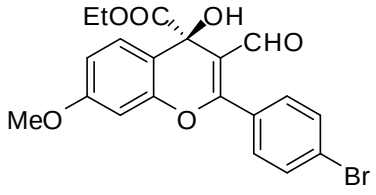
(*R*)-Ethyl 3-formy-4-hydroxy-7-methoxy-2-p-tolyl-4*H*-chromene-4-carboxylate (7g) (Table 3.5, entry 7).

The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.55(s, 1H),7.53(d, J = 8.1Hz, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.81 (dd, J = 8.7, 2.4 Hz, 1H), 6.71(d, J = 2.4 Hz, 1H), 4.76(s, 1H), 4.12~4.28 (m, J = 6.9 Hz, 2H), 3.82 (s,3H), 2.45 (s, 3H), 1.17 (t, J = 6.9 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 191.8, 173.4, 167.0, 160.8, 150.0, 142.0, 130.1, 129.3, 128.1, 127.8, 116.0, 113.7, 113.1, 101.3, 68.2, 62.6, 55.6, 21.5, 14.0.; HPLC (Chiralcel AD, EtOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 62.05 min, t_{major} = 54.31 min, ee = 99%; $[\alpha]_D^{25}$ = -4 (c = 1.0 in $CHCl_3$); HRMS (ESI): $C_{21}H_{20}O_6$+Na, calcd: 391.1152, found: 391.1149; IR ($CHCl_3$, cm^{-1}): 3483, 2957, 2921, 2851, 1739, 1663, 1634, 1506, 1332, 1236, 1197, 1172, 1115, 1067, 1033, 889, 827.



(*R*)-Ethyl 2-(4-chloro-phenyl)-3-formy-4-hydroxy-7-methoxy-4*H*-chromene-4-carboxylate (7h) (Table 3.5, entry 8).

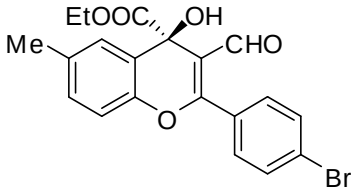
The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.54 (s, 1H),7.69 (m,2H), 7.52 (m, 2H), 7.44 (d, J = 8.7 Hz, 1H), 6.83 (dd, J = 8.7, 2.7 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 4.75 (s, 1H), 4.11~4.29(m, J = 6.9 Hz, 2H), 3.82(s, 3H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}CNMR ($CDCl_3$, 300 MHz): δ 191.0, 173.2, 165.6, 160.9, 149.9, 137.8, 131.5, 129.1, 129.0, 128.1, 116.5, 113.5, 113.3, 101.3, 68.0, 62.7, 55.6, 14.0; HPLC (Chiralcel AD, EtOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254nm): t_{minor} = 73.10 min, t_{major} = 61.60 min, ee = 99%; $[\alpha]_D^{25}$ = -2 (c = 1.0 in $CHCl_3$); HRMS(ESI): $C_{20}H_{17}O_6Cl$+Na, calcd: 411.0606, found: 411.0617; IR ($CHCl_3$, cm^{-1}): 3481, 2976, 2932,2855, 1739, 1665, 1635, 1507, 1333, 1237, 1197, 1173, 1115, 1067, 1032, 888, 838, 762.



(*R*)-Ethyl 2-(4-Bromo-phenyl)-3-formy-4-hydroxy-7-methoxy-4*H*-chromene-4-carboxylate (7i) (Table 3.5, entry 9).

The title compound was prepared according to the general procedure, asdescribed above in 99% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.54 (s,1H), 7.68 (d,J = 8.3 Hz, 2H), 7.52 (d,

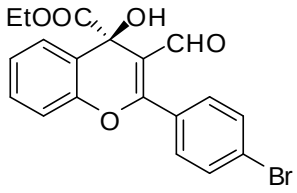
J = 8.3 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz,1H), 4.73 (s, 1H), 4.14~4.29 (m, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 1.18 (t, *J* = 6.9 Hz,3H); ^{13}CNMR($CDCl_3$, 75 MHz): δ 191.0, 173.2, 165.6, 160.9, 149.9, 132.0, 131.6, 129.6, 128.1, 126.2, 116.5, 113.4, 113.3, 101.3, 68.0, 62.7, 55.6, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 20/80, flow rate = 1.0mL/min, λ = 254 nm): t_{minor} = 65.97 min, t_{major} = 56.51 min, ee = 99%; $[\alpha]_D^{25}$ = -5 (*c* = 1.0 in$CHCl_3$); HRMS (ESI): $C_{20}H_{17}BrO_6$+Na, calcd: 455.0101, found: 455.0110; IR ($CHCl_3$, cm^{-1}): 3480, 2977, 2933, 2861, 1738, 1664, 1634, 1507, 1331, 1237, 1197, 1173, 1115, 1067, 1032, 887, 834, 757.



(*R*)-Ethyl 2-(4-bromo-phenyl)-3-formy-4-hydroxy-6-methyl-4*H*-chromene-4-carboxylate (7j) (Table 3.5, entry 10).

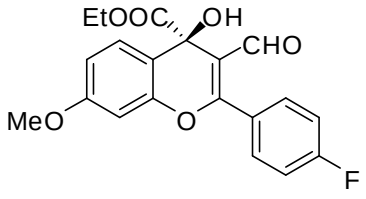
The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 9.54 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.32 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.80 (s, 1H), 4.30~4.14 (m, 2H), 2.35 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}CNMR($CDCl_3$, 125 MHz): δ 191.0, 173.1, 165.7, 147.0, 135.8, 131.9, 131.6, 131.0, 129.7, 127.1, 126.1, 120.8, 116.8, 116.1, 68.2, 62.7, 20.9, 13.9; HPLC (Chiralpak IC, *i*-PrOH/hexane = 20/80,

flowrate = 0.6 mL/min, λ = 254nm): t_{minor} = 58.48 min, t_{major} = 46.10 min, ee = 98%; $[\alpha]_D^{20}$= -24.3 (*c* = 1.0 in $CHCl_3$).



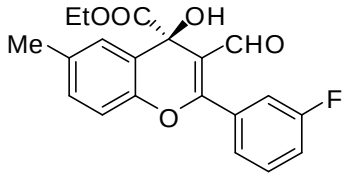
(*R*)-Ethyl 2-(4-bromo-phenyl)-3-formy-4-hydroxy-4*H*-chromene-4-carboxylate (7k) (Table 3.5, entry 11).

The title compound was prepared according to the general procedure, as describedabove in 98% yield. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 9.55 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.55~7.52 (m, 3H), 7.41~7.38 (m, 1H), 7.28~7.21 (m, 2H), 4.83 (s, 1H), 4.30~4.16 (m, 2H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}CNMR ($CDCl_3$, 125 MHz): δ 190.9, 173.0, 165.6, 148.9, 131.9, 131.6,130.2, 129.6, 127.2, 126.2, 125.9, 121.3, 117.1, 116.2, 68.1, 62.8, 13.9; HPLC (Chiralpak IC, *i*-PrOH/hexane = 10/90, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 125.31 min, t_{major} = 87.56 min, ee = 98%; $[\alpha]_D^{20}$ = -11.3 (*c* = 1.0 in $CHCl_3$).



(*R*)-Ethyl 2-(4-Fluoro-phenyl)-3-formy-4-hydroxy-7-methoxy-4*H*-chromene-4-carboxylate (7l) (Table 3.5, entry 12).

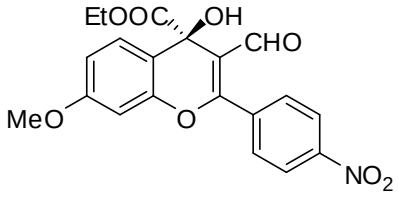
The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.54 (s,1H) ,7.66 (m, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.22 (m,2H),6.83(dd, J = 8.7, 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 4.77 (s,1H), 4.14~4.29 (m, J = 7.2 Hz, 2H), 3.82(s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 191.2, 173.3, 165.8, 160.9, 149.9, 132.4, 132.3, 128.1, 126.8, 116.2, 115.8, 113.5, 113.3, 101.3, 68.0, 62.7, 55.6, 14.0; HPLC (Chiralcel AD, EtOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254nm): t_{minor} = 48.76 min, t_{major} = 43.86 min, ee = >99%; $[\alpha]_D^{25}$ = 0 (c = 1.0 in $CHCl_3$); HRMS (ESI): $C_{20}H_{17}O_6F$+Na, calcd: 395.0901, found: 395.0905; IR ($CHCl_3$, cm^{-1}): 3483, 2962, 2933,2856, 1740, 1666, 1636, 1507, 1333, 1235, 1198, 1172, 1115, 1068, 1033, 891, 846, 814, 627,517.



(*R*)-Ethyl 2-(3-Fluoro-phenyl)-3-formy-4-hydroxy-6-methyl-4*H*-chromene-4-carboxylate (7m) (Table 3.5, entry 13).

The title compound was prepared according to the general procedure, as described above in 93% yield. ^{1}HNMR ($CDCl_3$, 500 MHz): δ 9.56 (s, 1H), 7.53~7.48 (m, 1H), 7.42~7.38 (m, 2H), 7.33 (s, 1H), 7.31~7.26 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0

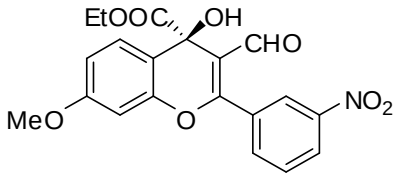
Hz,1H), 4.80 (s, 1H), 4.32~4.26 (m, 1H), 4.19~4.13 (m, 1H), 2.35 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}CNMR ($CDCl_3$, 125 MHz): δ 191.1, 173.1, 165.3, 163.4, 161.5, 147.0, 135.8, 132.7 (*J* = 8.3Hz), 131.0, 130.3 (*J* = 8.1 Hz), 127.1, 126.2, 120.8, 118.4 (*J* = 21 Hz), 117.1, 116.9 (*J* = 7.9 Hz), 116.2, 68.2, 62.7, 20.9, 13.9; HPLC (Chiralpak IC, *i*-PrOH/hexane = 20/80, flow rate = 0.6mL/min, λ = 254nm): t_{minor} = 53.52 min, t_{major} = 44.73 min, ee = 98%; $[\alpha]_D^{20}$ = -42.4 (*c* = 1.0 in$CHCl_3$).



(*R*)-Ethyl 3-formy-4-hydroxy-7-methoxy-2-(4-nitro-phenyl)-4*H*-chromene-4-carboxylate (7n) (Table 3.5, entry 14).

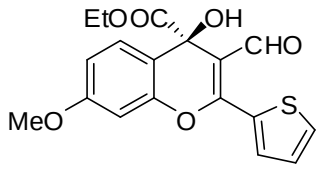
The title compound was prepared according to the general procedure, asdescribed above in 98% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.53 (s, 1H),8.40(d,*J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.44(d, *J*=8.7 Hz, 1H), 6.86(dd, *J*=8.7, 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz,1H), 4.74 (s, 1H), 4.16~4.30 (m, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}CNMR($CDCl_3$, 75 MHz): δ 191.1, 172.9, 164.0, 161.0, 149.7, 149.4, 136.7, 131.2, 128.2, 123.8, 117.4, 113.6, 113.4, 101.3, 67.8, 62.9, 55.6, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 78.30 min, t_{major} = 102.15 min, ee = 99%; $[\alpha]_D^{25}$ = -10 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): $C_{20}H_{17}NO_8$+Na,

calcd: 422.0846, found: 422.0838; IR ($CHCl_3$, cm^{-1}): 3472, 2976,2931, 2861, 1738, 1666, 1637, 1524, 1347, 1238, 1197, 1174, 1114, 1067, 1031, 932, 851, 753, 702.



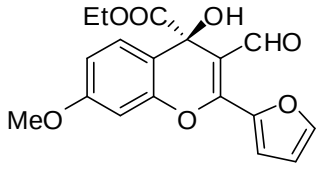
(*R*)-Ethyl 3-Formy-4-hydroxy-7-methoxy-2-(3-nitro-phenyl)-4*H*-chromene-4-carboxylate (7o) (Table 3.5, entry 15).

The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.54(s, 1H),8.56 (s, 1H), 8.45 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.75 (dd, J = 8.1, 7.5 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 8.7, 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 4.74 (s, 1H), 4.16~4.30 (m, J = 6.9 Hz, 2H), 3.83 (s, 3H), 1.17 (t, J = 6.9 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 190.0, 172.9, 163.8, 161.0, 148.3, 136.0, 132.4, 129.8, 128.1, 126.0, 124.9, 117.3, 113.7, 113.4, 101.3, 67.8, 62.9, 55.7, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 65.94 min, t_{major} = 51.11 min, ee = 99%; $[\alpha]_D^{25}$ = + 2 (c = 1.0 in $CHCl_3$); HRMS (ESI): $C_{20}H_{17}NO_8$+Na, calcd: 422.0846, found: 422.0840; IR ($CHCl_3$, cm^{-1}): 3423, 3088, 2966, 2931, 2867, 1738, 1666, 1637, 1533, 1348, 1237, 1198, 1174, 1114, 1067, 1033, 935, 854, 814, 763, 741, 699.



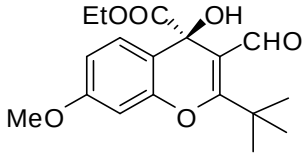
(*R*)-Ethyl 3-formy-4-hydroxy-7-methoxy-2-thiophen-2-yl-4*H*-chromene-4-carboxylate (7p) (Table 3.5, entry 16).

The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.02 (s, 1H), 9.84 (s, 1H), 7.81 (d, *J* = 3.9 Hz, 1H), 7.54 (d, *J* = 3.9 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* =8.7, 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 4.73 (s, 1H), 4.13~4.28 (m, 2H), 3.83 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 189.8, 182.8, 172.8, 161.0, 149.5, 147.1, 140.1, 134.9, 133.1, 128.0, 117.7, 113.7, 113.2, 101.2, 68.0, 62.9, 55.6, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 74.02 min, t_{major} = 66.40 min, ee = 99%; $[\alpha]_D^{25}$ = -50 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): $C_{18}H_{16}O_6S$+Na, calcd: 383.0565, found 383.0561; IR ($CHCl_3$, cm^{-1}): 3470, 3094, 2954, 2925, 2853, 1740, 1665, 1631, 1507, 1341, 1286, 1236, 1211,1169, 1111, 1065, 1029, 854, 818.



(*R*)-Ethyl 3-formy-2-furan-2-yl-4-hydroxy-7-methoxy-4*H*-chromene-4-carboxylate (7q) (Table 3.5, entry 17).

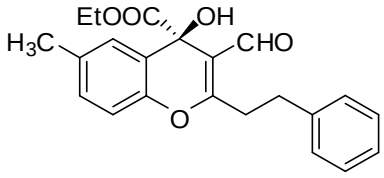
The title compound was prepared according to the general procedure, as describedabove in 97% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.30 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 3.0 Hz, 1H), 6.80 (dd, J =8.7, 2.4 Hz, 1H), 6.73 (d, J = 2.4 Hz,1H), 6.64 (dd, J = 3.0, 1.8 Hz, 1H), 4.11~4.26 (m, J = 7.2 Hz, 2H), 3.83 (s,3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 191.5, 173.3, 160.9, 154.1, 149.4, 146.5, 146.0, 128.0, 116.8, 115.2, 113.3, 113.1, 112.1, 101.1, 68.0, 62.6, 55.6, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 46.07 min, t_{major} = 38.55 min, ee = 96%; $[\alpha]_D^{25}$ = -27 (c = 1.0 in $CHCl_3$); HRMS (ESI): $C_{18}H_{16}O_7$+Na, calcd: 367.0788, found: 367.0782; IR ($CHCl_3$, cm^{-1}): 3455, 3148, 2973, 2927, 1735, 1631, 1400, 1234, 1208, 1111, 1064, 1027, 832, 764.



(*R*)-Ethyl 2-tert-butyl-3-formy-4-hydroxy-7-methoxy-4*H*-chromene-4-carboxylate (7r) (Table 3.5, entry 18).

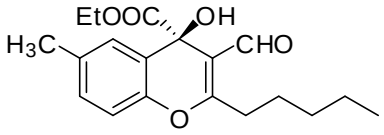
The title compound was prepared according to the general procedure, as describedabove in 91% yield. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.35 (s, 1H), 7.39 (d, J = 8.7Hz, 1H), 6.76 (dd, J = 8.7, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 4.67 (s, 1H), 4.05~4.24 (m, J = 7.2 Hz,2H), 3.81 (s, 3H), 1.54 (s, 9H), 1.14 (t, J =7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz): δ 190.5, 174.7, 173.6, 160.7, 149.3, 127.8, 115.8, 113.1, 113.0, 100.8, 68.8, 62.2, 55.5,

38.5, 31.3, 13.9; HPLC (Chiralcel AD, EtOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 17.29 min, t_{major} = 21.26 min, ee = 98%; $[\alpha]_D^{25}$ = -34 (*c* = 1.0 in $CHCl_3$); HRMS (ESI): $C_{18}H_{22}O_6$+Na, calcd: 357.1309, found: 357.1318; IR ($CHCl_3$, cm^{-1}): 3511, 2959, 2923, 2853, 1739, 1653, 1632, 1571, 1508, 1291, 1231, 1205, 1178, 1117, 1036, 934, 757.



(*R*)-Ethyl 3-formyl-4-hydroxy-6-methyl-2-phenethyl-4*H*-chromene-4-carboxylate (7s) (Table 3.5, Entry 19)

The title compound was prepared according to the general procedure, as described above in 69% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (s, 1H), 7.29~7.26 (m, 3H), 7.22~7.18 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 4.64 (s, 1H), 4.24~4.18 (m, 1H), 4.13~4.07 (m, 1H), 3.14~3.08 (m, 4H), 2.32 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.8, 173.3. 168.0, 146.7, 139.4, 135.4, 130.8, 128.7, 128.5, 127.0, 126.7, 121.0, 116.5, 116.0, 67.8, 62.5, 33.9, 32.0, 20.8, 13.9; HPLC (Chiralpak IC, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 126.8 min, t_{major} = 78.9 min, ee = 97%; $[\alpha]_D^{17}$= -32.2 (*c* = 1.0 in $CHCl_3$).



(*R*)-Ethyl 3-formyl-4-hydroxy-6-methyl-2-pentyl-4*H*-chromene-4-carboxylate (7t) (Table 3.5, Entry 20)

The title compound was prepared according to the general procedure, as described above in 75% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.93 (s, 1H), 7.28 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 4.71 (s, 1H), 4.28~4.21 (m, 1H), 4.14~4.07 (m, 1H), 2.89~2.78 (m, 2H), 2.32 (s, 3H), 1.81~1.76 (m, 2H), 1.41~1.35 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.2, 173.4, 169.7, 146.7, 135.3, 130.8, 127.0, 121.0, 116.5, 115.6, 67.9, 62.5, 31.1, 29.8, 27.7, 22.3, 20.8, 13.9; HPLC (Chiralpak IC, *i*-PrOH/hexane = 20/80, flow rate = 0.6 mL/min, λ = 254nm): t_{minor} = 75.1 min, t_{major} = 50.4 min, ee = 99%; $[\alpha]_D^{17}$= -48.0 (c = 1.0 in $CHCl_3$).

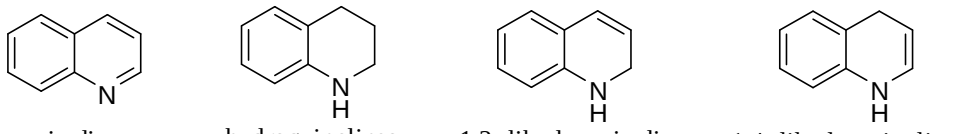
3.6 Efficient Synthesis of Polysubstituted Quinolines and Chiral 1,4-Dihydroquinolines by a Divergent Organocatalytic Cascade Approach. An Unexpected Effect of "*N*" Protecting Groups on Formed Products

3.6.1 Introduction

The development of new synthetic methodologies that enable to facilely construct synthetically and biologically important complex molecular architectures in an efficient way from readily available starting materials is of considerable significance in chemical

synthesis. Quinolines **A** and related chiral hydroquinolines **B**-**D** are 'privileged' structures, widely distributed in natural products and synthetic substances with a broad spectrum of intriguing biological properties (Figure 3.8)[35]. Therefore, they have long been a mainstay of organic synthesis[36]. The general strategies for the construction of quinoline scaffolds include Friedländer[37], Skraup[38], Doebner-VonMiller[39], Pfitzinger[40], and Combes[41] annulation reactions. Moreover, recently, new improving catalytic approaches also have been developed to meet their synthetic demand[42]. On the other hand, while significant efforts have been made toward the chiral hydroquinolines **B**[43,44] and 1,2-dihydroquinolines **C**[45,46], surprisingly asymmetric synthesis of 1,4-dihydroquinoline architectures **D** remains elusive[47] and only a single example, reported by Mangeney, Alexakis and co-workers, was found by using chiral auxiliary as stereo-control[48]. To our knowledge, a catalytic version has not been reported.

Figure 3.8 Skeletons of Quinolines **A** and Hydroquinolines **B**-**D**



quinolines **A** | hydroquinolines **B** | 1,2-dihydroquinolines **C** | 1,4-dihydroquinolines **D**

In this part, we would like to report a powerful divergent organocatalytic cascade approach involving an unprecedented aza-Michael-aldol and/or aromatization sequence to both chiral 1,4-dihydroquinolines and quinolines, respectively. Notably, in the study we have made an unexpected discovery that the nature of products formed is governed by the form of *N*-protective groups[49]. When aryl sulfonyls bearing electron-donating groups

are used as protecting groups for the nitrogen, a Michael-aldol-aromatization cascade proceeds to give polysubstituted quinolines; whereas chiral 1,4-dihydroquinolines are produced instead via a highly enantioselective Michael-aldol cascade with electron-withdrawing moieties such as trifilic group.

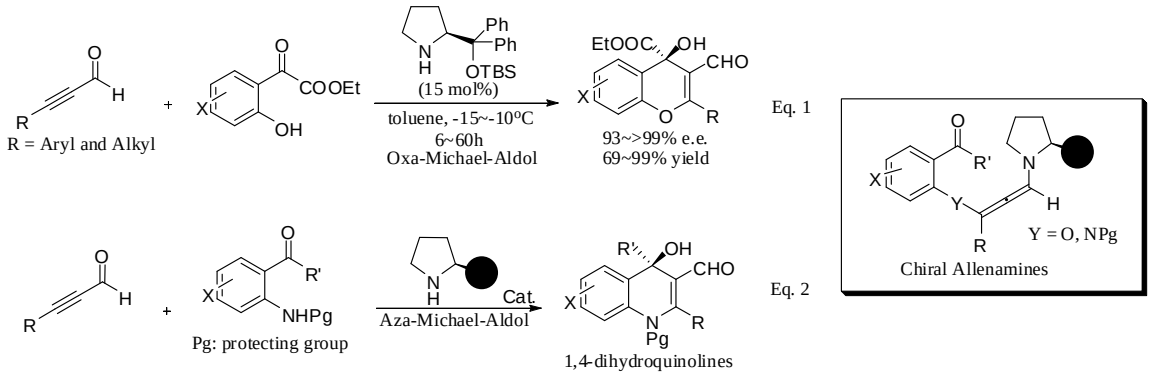
3.6.2 Results and Discussion

3.6.2.1 An unexpected organocatalytic aza-Michael-aldol-aromization cascade

1) Exploration of aza-Michael-aldol cascade: an unanticipated effect of *"N"*protecting groups on products formed.

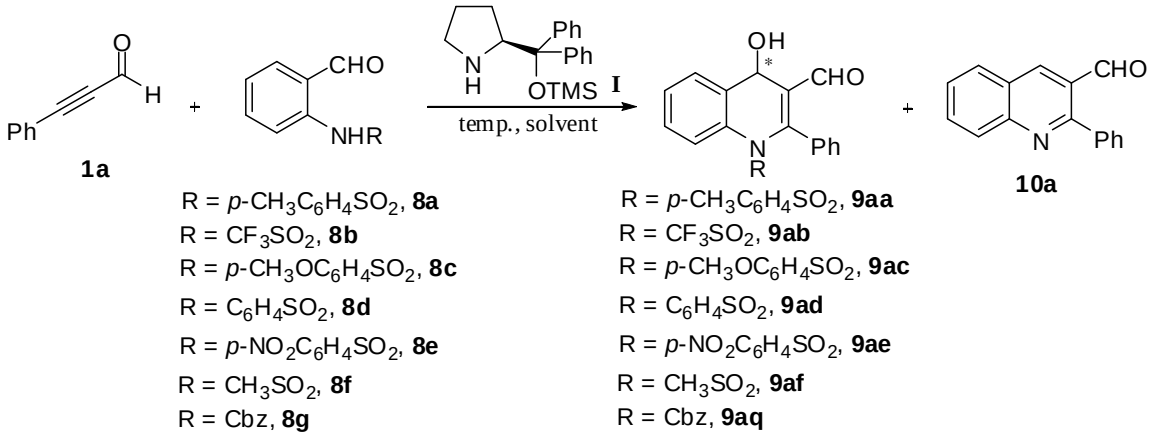
As shown above, recently we have uncovered organocatalytic enantioselective allenamine involved oxa-Michael-aldol (Scheme 3.7, Eq. 1) and -Michael cascade reactions[50]. In our continuing effort on expanding the efficient cascade strategy, we envisioned that the use of nitrogen-centered nucleophiles instead of "*O*" could lead to a new aza-Michael-aldol cascade approach to chiral 1,4-dihydroquinolines, a synthetically much less studied class of compounds (Scheme 3.7, Eq. 2).

Scheme 3.7 Organocatalytic Michael-aldol Cascade Reactions Involving Chiral Allenamines



Our initial investigation focused on the model reaction of *N*-tosyl (Ts) 2-aminobenzaldehyde **8a** with phenylpropargyl aldehyde **1a** in the presence of 30 mol% of diphenylpyrrolinol TMS ether **I** in $CHCl_3$ at r.t. (Table 3.7, entry 1). It is noteworthy that the Ts was selected as protecting group for "*N*" since its strong electron-withdrawing capacity enhances the NH acidity for easy ionization to produce more nucleophilic "*N*" anion for the initial Michael addition[46a]. TLC and crude ^{1}H NMR analysis showed that the seemingly aza-Michael-aldol product **9aa** was produced. However, when the reaction mixture was subjected to purification on silica gel, unexpected compound **10a** was obtained instead in 54% yield (Table 3.7, entry 1). It appeared that the product **9aa** was transformed into **10a** in the presence of silica gel. The unanticipated discovery prompted us to investigate the interesting process in depth since the successful realization of the reaction could generatea new approach to the synthetically valuable polysubstituted quinolines.

Table 3.7 Exploration of Organocatalytic Aza-Michael-aldol-aromatization Cascade Reaction[a]



Entry	R	Additive	Solvent	Cat. Loading	T (^oC)	*t* (h)	% Yield [b] and ee [c] 9a	% Yield 10a[b]
1	**8a**	none	$CHCl_3$	30	rt	30	0	54
2	**8b**	none	$CHCl_3$	30	rt	28	64 (7%)[d]	0
3	**8c**	none	$CHCl_3$	30	rt	35	0	51
4	**8d**	none	$CHCl_3$	30	rt	30	0	46
5	**8e**	none	$CHCl_3$	30	rt	5	65 (8%)[d]	0
6	**8f**	none	$CHCl_3$	30	rt	120	0	19
7	**8g**	none	$CHCl_3$	30	rt	120	0	0
8	**8c**	none	$CHCl_3$	30	60	5	0	<10[e]
9	**8c**	none	EtOAc	30	rt	48	0	44[e]
10	**8c**	none	CH_3CN	30	rt	48	0	9[e]
11	**8c**	none	toluene	30	rt	48	0	24[e]
12	**8c**	none	MeOH	30	rt	48	0	10[e]
13	**8c**	none	THF	30	rt	48	0	37[e]

14[f]	**8c**	none	$CHCl_3$	30	rt	4	0	32
15[g]	**8c**	none	$CHCl_3$	30	rt	4	0	28
16	**8c**	Cs_2CO_3 (1.0 equiv.)	$CHCl_3$	30	rt	5	0	31
17	**8c**	Na_2CO_3 (1.0 equiv.)	$CHCl_3$	30	rt	42	0	45
18	**8c**	K_2CO_3 (1.0 equiv.)	$CHCl_3$	30	rt	7	0	56
19	**8c**	K_2CO_3 (0.1 equiv.)	$CHCl_3$	10	50	16	0	99[h]

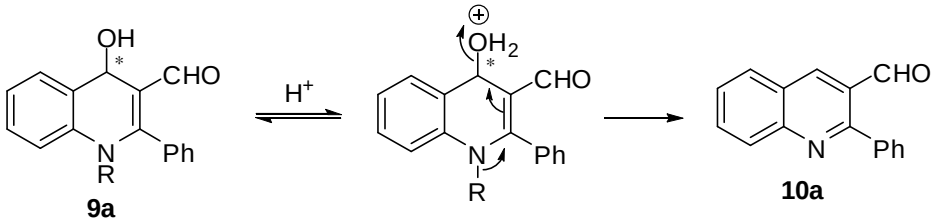
[a] Reaction conditions: unless specified, a mixture of ynal **1a** (0.16 mmol) and compound **8** (0.15 mmol) and cat. **I** (0.045 mmol) and an additive in a solvent (1.0 mL) was stirred at specified temperature for a defined time and see Experimental Section and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC (Chiralpak AS-H column). [d] In parenthesis, ee value. [e] Calculated based on crude ^{1}H NMR. [f] **1a** in chloroform (1.0 mL, 0.013 mol/L) was injected into the reaction solution at 0.05 mL/min. [g] **8c** in chloroform (1.0 mL, 0.006 mol/L) was injected into the reaction solution at 0.03 mL/min. [h] After reaction completion, then silica gel (80 mg) was added and stirred at r.t. for 24 h. Et_3N (0.18 mmol) was added and stirred at r.t. for 3 h to get free deprotonated quinoline **10a**.

2) Optimization of reaction conditions.

(1)Effect of "N" protecting groups. It is believed that acidic silica gel promotes an aromatization process through a dehydration-deprotection of the sulfonyl group cascade sequence (Scheme 3.8). The driving force for the observed product may come from the dehydration of the aromatization tending 1,4-dihydroquinolines under an acidic condition. An aromatic sulfonamide bearing an electron-donating moiety assists the carbocation character development for a favorable dehydration-aromatization process; while a strong electron-withdrawing one will retard it. Indeed, as shown, when Tf was

used, no aromatization product **10a** was formed (Table 3.7, entry 2). Instead, a stable chiral 1,4-dihydroquinoline **9ab** (R = CF_3SO_2) was obtained in 64% yield but with only 7% ee after silica gel chromatography. We also found that the Michael-aldol cascade proceeded rapidly (5 h) presumably due to the more acidic TfNH moiety to easier produce TfN^-. The electronic effect was further demonstrated in cases of aromatic sulfonyls bearing electron-donating (**8c**, Table 3.7, entry 3), -neutral (**8d**, Table 3.7, entry 4), and -withdrawing (**8e**, Table 3.7, entry 5) substituents. With the electron-donating (**8c**, Table 3.7, entry 3) and -neutral (**8d**, Table 3.7, entry4) groups, quinoline **10a** was obtained exclusively when treated with silica gel. However, the electron-withdrawing *p*-$NO_2C_6H_4SO_2$- moiety dictated product 1,4-dihydroquinoline **9ae**. Moreover, it should be noted that there is an essential electronic balance of the "*N*" protecting form for nucleophilic reactivity and stabilizing the carbocation feature. It is anticipated that although a sulfonyl functionality having an electron-donating group facilitates the aromatization process, the initial conjugate addition becomes more difficult as a result of reducing NH acidity. As shown, only 19% yield of product **10a** (Table 3.7, entry 6) and no reaction was observed when Ms- (Table 3.7, entry 6,) and Cbz- (Table 3.7, entry 7) were used, respectively. We decided to choose *p*-$MeOC_6H_4SO_2$ as masking group to further optimize the reaction conditions.

Scheme 3.8 Organocatalytic aza-Michael-aldol-aromatization Reaction



2) Effects of reaction temperature, solvents, reactant addition sequence and additives. In consideration of higher temperate facilitating a reaction, accordingly we raised the reaction temperature to 60 ºC (Table 3.7, entry 8). However, it became worse and a significant amount of **1a** was decomposed with only 50% conversion observed. The desired product was calculated based on ^{1}H NMR in <10% yield. Solvents play an important role in governing the reaction rate and prodcuts formed. Therefore, we probed the effect of reaction medium on the **I**-promoted cascade process. Solvents including commonly used EtOAc, MeCN, toluene, MeOH and THF were screened (Table 3.7, entries 9-13). It was found that $CHCl_3$ was a preferred medium for the process. Since substrate ynal **1a** is relatively labile, its slow addition in $CHCl_3$ was employed (Table 3.7, entry 14). Disappointingly, a lower reaction yield (37%) was obtained. A similar outcome was observed in a reverse order addition (Table 3.7, entry 15). We envisioned that due to the relatively weak acidic property of NH group induced by the *para*-methoxysulfonyl group, addition of a base may assist the deprotonation to produce more nucleophilic negative nitrogen species, which may speed up the process. Accordingly, base additives Cs_2CO_3, K_2CO_3, and Na_2CO_3 were examined in $CHCl_3$. Indeed, it appeared that they were beneficial to the process (Table 3.7, entries 16~18). The best

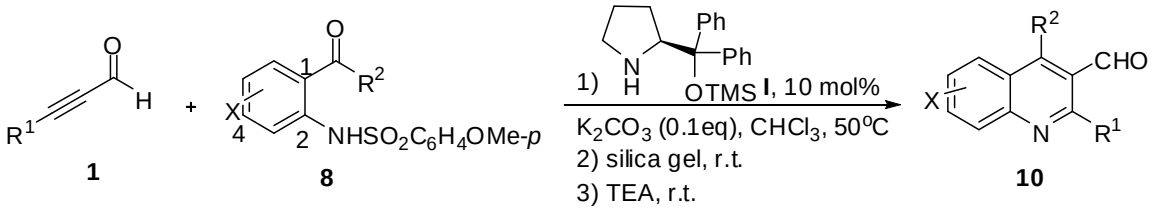
condition was identified that the use of K_2CO_3 (0.1 equiv.) at 50 ºCwith 10 mol% catalyst loading (Table 3.7, entry 19). It should be noted that pretreatment of the reaction mixture with TEA was necessary in order to get a consistent yield of the free deprotonated quinoline product **10a**.

3) Scope of the cascade Michael-aldol-aromatization reactions.

The optimal reaction conditions, uncovered in the exploratory effort, are exploited to probe the scope of the organocatalyst **I** catalyzed Michael-aldol-aromatization cascade reactions. As revealed in Table 3.8, the tandem process serves as a general approach to the preparation of ploysubstitued quinolines. In the cascade process, notably the reactions proceeded in high yield (76-99%) with a broad substrate scope. It seems that the electronic effect of aromatic alkynals **1** has limited influence on the process. The neutral (Table 3.8, entries 1, 15, 17-20, and 23), electron-donating (entries 3-4, 9, and 11) and -withdrawing (entries 2, 5-8, 12, 16, 21-22, and 24) substituents could be tolerated with a significant structural variation. A similar trend was observed for heteroaromatic alkynals, as shown with thiophen-2-yl-propynal (Table 3.8, entry 10). Furthermore, the reaction also worked well with less reactive aliphatic alkynals **1** (Table 3.8, entries 13-14) although a higher catalyst loading (20 mol%) was needed and relatively low yields were observed. On the other hand, the reaction could be applied to substrates **8** with a broad structural scope. Again the survey of the electronic effect reveals that such impact is limited. Both electron-donating (Table 3.8, entries 15-16) and -withdrawing (Table 3.8, entries 17-18) groups can be well tolerated. Moreover, significantly more hindered and

less reactive ketones instead of aldehydes in substrates **8** (e.g., $R^2 \neq H$) are compatible with this methodology (Table 3.8, entries19-24). Structurally diverse ketones can be engaged in the process to give trisubstituted quinolines **10** in high efficiency. A trend of increase of the steric hindrance of R^1 group from H- to -CH_3, (*E*)-CH=CHC_6H_5 and –Ph requiring more drastic conditions for aromatization is seen, but still relatively mild conditions with achieving high yields (76-98%).

Table 3.8 Substrate Scope of **I**-Catalyzed "one-pot" Synthesis of Quinolines **10**[a]



Entry	R^1	R^2	X	**10**	*t*(h)	% yield[b]
1	Ph	H	H	**10a**	16	99
2	4-Br-C_6H_4	H	H	**10b**	16	97
3	4-CH_3-C_6H_4	H	H	**10c**	24	92
4	4-CH_3O-C_6H_4	H	H	**10d**	21	95
5	2-Cl-C_6H_4	H	H	**10e**	16	96
6	4-F-C_6H_4	H	H	**10f**	16	98
7[c]	4-CN-C_6H_4	H	H	**10g**	20	91
8	4-Cl-C_6H_4	H	H	**10h**	16	92
9[d]	2-CH_3O-C_6H_4	H	H	**10i**	16	95
10	2-thienyl	H	H	**10j**	16	92
11[d]	3-CH_3O-C_6H_4	H	H	**10k**	16	97

12[c]	3-CN-C_6H_4	H	H	**10l**	13	95
13[c]	*n*-C_5H_{11}	H	H	**10m**	16	80
14[c]	$PhCH_2CH_2$	H	H	**10n**	20	83
15[d]	Ph	H	6-CH_3	**10o**	24	98
16[d]	4-Cl-C_6H_4	H	6-CH_3	**10p**	24	90
17	Ph	H	4-Cl	**10q**	16	94
18	Ph	H	5-Cl	**10r**	16	91
19[c]	Ph	CH_3	H	**10s**	22	84
20[c,e]	Ph	(*E*)-CH=CHPh	H	**10t**	12	80
21[c,e]	4-Cl-C_6H_4	(*E*)-CH=CHPh	H	**10u**	12	78
22[e]	4-F-C_6H_4	(*E*)-CH=CHPh	H	**10v**	16	76
23[f]	Ph	Ph	H	**10w**	16	96
24[f]	4-Br-C_6H_4	Ph	H	**10x**	16	98

[a] Reaction conditions: unless specified, a mixture of propynal **1** (0.16mmol), compound **8** (0.15mmol), specific amount of organocatalyst **I** and K_2CO_3 (0.015mmol) in chloroform (1.0 mL) was stirred at 50°C for a specified time. After reaction finish, then 80mg silcal gel was added and stirred at r.t. for 24h, then Et_3N (0.18mmol) was added and stirred at r.t. for 3h. [b] Isolated yields. [c] 20 mol% **I** use. [d] 15 mol% **I** used. [e] Aromatization step required heating at 50 ºC for 3 h in the presence of silica gel. [f] 1.0 eq of $NaHSO_4.H_2O$ was added and stirred at 50 ºC for 24 h.

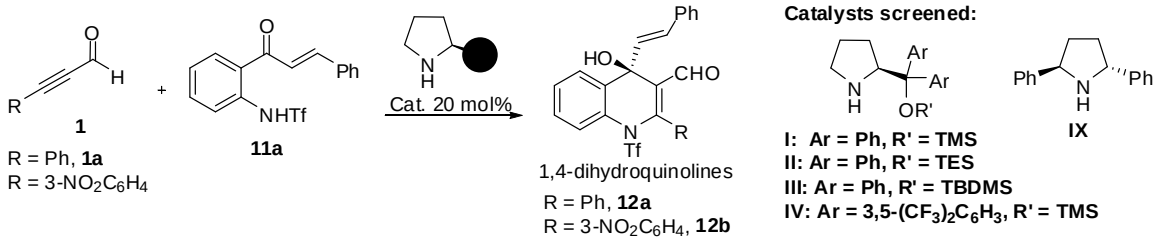
3.6.2.2 Organocatalytic enantioselective Michael-aldol cascade reactions

1) Optimization of reaction conditions for one-pot synthesisof chiral 1,4-dihydroquinolines.

Having established an efficient protocol for the preparation of quinolines using an organocatalytic aza-Michael-aldol-aromatization cascade process, we turned our attention on the optimization of aza-Michael-aldol cascade for the "one-pot" preparation of structurally different chiral 1,4-dihydroquinolines. The above study unveiled that the use of Tf as masking group led to the product without subsequent aromatization (Table 3.7, entry 2). However, only 7% ee was obtained with catalyst **I**. We found that when more bulky ketone **11a** was used, the enantioselectivity induced by (*S*)-diphenylpyrrolinol TMS ether **I** under similar reaction conditions was improved dramatically (Table 3.9, entry 1, 76% ee, 99% yield). A range of chiral α, α-diaryl prolinol silyl ether catalysts (**I-IV**) were probed accordingly. Disappointedly, the results were not encouraging (Table 3.9, entries 2-4). It should be pointed out that for the model reaction of phenylpropargyl aldehyde **1a** with 2'-(trifluoromethanesulfonyl)aminochalcone **11a**, the formed product **12a** and **11a** have the same polarity which rendered the optimization process tedious because of difficult purification. To minimize the work load, we chose more polar 3-nitrophenyl propargyl aldehyde as model substrate for the subsequent optimization. A similar level of enantioselectivity was attended with catalyst **I** (Table 3.9, entry 5, 72% ee). Gratifyingly, when C_2-symmetry catalyst (*2R, 5R*)-diphenylpyrrolidine **IX**[51] was employed, the enantioselectivity was significantly enhanced to 87% and full conversion was obtained in only 1 h (Table 3.9, entry 6). Furthermore, solvent screening revealed that the enantioselectivity was highly solvent dependent. Remarkably, compared with dichlomethane, significantly higher enantioselectivity was observed for toluene and TBME (*t*-BuOMe) (Table 3.9, entries 8 and 10). Polar protic solvent, such as MeOH, had

a deleterious effect on both the reaction yield and enantioselectivity (Table 3.9, entry 9). Given the fast reaction rate and the practical advantage of carrying out the reaction at 0 °C, the catalyst loading was dramatically reduced to 1 mol% at 0 °C in toluene and the reaction afforded the desired product in almost quantitative yield and with 99% ee within only 3 h (Table 3.9,entry 11).

Table 3.9 Optimization of Reaction Conditions for Organocatalytic Enantioselective Aza-Michael-aldol Cascade Reactions[a]



Entry	R	Cat.	Solvent	*t* (h)	Yield (%) [b]	ee (%) [c]
1	Ph	**I**	CH_2Cl_2	12	99	76
2	Ph	**II**	CH_2Cl_2	12	93	75
3	Ph	**III**	CH_2Cl_2	12	92	71
4	Ph	**IV**	CH_2Cl_2	12	84	40
5	3-$NO_2C_6H_4$	**I**	CH_2Cl_2	12	93	72
6	3-$NO_2C_6H_4$	**IX**	CH_2Cl_2	1	97	87
7	3-$NO_2C_6H_4$	**IX**	$Cl(CH_2)_2Cl$	1	99	94
8	3-$NO_2C_6H_4$	**IX**	Toluene	1	99	98
9	3-$NO_2C_6H_4$	**IX**	MeOH	6	61	75
10	3-$NO_2C_6H_4$	**IX**	TBME	4	96	98

11[d]	3-$NO_2C_6H_4$	**IX**	Toluene	3	99	99

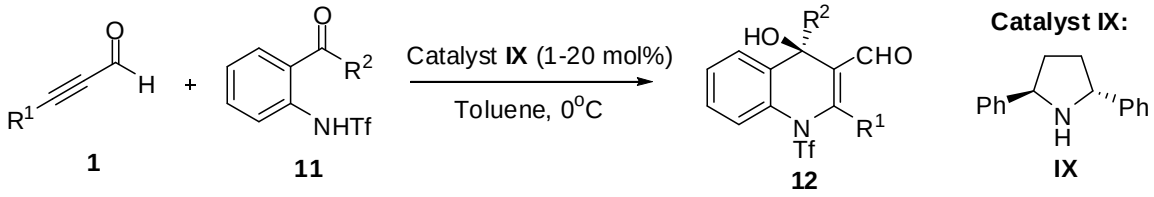
[a] Reaction conditions: unless specified, a solution of alkynal **1** (0.08 mmol), organocatalyst (0.016 mmol) in a solvent (0.8 mL) was added *N*-protected 2'-aminochalcone **11a** (0.08 mmol). The resulting solution was stirred at r.t. for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or IB column). [d] Reaction performed at 0 °C with 1 mol% of catalyst loading.

2) Scope of IX-catalyzed aza-Michael-aldol cascade reactions.

As revealed in Table 3.10, the optimized protocol has been demonstrated to be general to a variety of ynals **1** and 2'-(trifluoromethanesulfonyl)aminoketones **11**. Notably, the reactions served as synthetically efficient "one-pot" access to enantioenriched diverse 1,4-dihydroquinolines with creation of a quaternary stereogenic center. They proceeded in high yields (70-99%) and with excellent levels of enantioselectivities (94-99%). Both substrates ynals **1** and aminoketones **11** with significant structural variations can be tolerated. The electronic and steric factors associated with the α,β-unsaturated ketone moieties of 2'-(trifluoromethanesulfonyl) aminochalcone **11** appeared to have minimal impact on the reaction efficiencies in terms of enantioselectivity and yields (Table 3.10, entries 1-14). It is observed that electronic effect of ynals **1** play a role in the reaction rate. The electron-withdrawing groups on aromatic ynal substrates tended to accelerate the reaction illustrated by the higher turnover (1 mol% of catalyst loading and short reaction time (Table 3.10, entries 3-9, 3-9 h). While for the ynals **1** bearing neutral (Table 3.10, entries 1 and 2) or electron-donating substitutents (Table 3.10, entry 2), increase of catalyst loading is necessary to assure full conversion. Less reactive aliphatic ynals can also efficiently participate in the process to

give desired products **12l** and **12m** in excellent yields (99 and 98%, respectively) and with excellent ee values (96 and 97%, respectively) except relatively slow reaction rates (Table 3.10, entries 13 and 14). We have also investigated more steric aliphatic alkynals, such as *tert*-butyl propynal and cyclopentyl propynal, however, no reaction was observed. Structural alternation of ketones besides chalcone moieties in **11**, as shown with acetophenone and benzophenone is also amenable to the protocol with high efficiency (Table 3.10, entries 15 and 16). The absolute configuration of **12g** prepared under the optimal condition was determined by X-ray crystallography (Figure 3.9).

Table 3.10 Enantioselective Organocatalytic Cascade Aza-Michael-aldol Reactions between Ynals **1** and 2'-(Trifluoromethanesulfonyl)aminoketones **11**[a]

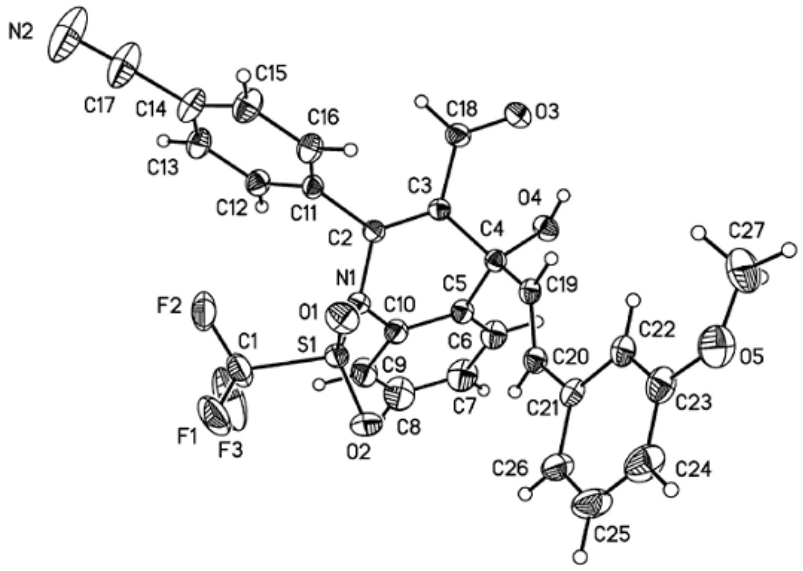


Entry	R^1	R^2	**12**	*t*(h)	% yield [b]	% ee [c]
1[d]	Ph	*trans*-PhCH=CH	**12a**	18	95	97
2[d]	Ph	*trans*-4-BrC_6H_4CH=CH	**12b**	18	93	98
3	3-$NO_2C_6H_4$	*trans*-PhCH=CH	**12c**	3	99	99
4	3-$NO_2C_6H_4$	*trans*-4-BrC_6H_4CH=CH	**12d**	3	99	98
5	4-ClC_6H_4	*trans*-PhCH=CH	**12e**	4	99	98
6	4-CNC_6H_4	*trans*-4-BrC_6H_4CH=CH	**12f**	3	91	99
7	4-CNC_6H_4	*trans*-3-$MeOC_6H_4$CH=CH	**12g**	8	98	98

8	4-BrC_6H_4	*trans*-4-$NO_2C_6H_4CH$=CH	**12h**	5	96	98
9	4-BrC_6H_4	*trans*-2-MeC_6H_4CH=CH	**12i**	9	99	97
10[d]	4-$MeOC_6H_4$	*trans*-PhCH=CH	**12j**	18	92	96
11	2-thienyl	*trans*-PhCH=CH	**12k**	9	90	96
12[d]	$PhCH_2CH_2$	*trans*-PhCH=CH	**12l**	12	99	96
13[e]	*n*-C_5H_{11}	*trans*-PhCH=CH	**12m**	20	98	97
14[f]	*trans*-PhCH=CH	*trans*-PhCH=CH	**12n**	18	70	94
15[f]	Ph	CH_3	**12o**	18	96	95
16[e,g]	3-$NO_2C_6H_4$	Ph	**12p**	3	84	99

[a] Reaction conditions: unless specified, a solution of alkynal **1** (0.08mmol), organocatalyst **IX** (1~20 mol%) in toluene (0.8mL) was added 2'-(trifluoromethanesulfonyl)aminoketones **11** (0.08mmol). The resulting solution was stirred at 0°C for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or IB column). [d] 5 mol% of catalyst **IX** used. [e] 20 mol% of catalyst **IX** used. [f] 8 mol% of catalyst **IX** used. [g] Reaction carried out at r.t..

Figure 3.9 X-ray Crystal Structure of Compound **12g**



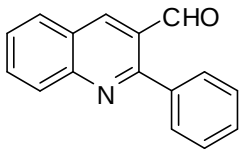
3.6.3 Conclusion

While organocatalytic cascade reactions have been established as a viable route in organic synthesis[1], the examples of combining powerful divergent synthesis and organocatalytic cascade strategy are rare[52]. In this investigation, we have illustrated a divergent organocatalytic cascade approach to synthetic valuable polysubstituted quinolines and highly enantioenriched 1,4-dihydroquinolines. The key to the fate of products formed depends on the protecting sulfonyls used for the "*N*" initiated an aza-Michael-aldol cascade. The electron-donating aryl sulfonamides facilitate the dehydration-aromatization of the aza-Michael-aldol adducts to give polysubstituted quinolines in good to high yields (76-99%) with a broad substrate scope. However, when strong electron-withdrawing Tf (CF_3SO_2-) is used, chiral 1,4-dihydroquinolines products are produced. Notably, the process, efficiently catalyzed by (*2R, 5R*)-diphenylpyrrolidine

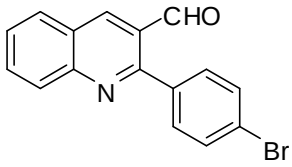
using as low as 1 mol% loading, leads to the first catalytic enantioselective access to the chiral scaffold with excellent level of enantioselectivity (94-99% ee). The studies show a scarce example of the electronic effect on the nature of reaction course and products[49].

3.6.4 Supporting Information

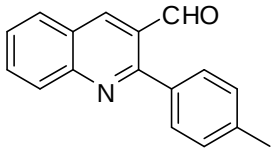
General Procedure for aza-Michael-aldol-aromatization Cascade Reactions (Table 3.8): To a solution of ynal **1** (0.16 mmol), organocatalyst **I** (10~20 mol%) in chloroform (1.0 mL) was added compound **8** (0.15 mmol) and K_2CO_3 (0.015 mmol). The resulting solution was stirred at 50 ºC for a specified time. After reaction finish monitored by TLC, then silica gel (80 mg) was added and stirred at r.t. for 24h, then Et_3N (0.18 mmol) was added and stirred at r.t. for 3h. The reaction mixture was directly purified by column chromatography, eluted with hexane/EtOAc to afford the desired product.



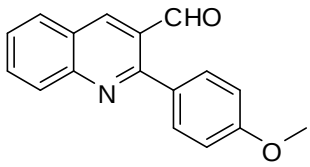
2-phenylquinoline-3-carbaldehyde (10a) (Table 3.8, Entry 1): The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.19 (s, 1H), 8.85 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.90~7.86 (m, 1H), 7.70~7.69 (m, 2H), 7.66~7.63 (m, 1H), 7.59~7.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.5, 160.3, 149.6, 138.1, 137.8, 132.6, 130.2, 129.6, 129.43, 129.38, 128.7, 127.6, 127.5, 126.4.



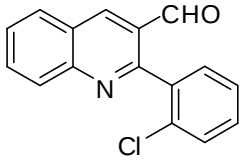
2-(4-bromophenyl)quinoline-3-carbaldehyde (10b) (Table 3.8, Entry 2): The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.17 (s, 1H), 8.84 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.90~7.87 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.67~7.64 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 190.9, 158.9, 149.6, 138.6, 136.7, 132.8, 131.9, 131.8, 129.6, 129.4, 127.7, 127.5, 126.4, 124.1.



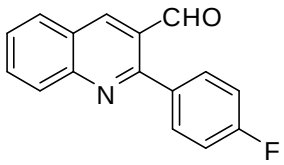
2-p-tolylquinoline-3-carbaldehyde (10c) (Table 3.8, Entry 3): The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.19 (s, 1H), 8.82 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.87~7.84 (m, 1H), 7.63~7.58 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.7, 160.3, 149.6, 139.5, 138.0, 134.9, 132.5, 130.2, 129.5, 129.4, 127.7, 127.3, 126.3, 21.3.



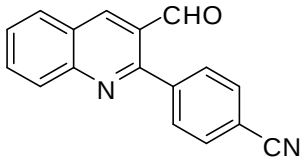
2-(4-methoxyphenyl)quinoline-3-carbaldehyde (10d) (Table 3.8, Entry 4): The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.19 (s, 1H), 8.80 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.86~7.83 (m, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.62~7.59 (m, 1H), 7.08 (d, J = 8.5 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.7, 160.7, 159.8, 149.7, 138.2, 132.5, 131.7, 130.2, 129.5, 129.4, 127.6, 127.2, 126.2, 114.2, 55.4.



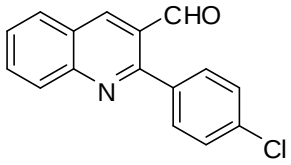
2-(2-chlorophenyl)quinoline-3-carbaldehyde (10e) (Table 3.8, Entry 5): The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.95 (s, 1H), 8.86 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.90~7.87 (m, 1H), 7.69~7.65 (m, 1H), 7.61~7.59 (m, 1H), 7.54~7.51 (m, 1H), 7.49~7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 190.4, 158.0, 149.7, 137.5, 136.9, 133.1, 132.7, 131.4, 130.6, 129.64, 129.61, 129.5, 127.9, 127.7, 127.4, 126.8.



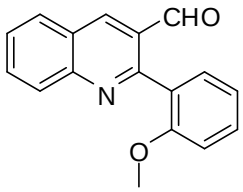
2-(4-fluorophenyl)quinoline-3-carbaldehyde (10f) (Table 3.8, Entry 6): The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.17 (s, 1H), 8.83 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.69~7.62 (m, 3H), 7.26 (t, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.1, 165.3, 161.9, 159.0, 149.5, 138.5, 133.9, 132.8, 132.2, 132.1, 129.5, 129.4, 127.6, 126.4, 116.0, 115.7.



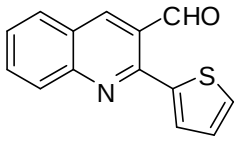
4-(3-formylquinolin-2-yl)benzonitrile (10g) (Table 3.8, Entry 7): The title compound was prepared according to the general procedure, as described above in 91% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.16 (s, 1H), 8.88 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.94~7.91 (m, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 190.2, 157.8, 149.5, 142.4, 139.4, 133.2, 132.4, 130.8, 129.7, 129.5, 128.2, 127.4, 126.6, 118.4, 113.2.



2-(4-chlorophenyl)quinoline-3-carbaldehyde (10h) (Table 3.8, Entry 8): The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.17 (s, 1H), 8.84 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 8.5Hz, 1H), 7.90~7.87 (m, 1H), 7.66~7.63 (m, 3H), 7.54 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 190.9, 158.9, 149.6, 138.6, 136.2, 135.8, 132.8, 131.5, 129.6, 129.4, 128.9, 127.7, 127.5, 126.4.

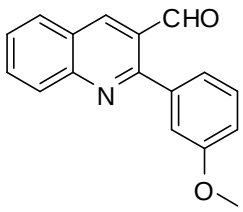


2-(2-methoxyphenyl)quinoline-3-carbaldehyde (10i) (Table 3.8, Entry 9): The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.99 (s, 1H), 8.77 (S, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.85~7.82 (m, 1H), 7.69 (dd, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.63~7.60 (m, 1H), 7.52~7.49 (m, 1H), 7.20 (t, J = 8 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.5, 157.6, 156.6, 150.1, 136.2, 132.0, 131.4, 131.2, 129.6, 129.4, 128.2, 127.3, 126.9, 126.6, 121.7, 110.7, 55.3.

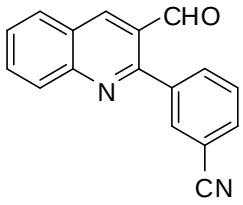


2-(thiophen-2-yl)quinoline-3-carbaldehyde (10j) (Table 3.8, Entry 10): The title compound was prepared according to the general procedure, as described above in 92%

yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.45 (s, 1H), 8.77 (s, 1H), 8.15 (*d*, J = 9.0 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.86~7.83 (m, 1H), 7.61~7.58 (m, 2H), 7.353~7.346 (m, 1H), 7.23~7.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.2, 153.0, 149.6, 141.2, 138.5, 132.7, 130.8, 129.6, 129.3, 128.0, 127.5, 127.4, 126.1.

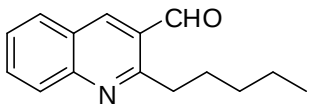


2-(3-methoxyphenyl)quinoline-3-carbaldehyde (10k) (Table 3.8, Entry 11): The title compound was prepared according to the general procedure, as described above in 97% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.18 (s, 1H), 8.84 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.89~7.86 (m, 1H), 7.65~7.62 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.09~7.07 (m, 1H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.5, 160.2, 159.9, 149.5, 139.1, 138.0, 132.6, 129.7, 129.6, 129.4, 127.7, 127.5, 126.4, 122.8, 115.4, 115.3, 55.4.

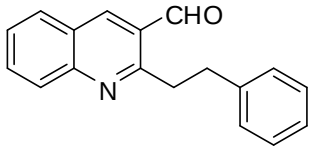


3-(3-formylquinolin-2-yl)benzonitrile (10l) (Table 3.8, Entry 12): The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.17 (s, 1H), 8.88 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.05 (d,

J = 7.5 Hz, 2H), 7.94~7.91 (m, 1H), 7.89~7.87 (m, 1H), 7.84~7.82 (m, 1H), 7.71~7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 190.2, 157.4, 149.5, 139.5, 139.3, 134.4, 133.5, 133.2, 132.7, 129.6, 129.4, 129.4, 128.2, 127.4, 126.6, 118.2, 113.2.

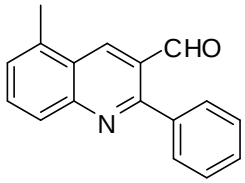


2-pentylquinoline-3-carbaldehyde (10m) (Table 3.8, Entry 13): The title compound was prepared according to the general procedure, as described above in 80% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.39 (s, 1H), 8.62 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 3.35 (t, *J* = 8.0 Hz, 2H), 1.81~1.75 (m, 2H), 1.49~1.43 (m, 2H), 1.42~1.36 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.1, 162.5, 149.4, 142.0, 132.5, 129.1, 128.9, 127.6, 126.8, 126.1, 36.4, 31.9, 30.1, 22.5, 14.0.

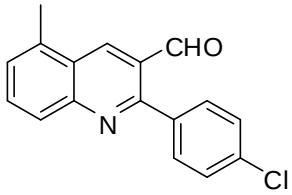


2-phenethylquinoline-3-carbaldehyde (10n) (Table 3.8, Entry 14): The title compound was prepared according to the general procedure, as described above in 83% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.27 (s, 1H), 8.60 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.88~7.85 (m, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.33~7.28 (m, 4H), 7.21 (t, *J* = 7.0 Hz, 1H), 3.69~3.66 (m, 2H), 3.13 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.0, 161.0, 149.3, 142.7, 141.4, 132.6, 129.03, 128.97, 128.6, 128.4, 127.8, 127.0,

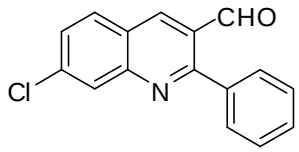
126.1, 38.2, 35.7.



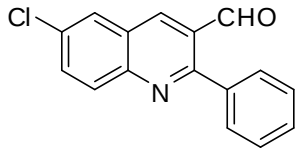
5-methyl-2-phenylquinoline-3-carbaldehyde (10o) (Table 3.8, Entry 15): The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.20 (s, 1H), 9.02 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.76~7.73 (m, 1H), 7.70~7.68 (m, 2H), 7.58~7.53 (m, 3H), 7.44 (d, J = 7.0 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.7, 159.9, 150.1, 137.7, 136.9, 134.6, 132.5, 130.3, 129.3, 128.7, 127.8, 127.0, 125.9, 18.7.



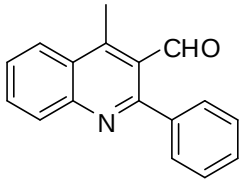
2-(4-chlorophenyl)-5-methylquinoline-3-carbaldehyde (10p) (Table 3.8, Entry 16): The title compound was prepared according to the general procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.18 (s, 1H), 9.01 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.0 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.2, 158.5, 150.1, 136.9, 136.2, 135.8, 135.1, 132.7, 131.6, 128.9, 128.0, 127.8, 126.9, 126.0, 18.7.



7-chloro-2-phenylquinoline-3-carbaldehyde (10q) (Table 3.8, Entry 17): The title compound was prepared according to the general procedure, as described above in 94% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.16 (s, 1H), 8.80 (s, 1H), 8.20 (s, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.68~7.67 (m, 2H), 7.58~7.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.1, 161.3, 149.8, 138.8, 137.9, 137.3, 130.5, 130.2, 129.7, 128.8, 128.7, 127.7, 124.7.

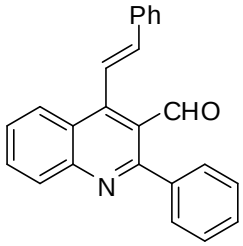


6-chloro-2-phenylquinoline-3-carbaldehyde (10r) (Table 3.8, Entry 18): The title compound was prepared according to the general procedure, as described above in 91% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.17 (s, 1H), 8.74 (s, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.69~7.67 (m, 2H), 7.57~7.56 (m, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 191.1, 160.4, 147.9, 137.4, 137.1, 133.4, 133.3, 131.2, 130.2, 129.6, 128.8, 128.2, 127.7, 126.9.

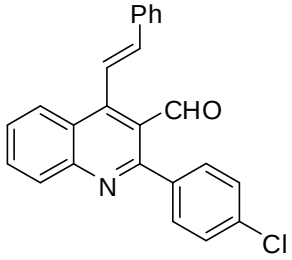


4-methyl-2-phenylquinoline-3-carbaldehyde (10s) (Table 3.8, Entry 19): The title

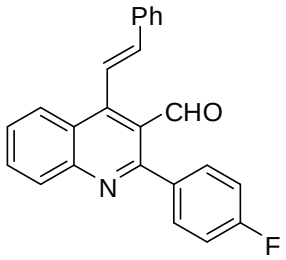
compound was prepared according to the general procedure, as described above in 84% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.12 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.85~7.82 (m, 1H), 7.66~7.63 (m, 3H), 7.53~7.52 (m, 3H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 194.2, 160.4, 148.04, 147.98, 139.0, 131.6, 130.3, 130.1, 129.2, 128.7, 127.1, 127.0, 125.2, 14.8.



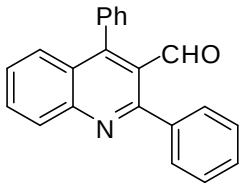
(*E*)-2-phenyl-4-styrylquinoline-3-carbaldehyde (10t) (Table 3.8, Entry 20): The title compound was prepared according to the general procedure, as described above in 80% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.21 (s, 1H), 8.41 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 16.5 Hz, 1H), 7.89~7.86 (m, 1H), 7.67 (d, J = 7.5 Hz, 4H), 7.64~7.61 (m, 1H), 7.56~7.52 (m, 3H), 7.47~7.44 (m, 2H), 7.40~7.37 (m, 1H), 6.89 (d, J = 17 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 193.1, 160.4, 149.2, 148.2, 139.5, 139.0, 136.3, 132.0, 130.1, 129.2, 128.9, 128.6, 127.2, 127.1, 125.4, 125.1, 123.1.



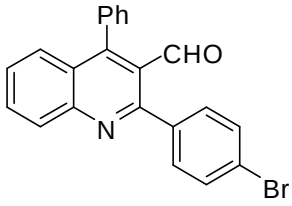
(E)-2-(4-chlorophenyl)-4-styrylquinoline-3-carbaldehyde (10u) (Table 3.8, Entry 21): The title compound was prepared according to the general procedure, as described above in 78% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.23 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.92~7.86 (m, 2H), 7.66~7.59 (m, 5H), 7.51 (d, J = 8.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.88 (d, J = 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 192.6, 158.9, 149.0, 148.6, 140.1, 137.6, 136.1, 135.5, 132.2, 131.3, 130.1, 129.0, 128.9, 128.8, 127.4, 127.2, 127.0, 125.5, 125.1, 122.5.



(*E*)-2-(4-fluorophenyl)-4-styrylquinoline-3-carbaldehyde (10v) (Table 3.8, Entry 22): The title compound was prepared according to the general procedure, as described above in 76% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.22 (s, 1H), 8.39 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 16.5 Hz, 1H), 7.88~7.86 (m, 1H), 7.67~7.61 (m, 5H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 8.5 Hz, 2H), 6.89 (d, J = 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 192.8, 165.1, 159.1, 149.0, 148.5, 139.9, 136.2, 135.2, 132.1, 132.0, 131.9, 130.0, 129.0, 128.9, 127.3, 127.1, 127.0, 125.4, 125.2, 122.7, 115.8, 115.5.



2,4-diphenylquinoline-3-carbaldehyde (10w) (Table 3.8, Entry 23): The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.04 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.86~7.82 (m, 1H), 7.66~7.65 (m, 2H), 7.61 (d, J = 8.5 Hz, 1H), 7.57~7.49 (m, 7H), 7.39~7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 192.5, 159.0, 151.9, 148.5, 139.5, 134.6, 131.9, 129.8, 129.7, 128.9, 128.6, 128.4, 128.3, 127.3, 126.6, 126.3.



2-(4-bromophenyl)-4-phenylquinoline-3-carbaldehyde (10x) (Table 3.8, Entry 24): The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.01 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 7.0 Hz, 1H), 7.64~7.61 (m, 3H), 7.56~7.50 (m, 6H), 7.39~7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 192.2, 157.5, 152.9, 148.5, 138.7, 134.1, 132.1, 131.5, 131.2, 129.8, 128.9, 128.5, 127.5, 127.2, 126.3, 123.4.

General procedure for the preparation of substrates 11:

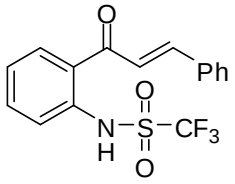
Substrates were synthesized via the following two steps.

Step 1: Claisen-Schmidt condensation of benzaldehyde with 2'-amino acetophenone to trans-2'-amino-chalcone[53]

A mixture of 2'-amino acetophenone (3.0 mmol, 0.36 mL) and benzaldehyde (3.0 mmol) in ethanol was added sodium hydroxide (15%, 0.9 mL) under stirring with ice-bath. Then the solution was stirred at r.t. for 24h. The reaction mixture was neutralized with 1M HCl. The solid was filtrated and crystallized from ethanol.

Step 2: Synthesis of corresponding trifluoromethanesulfonamides[54]

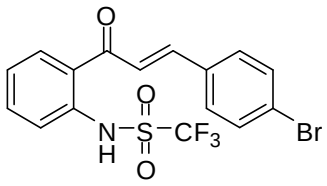
A solution of trans-2'-amino-chalcone (1.5 mmol) and triethylamine (0.23 mL, 1.65 mmol) in dry CH_2Cl_2 at -78 ^oC was treated dropwise with trifluoromethanesulfonic anhydride (0.28 mL, 1.65 mmol). The mixture was stirred at -78 ^oC for 1.5h and then at room temperature for 2.5h. The reaction was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane, and the combined organic phases was washed with brine, dried and concentrated. The residue was purified by column chromatography, eluted with hexane/EtOAc to afford the desired product.



(*E*)-*N*-(2-cinnamoylphenyl)-1,1,1-trifluoromethanesulfonamide

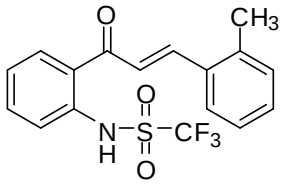
The title compound was prepared according to the general procedure, as described above in 57% yield for two steps. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.07 (d, J = 8.0 Hz, 1H), 7.92

(d, *J* = 15.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.68~7.67 (m, 2H), 7.64~7.58 (m, 2H), 7.48~7.45 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.9, 147.3, 138.3, 134.9, 134.1, 131.3, 130.9, 129.0, 128.8, 124.6, 124.0, 123.6, 121.0, 120.8, 119.9, 118.4, 115.9.



(*E*)-*N*-(2-(3-(4-bromophenyl)acryloyl)phenyl)-1,1,1-trifluoromethanesulfonamide

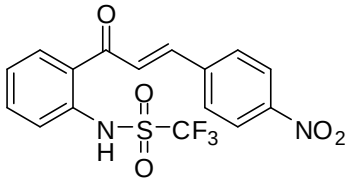
The title compound was prepared according to the general procedure, as described above in 52% yield for two steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.84~7.81 (m, 2H), 7.63~7.56 (m, 4H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.7, 145.8, 138.4, 135.1, 133.1, 132.4, 130.8, 130.1, 125.8, 124.6, 124.1, 123.6, 121.6, 121.0, 120.2, 118.5, 115.9.



(*E*)-1,1,1-trifluoro-*N*-(2-(3-o-tolylacryloyl)phenyl)methanesulfonamide

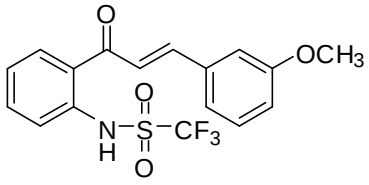
The title compound was prepared according to the general procedure, as described above in 47% yield for two steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, *J* = 15.5 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* =

7.5 Hz, 1H), 7.53 (d, J = 15.0 Hz, 1H), 7.37~7.32 (m, 2H), 7.30~7.26 (m, 2H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.0, 144.9, 138.9, 138.5, 135.0, 133.2, 131.1, 130.9, 126.6, 126.5, 124.6, 124.2, 123.6, 122.0, 121.1, 120.1, 118.5, 115.9, 19.7.



(*E*)-1,1,1-trifluoro-*N*-(2-(3-(4-nitrophenyl)acryloyl)phenyl)methanesulfonamide

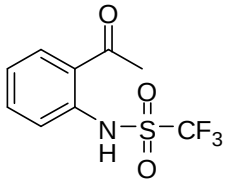
The title compound was prepared according to the general procedure, as described above in 41% yield for two steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.30 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 15.5 Hz, 1H), 7.85~7.82 (m, 3H), 7.72~7.64 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.3, 149.0, 143.8, 140.2, 138.6, 135.6, 131.0, 129.3, 125.0, 124.8, 124.3, 123.9, 121.0, 120.4, 118.4.



(*E*)-1,1,1-trifluoro-*N*-(2-(3-(3-methoxyphenyl)acryloyl)phenyl)methanesulfonamide

The title compound was prepared according to the general procedure, as described above in 69% yield for two steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (d, J = 8.0 Hz, 1H), 7.87~7.81 (m, 2H), 7.62~7.55 (m, 2H), 7.38~7.31 (m, 2H), 7.26 (d, J = 7.5 Hz, 1H), 7.16 (s, 1H), 7.02~7.00 (m, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.9, 160.0,

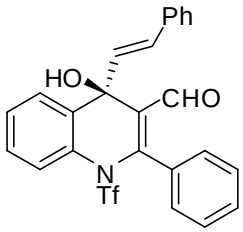
147.3, 138.4, 135.5, 135.0, 130.9, 130.1, 124.6, 124.2, 123.6, 121.4, 121.3, 121.0, 120.1, 118.5, 117.1, 115.9, 113.8, 55.3.



***N*-(2-acetylphenyl)-1,1,1-trifluoromethanesulfonamide**

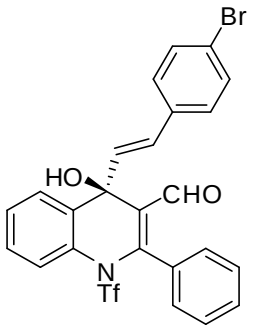
The title compound was prepared according to the general procedure, as described above for step 2 in 75% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.2, 138.1, 135.5, 132.0, 124.5, 123.6, 122.6, 121.0, 119.4, 118.4, 115.9, 28.0.

General Procedure for Cascade aza-Michael-aldol Reaction (Table 3.10): To a solution of ynal **1** (0.08 mmol), organocatalyst **IX** (1 mol%) in toluene (0.8 mL) was added 2'-NHTf ketone **11** (0.08 mmol). The resulting solution was stirred at 0 ºC for a specified time. Then the reaction mixture was directly purified by column chromatography, eluted with hexane/EtOActo afford the desired product and ees are determined by chiral HPLC analysis.



(*R*)-(*E*)-4-hydroxy-2-phenyl-4-styryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12a) (Table 3.10, Entry 1):

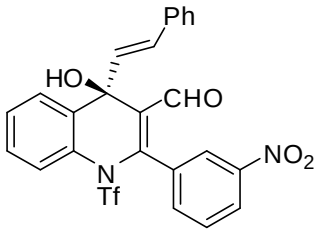
The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.35 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.58~7.51 (m, 7H), 7.47~7.44 (m, 1H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.26~7.22 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 5.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.1, 153.3, 137.2, 135.9, 133.9, 133.7, 131.3, 131.1, 130.8, 130.3, 128.7, 128.5, 128.4, 128.3, 128.1, 127.0, 125.9, 122.6, 120.2, 117.6, 72.3; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 10/90, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 19.16 min, t_{major} = 24.81 min, ee = 97%; $[\alpha]_D^{30}$= +117.1 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-4-(4-bromostyryl)-4-hydroxy-2-phenyl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12b) (Table 3.10, Entry 2):

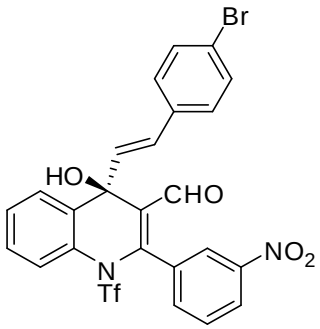
The title compound was prepared according to the general procedure as described above in 93% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.34 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.58~7.55 (m, 1H), 7.52~7.44 (m, 7H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.42 (d, *J* = 15.5 Hz, 1H), 5.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.2, 153.5, 137.1, 134.9, 133.8, 131.8, 131.7, 131.4, 130.7, 129.2, 128.7,

128.5, 128.4, 125.9, 122.6, 122.1, 120.1, 117.6, 72.3; HPLC (Chiralpak IB, *i*-PrOH/hexane = 15/85, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 11.90 min, t_{major} = 19.76 min, ee = 98%; $[\alpha]_D^{30}$= +97.1 (c = 1.0 in $CHCl_3$).



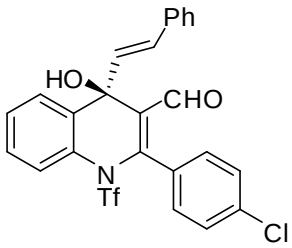
(*R*)-(*E*)-4-hydroxy-2-(3-nitrophenyl)-4-styryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12c) (Table 3.10, Entry 3):

The title compound was prepared according to the general procedure as described above in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.35 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.38 (s, 1H), 7.94 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 6.5 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.55~7.50 (m, 3H), 7.37~7.35 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.26~7.25 (m, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.45 (d, *J* = 15.5 Hz, 1H), 5.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.6, 149.7, 147.9, 136.6, 135.5, 133.2, 132.5, 130.8, 130.5, 129.6, 129.0, 128.6, 128.5, 128.3, 126.9, 126.2, 125.8, 122.5, 120.9, 116.6, 72.2. HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 15/85, flow rate = 0.55 mL/min, λ = 254nm): t_{minor} = 24.82 min, t_{major} = 47.05 min, ee = 99%; $[\alpha]_D^{30}$= +104.9 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-4-(4-bromostyryl)-4-hydroxy-2-(3-nitrophenyl)-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12d) (Table 3.10, Entry 4):

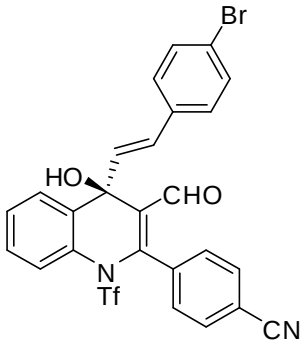
The title compound was prepared according to the general procedure, as described above in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.35 (s, 1H), 8.43 (d, J = 7.0 Hz, 1H), 8.38 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.75~7.72 (m, 1H), 7.56~7.50 (m, 3H), 7.43~7.41 (m, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.47~6.41 (m, 2H), 5.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.6, 150.0, 148.0, 136.5, 135.5, 134.5, 133.3, 132.5, 131.8, 131.3, 129.8, 129.7, 129.1, 128.8, 128.5, 126.3, 126.0, 122.6, 122.3, 120.1, 117.5, 72.2; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 15/85, flow rate = 0.55 mL/min, λ = 254nm): t_{minor} = 25.76 min, t_{major} = 44.58 min, ee = 98%; $[\alpha]_D^{30}$= +59.5 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-2-(4-chlorophenyl)-4-hydroxy-4-styryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12e) (Table 3.10, Entry 5):

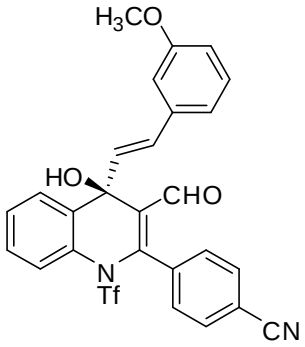
The title compound was prepared according to the general procedure as described above in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.35 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.53~7.44 (m, 7H), 7.35 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.25~7.22 (m, 1H), 6.54 (d, J = 15.5 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 5.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.5, 151.8, 137.9, 137.1, 135.8, 134.5, 133.6, 130.9, 130.5, 129.3, 128.8, 128.6, 128.4, 128.2, 127.0, 126.1, 122.6, 120.2, 117.6, 72.3; HPLC (Chiralpak IB, *i*-

PrOH/hexane = 5/95, flow rate = 0.40 mL/min, λ = 254nm): t_{minor} = 19.14 min, t_{major} = 37.65 min, ee = 98%; $[\alpha]_D^{30}$= +123.4 (c = 1.0 in $CHCl_3$).



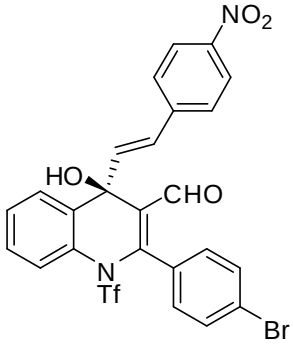
(*R*)-(*E*)-4-(4-(4-bromostyryl)-3-formyl-4-hydroxy-1-(trifluoromethylsulfonyl)-1,4-dihydroquinolin-2-yl)benzonitrile (12f) (Table 3.10, Entry 6):

The title compound was prepared according to the general procedure as described above in 91% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.32 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.55~7.48 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.8, 150.5, 136.5, 135.3, 135.2, 134.5, 133.4, 132.2, 132.1, 131.8, 131.3, 130.1, 129.7, 129.1, 128.8, 128.5, 126.3, 125.4, 123.7, 122.5, 122.3, 120.0, 117.5, 115.3, 72.2; HPLC (Chiralpak IB, *i*-PrOH/hexane = 15/85, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 27.43 min, t_{major} = 93.65 min, ee = 99%; $[\alpha]_D^{30}$= +142.2 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-4-(3-formyl-4-hydroxy-4-(3-methoxystyryl)-1-(trifluoromethylsulfonyl)-1,4-dihydroquinolin-2-yl)benzonitrile (12g) (Table 3.10, Entry 7):

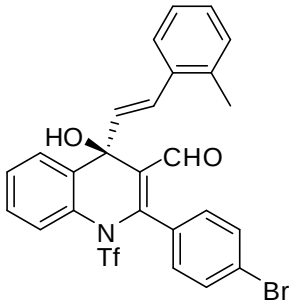
The title compound was prepared according to the general procedure as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.32 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.55~7.47 (m, 3H), 7.21 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.87 (s, 1H), 6.81~6.79 (m, 1H), 6.50 (d, J = 16.0 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 5.24 (s, 1H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.7, 159.8, 150.4, 137.0, 136.7, 135.3, 133.3, 132.1, 130.9, 130.8, 129.6, 129.0, 128.8, 128.6, 126.3, 122.5, 120.1, 119.6, 117.5, 115.2, 114.2, 113.6, 112.1, 72.2, 55.2; HPLC (Chiralpak IB, *i*-PrOH/hexane = 15/85, flow rate = 0.50 mL/min, λ = 254nm): t_{minor} = 79.73 min, t_{major} = 65.06 min, ee = 98%; $[\alpha]_D^{30}$= +156.1 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-2-(4-bromophenyl)-4-hydroxy-4-(4-nitrostyryl)-1-(trifluoromethylsulfonyl)-

1,4-dihydroquinoline-3-carbaldehyde (12h) (Table 3.10, Entry 8):

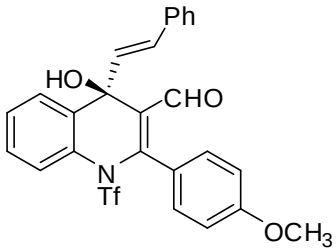
The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.35 (s, 1H), 8.17~8.14 (m,2H), 7.93~7.90 (m, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.57~7.54 (m, 1H), 7.53~7.46 (m, 4H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.60~6.54 (m, 2H), 5.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.6, 152.5, 147.4, 142.2, 136.5, 135.2, 133.9, 133.6, 131.9, 129.4, 129.0, 128.8, 128.3, 127.6, 126.5, 126.0, 124.0, 122.7, 120.1, 117.5, 72.2; HPLC (Chiralpak IB, *i*-PrOH/hexane = 15/85, flow rate = 0.50 mL/min, λ = 254nm): t_{minor} = 19.13 min, t_{major} = 50.19 min, ee = 98%; $[\alpha]_D^{30}$= +122.7 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-2-(4-bromophenyl)-4-hydroxy-4-(2-methylstyryl)-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12i) (Table 3.10, Entry 9):

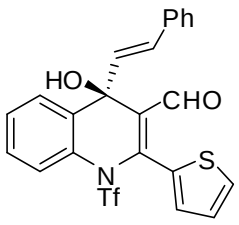
The title compound was prepared according to the general procedure as described above in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.36 (s, 1H), 7.94 (d, *J* = 7.0 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.53~7.44 (m, 3H), 7.41~7.38 (m, 3H), 7.15~7.12 (m, 3H), 6.79 (d, *J* = 16.0 Hz, 1H), 6.35 (d, *J* = 15.5 Hz, 1H), 5.33 (s, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.5, 151.6, 137.0, 136.1, 134.7, 134.4, 133.4, 132.2, 131.8, 130.3, 129.8,

128.8, 128.4, 128.3, 128.1, 126.2, 126.1, 126.0, 122.5, 120.1, 117.6, 72.3, 19.7; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 5/95, flow rate = 0.40 mL/min, λ = 254nm): t_{minor} = 21.89 min, t_{major} = 39.93 min, ee = 97%; $[\alpha]_D^{30}$= +127.0 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-4-hydroxy-2-(4-methoxyphenyl)-4-styryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12j) (Table 3.10, Entry 10):

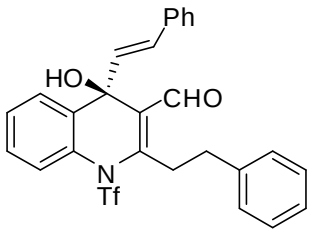
The title compound was prepared according to the general procedure as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.34 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.51~7.49 (m, 2H), 7.46~7.43 (m, 3H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.30~7.27 (m, 2H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.43 (d, *J* = 15.5 Hz, 1H), 5.53 (s, 1H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.2, 162.2, 153.4, 137.5, 136.0, 133.8, 133.3, 131.2, 130.2, 128.6, 128.5, 128.2, 128.1, 127.0, 125.9, 122.9, 122.7, 120.2, 117.7, 113.9, 72.3, 55.5; HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 10/90, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 25.85 min, t_{major} = 71.24 min, ee = 96%; $[\alpha]_D^{30}$= +126.3 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-4-hydroxy-4-styryl-2-(thiophen-2-yl)-1-(trifluoromethylsulfonyl)-1,4-

dihydroquinoline-3-carbaldehyde (12k) (Table 3.10, Entry 11):

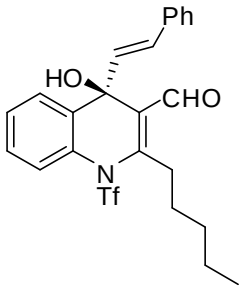
The title compound was prepared according to the general procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (s, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.67 (d, J = 5.0 Hz, 1H), 7.52~7.49 (m, 2H), 7.46~7.44 (m, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.25~7.23 (m, 1H), 7.18~7.16 (m, 1H), 6.55 (d, J = 15.5 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 5.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.5, 146.0, 137.2, 135.8, 135.5, 134.5, 133.5, 131.5, 131.3, 130.8, 130.7, 128.8, 128.5, 128.4, 128.2, 127.4, 127.0, 126.0, 123.0, 120.3, 117.8, 72.6; HPLC (Chiralpak IB, *i*-PrOH/hexane = 5/95, flow rate = 0.40 mL/min, λ = 254nm): t_{minor} = 18.93 min, t_{major} = 21.13 min, ee = 96%; $[\alpha]_D^{30}$= +76.3 (c = 1.0 in $CHCl_3$).



(*R*)-(*E*)-4-hydroxy-2-phenethyl-4-styryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12l) (Table 3.10, Entry 12):

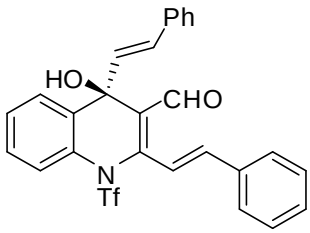
The title compound was prepared according to the general procedure as described above in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.67 (s, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.30~7.24 (m, 4H), 7.21~7.19 (m, 4H), 6.94~6.93 (m, 2H), 6.40 (d, J = 15.5 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 5.46 (s, 1H), 3.45~3.39 (m, 1H), 3.24~3.18 (m, 1H), 3.11~3.06 (m, 1H), 2.83~2.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.0, 153.8, 138.3, 137.7, 135.8, 135.1, 133.3, 130.5, 130.0, 128.7, 128.6, 128.52, 128.47, 128.3, 128.0, 127.0, 126.9, 125.7, 122.4,

120.4, 117.8, 115.2, 72.4, 35.5, 32.7; HPLC (Chiralpak IB, *i*-PrOH/hexane = 15/85, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 14.17 min, t_{major} = 23.86 min, ee = 96%; $[\alpha]_D^{30}$= +10.8 (c = 1.0 in $CHCl_3$).



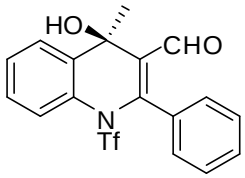
(*R*)-(*E*)-4-hydroxy-2-pentyl-4-styryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12m) (Table 3.10, Entry 13):

The title compound was prepared according to the general procedure, as described above in 98% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.1 (s, 1H), 7.88~7.85 (m, 1H), 7.49~ 7.42 (m, 2H), 7.40~7.36 (m, 1H), 7.34~7.29 (m, 4H), 7.23~7.20 (m, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.27 (d, *J* = 16.0 Hz, 1H), 5.60 (s, 1H), 3.28~3.20 (m, 1H), 2.87~2.77 (m, 1H), 1.75~1.72 (m, 1H), 1.55~1.52 (m, 1H), 1.334~1.327 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.2, 156.5, 137.7, 135.9, 134.0, 133.5, 130.6, 130.0, 128.6, 128.5, 128.3, 128.0, 126.9, 125.7, 122.4, 120.4, 117.8, 72.4, 31.3, 30.7, 29.8, 22.2, 13.8; HPLC (Chiralpak IB, *i*-PrOH/hexane = 15/85, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 11.67 min, t_{major} = 12.83 min, ee = 97%; $[\alpha]_D^{30}$= +35.8 (c = 1.0 in $CHCl_3$).



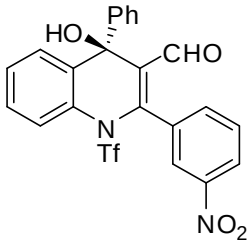
(*R*)-4-hydroxy-2,4-distyryl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12n) (Table 3.10, Entry 14):

The title compound was prepared according to the general procedure, as described above in 70% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.80 (s, 1H), 7.92~7.89 (m, 1H), 7.57~7.54 (m, 2H), 7.52~7.49 (m, 2H), 7.46~7.42 (m, 4H), 7.36~7.33 (m, 2H), 7.31~7.22 (m, 3H), 7.03 (d, *J* = 15.6 Hz, 1H), 6.87 (d, *J* = 15.6 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 5.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.3, 151.4, 145.1, 136.8, 135.9, 134.4, 134.2, 133.2, 131.1, 130.5, 130.2, 129.1, 128.5, 128.2, 128.1, 127.8, 126.9, 125.8, 122.8, 121.3, 117.9, 117.1, 72.3; HPLC (Chiralpak IB, *i*-PrOH/hexane = 10/90, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 16.66 min, t_{major} = 27.54 min, ee = 94%; $[\alpha]_D^{29}$= +360.0 (c = 1.0 in $CHCl_3$).



(*R*)-4-hydroxy-4-methyl-2-phenyl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12o) (Table 3.10, Entry 15):

The title compound was prepared according to the general procedure, as described above in 96% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.28 (s, 1H), 7.89~7.85 (m, 1H), 7.56~7.38 (m, 8H), 5.18 (s, 1H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.3, 152.0, 139.4, 136.0, 133.1, 131.2, 130.8, 128.6, 128.3, 128.0, 125.2, 122.5, 121.0, 116.8, 69.6, 31.6; HPLC (Chiralpak IB, *i*-PrOH/hexane = 10/90, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 10.48 min, t_{major} = 15.88 min, ee = 95%; $[\alpha]_D^{29}$= +187.2 (c = 1.0 in $CHCl_3$).



(*R*)-4-hydroxy-2-(3-nitrophenyl)-4-phenyl-1-(trifluoromethylsulfonyl)-1,4-dihydroquinoline-3-carbaldehyde (12p) (Table 3.10, Entry 16):

The title compound was prepared according to the general procedure, as described above in 84% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.39 (s, 1H), 8.45~8.41 (m, 1H), 8.38 (s, 1H), 8.10~8.07 (m, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H),7.59~7.48 (m, 3H), 7.45~7.29 (m, 5H), 5.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.9, 150.4, 148.0,143.3, 137.6, 136.5, 133.5, 132.7, 129.7, 129.0, 128.7, 128.5, 126.6, 126.0, 122.4, 120.7, 116.5, 73.9; HPLC (Chiralpak IB, *i*-PrOH/hexane = 20/80, flow rate = 0.45 mL/min, λ = 254nm): t_{minor} = 17.52 min, t_{major} = 51.50 min, ee = 99%; $[\alpha]_D^{30}$= +136.7 (c = 1.0 in $CHCl_3$).

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[52] (a) We have reported a divergent organocatalytic Michael-alkyation cascade: H.-X. Xie, L.-S. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886-10894; an other example from Ma and co-workers: (b) W. Yao, L. Pan, Y. Zhang, G. Wang, X. Wang, C. Ma, *Angew. Chem., Int. Ed.* **2010**, *49*, 9210-9214.

[53] G. Litkei, A. L. Tökés, *Synthetic Communications*, **1991**, *15&16*, 1597-1609.

[54] D. G. Batt, R. Goodman, D. G. Jones, J. S. Kerr, L. R. Mantegna, C. McAllister, R. C. Newton, S. Nurnberg, P. K. Welch, M. B. Covington, *J. Med. Chem.* **1993**,*36*,1434-1442.

Chapter 4

Organocatalytic 1,6-Addition Reactions

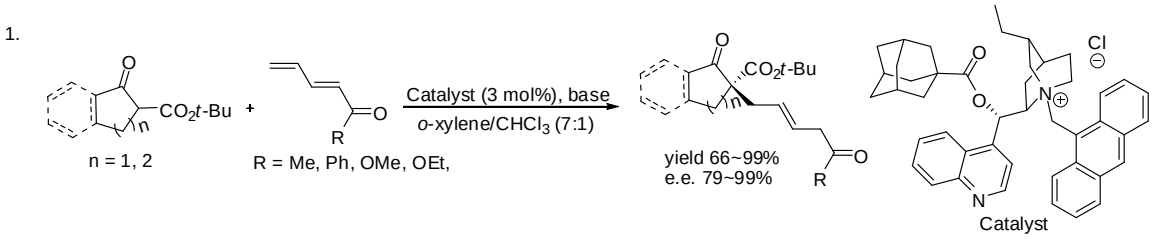
4.1 Background and Significance

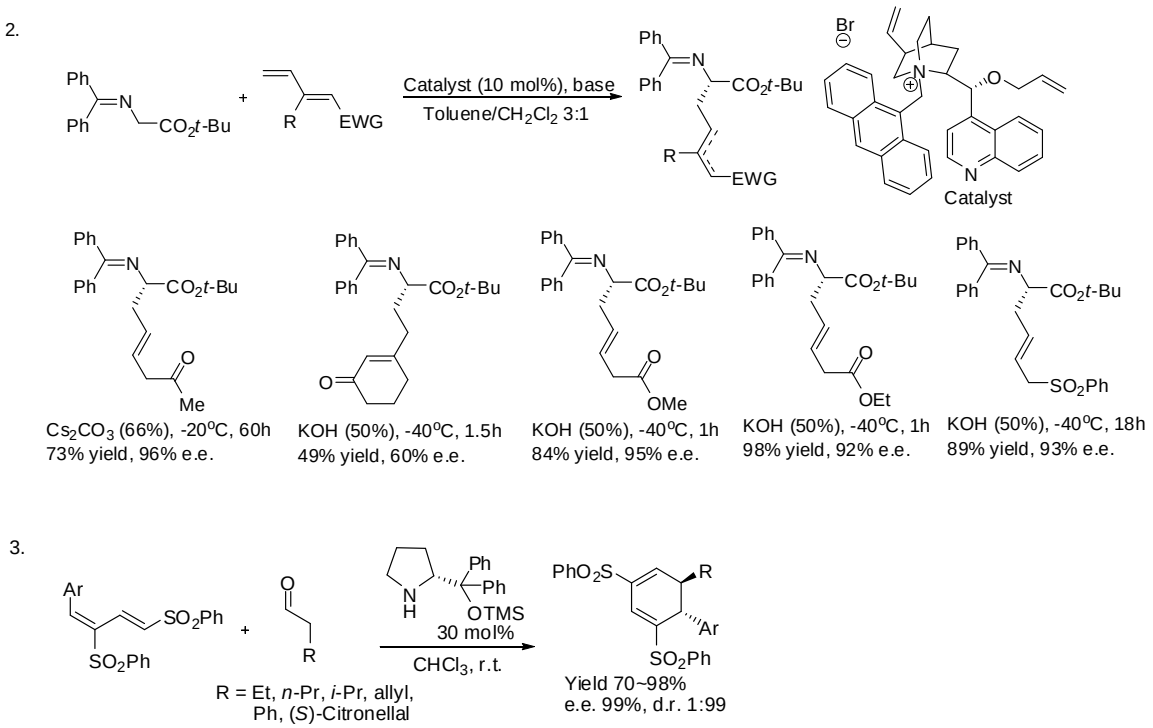
The catalytic 1, 4-addition[1] of various nucleophiles to electron-deficient olefin has developed into one of the most reliable methods for efficiently construction of C-C and C-heteroatom bonds. In this field, attention has been focused on both metal-catalyzed[2] and organocatalyst-catalyzed[3] processes (Scheme 4.2, eq (1)). Furthermore, major advances such as high regioselectivity (1,4- vs. 1,2-addition) and excellent control of stereoselectivity have been achieved in catalytic 1,4- addition.

On the other hand, catalytic 1,6-addition to extended conjugate systems has developed less rapidly due to the fact that there is considerable difficulties in controlling both the regioselectivity (1,2-, 1,4- vs. 1,6-addition) and stereoselectivity. Except metal-catalyzed nonasymmetric 1,6-selective conjugate addition[4], successful reports of asymmetric 1,6-addition to various α,β,γ,δ-unsaturated Michael acceptors such as 2,4-dienones, 2,4-dienoates and 2,4-dienamides catalyzed by copper[5], rhodium[6], iridium[7] and iron[8] complex have recently appeared. In contrast, the organocatalytic 1,6-addition to extended conjugated systems remains underdeveloped. The 1,4-additions to active dienes or enynes have been reported[9]. In these cases, the β-carbon is highly active in comparison with δ-carbon which accounts for the regioselectivity. Only two reports of asymmetric

1,6-addition promoted by organocatalyst are developed. In 2007, Jørgensen and co-workers[10] disclosed the first organocatalytic enantioselective 1,6-addition of β-ketoesters and benzophenone imine to electron-deficient δ-unsubstituted dienes using chiral phase-transfer catalyst (Scheme 4.1). It is noteworthy that the strategy for the control of regioselectivity here is to reduce the steric hindrance at the δ-carbon to bias the system towards 1,6-addition. Very recently, asymmetric enamine 1,6-conjugate addition of aldehydes to1,3-bis-(sulfonyl) butadienesin remarkable stereoselectivity (99% e.e. and 1:99 d.r.) was reported by A. Alexakis and J. C. Stephens[11] (Scheme 4.1). The exclusive regioselectivity is probably associated with the specific structural feature of the substrate designed based on the fact that a single activating sulfone group was not strong enough to activate the alkene to generate an enamine 1,4-addition product.

Scheme 4.1 Examples of Organocatalytic 1,6-Addition



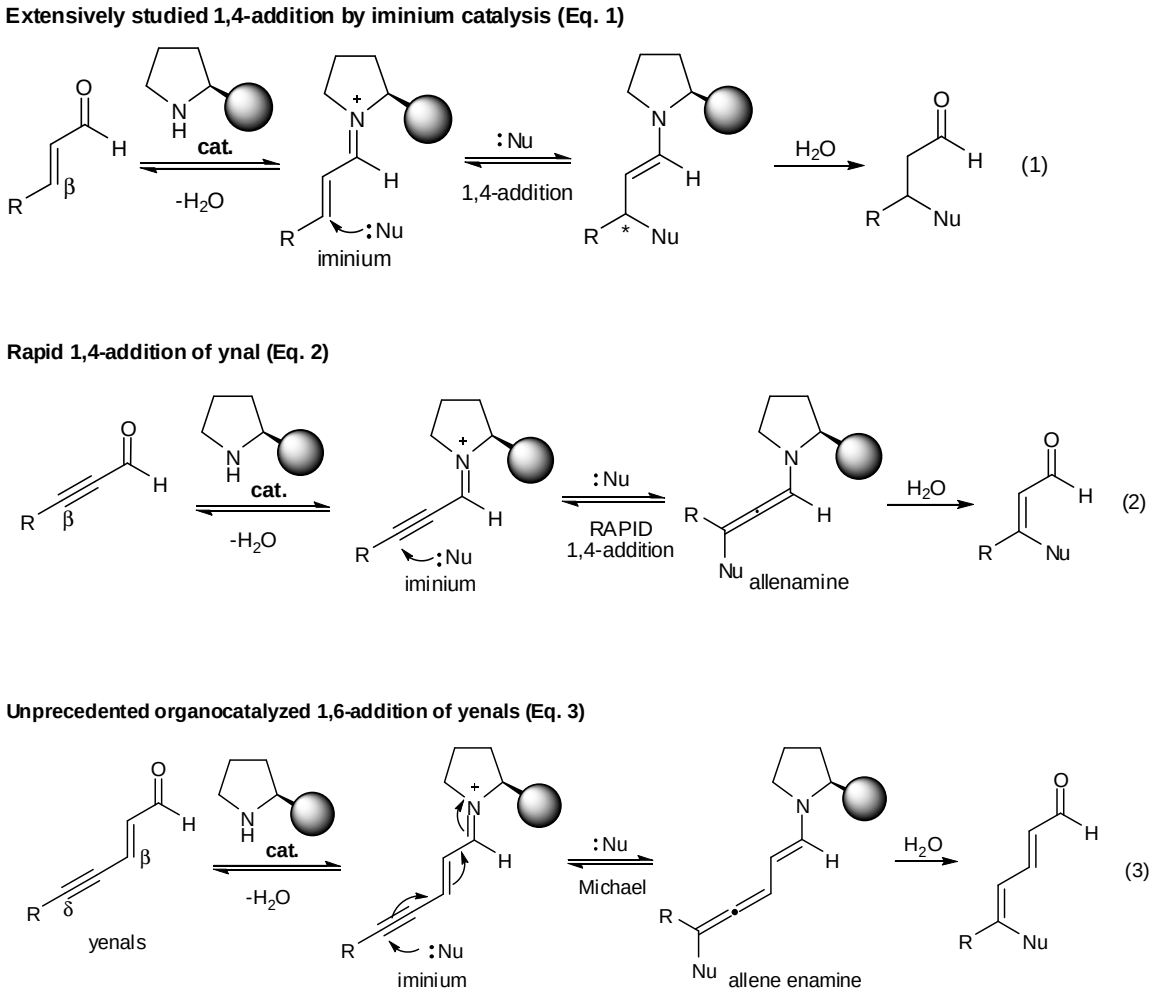


4.2 Research Design

Due to the poor propagation of electronic effect through the extended conjugated system, the development of catalytic 1,6-addition remain a challenging task and the preliminary successful studies were strongly dependent on the nature and structure of the substrates. Regioselective 1,6-conjugate addition of α,β,γ,δ-unsaturated aldehydes face even more significant obstacles. Unlike ketones, 1,2-addition of aldehydes is favorable. Moreover, in iminium catalysis, 1,4-addition occurs exclusively with dienic aldehydes without 1,6-additions[3a]. Considering alkynal is more active than enal in the presence of secondary amine (eq (2)), we hypothesized that insertion of another double bond between carbonyl group and alkyne group[12] where the 1,6-acceptor carbon is sp-hybridized while the 1,4-carbon acceptor is sp^2-hybridized would be able to promote the 1,6-addition over

1,4-addition (eq (3)). The plausible reasons are: (1) the sp hybridized carbon of a C≡C bond is more electron deficient than sp^2 C=C bond; (2) the steric effect may also favor the addition to the C≡C bond.

Scheme 4.2 Proposal for Organocatalytic 1,6-Addition

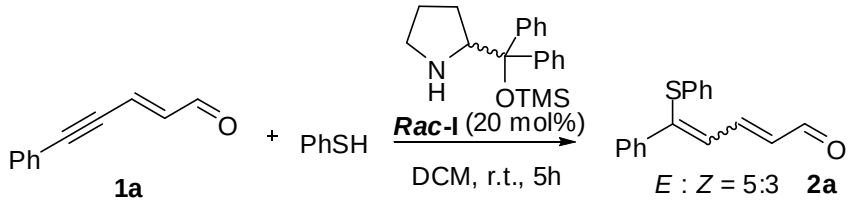


4.3 Results and Discussion

1) Investigation of sulfur-based nucleophiles

With the uncertainty and possibility of the chemistry faced, we started to investigate the simple conjugate addition of various nucleophiles to δ-substituted-2-en-4-ynal substrates. Our initial studies focused on the sulfur nucleophile. At first, the model reaction between (*E*)-5-phenylpent-2-en-4-ynal **1a** and thiophenol in dichloromethane at room temperature in the presence of 20 mol% of organocatalyst **I** was investigated. To my surprise, the reaction indeed happened with the exclusive formation of 1,6-addition product **2a** in high efficiency (87% yield) although the *Z* and *E* mixture were obtained (Scheme 4.3). To improve the *Z*/*E* selectivity, catalysts with different steric recognition were briefly screened. And it should make sense that the *Z*/*E* selectivity was not affected at all even simple pyrrolidine was applied because the catalyst is too far away from the δ-carbon position. One of the limitations related with the process is 1,4-addition product was generated exclusively using aliphatic thiol, such as ethanethiol and benzyl mercaptan.

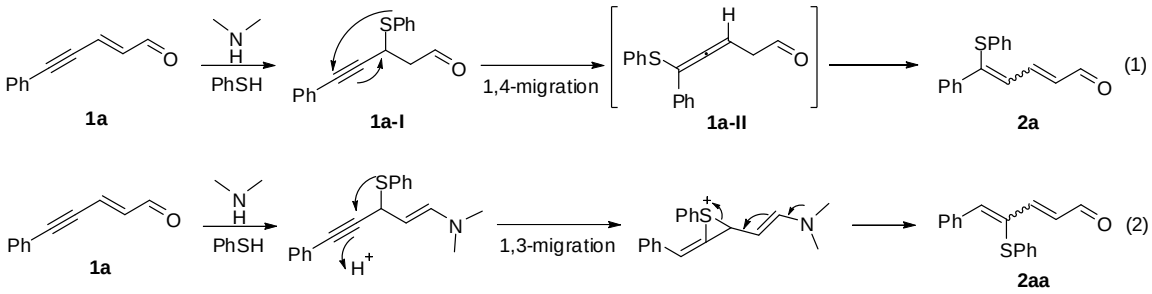
Scheme 4.3 Organocatalytic 1,6-Addition between (*E*)-5-Phenylpent-2-en-4-ynal **1a** and Thiophenol



In effort to gain an insight into the reaction mechanism, the reaction was conducted at lower temperature (-78 ºC) or in the presence of lower catalyst loading (3 mol%) and monitored carefully by running crude ^{1}HNMR. Unexpected, I found the

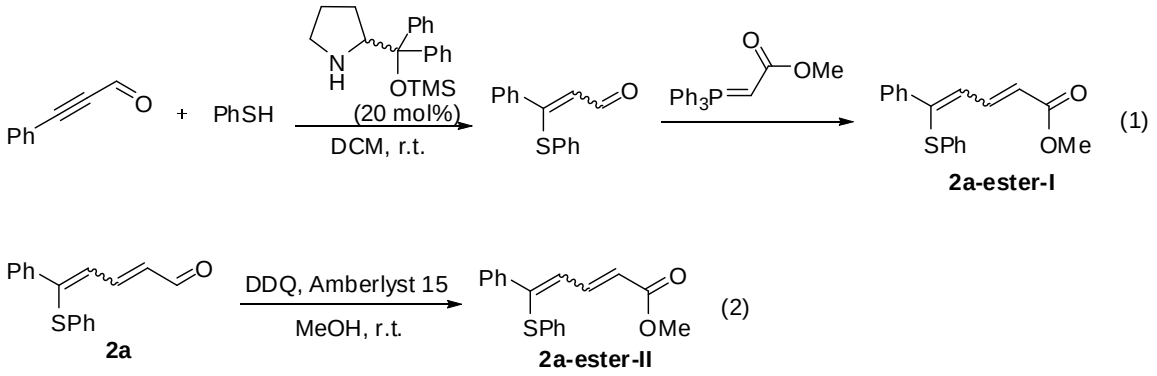
reaction went through 1,4-addition product **1a-I** which then underwent 1,4-migration of thio group resulted in an allene intermediate **1a-II**. The active allene intermediate **1a-II** would transformed into highly conjugated 1,6-addition product **2a** spontaneously (Scheme 4.4, eq (1)). Another possibility is the 1,3-migration of thio group to form compound **2aa** (eq (2))[13].

Scheme 4.4 Proposed Mechanism for 1,6-Addition of Thiophenol to (*E*)-5-Phenylpent-2-en-4-ynal **1a**



At this moment, it is necessary to verify the structure of 1,6-addition product **2a**. First, the compound **2a-ester-I** was prepared through Michael addition of thiophenol to 3-phenyl-2-propynal followed by Wittig chain extension (Scheme 4.5, eq (1)). And the ^{1}HNMR spectra of compound **2a-ester-I** is the same as the compound **2a-ester-II** transformed from the 1,6-addition product **2a**.

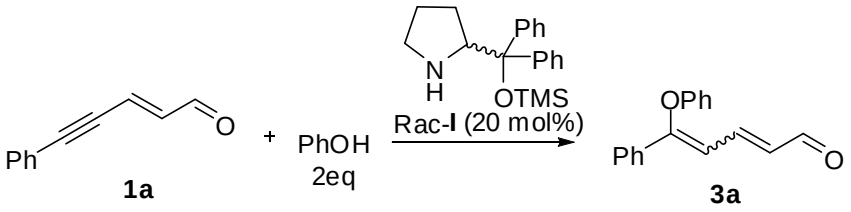
Scheme 4.5 Verification of the Structure of 1,6-Addition Product **2a**



2) Investigation of oxygen-based nucleophiles

Then the oxygen nucleophile was investigated. The model reaction between (*E*)-5-phenylpent-2-en-4-ynal **1a** and phenol in dichloromethane at room temperature in the presence of 20 mol% of organocatalyst **I** was tested. Different from thiophenol which is more nucleophilic towards the yenal subatrate, the conversion of the reaction is unsatisfactory. Ensuring the complete conversion, the amount of phenol was increased to 2 eq..Various base additives such as K_2CO_3, Cs_2CO_3, LiOH, NaH and *t*-BuOK were evaluated. Without base additive, the reaction proceeded slowly with low yield (28%) after 5 d (entry 1). By adding 0.1eq of K_2CO_3 additive, the reaction yield can be improved a little (entry 2). Accordingly, 1.0 eq of various base additives were tested with results listed in Table 4.1, entries 3~7. Higher yield was observed with 1.0 eq of K_2CO_3 additive (entry 3). The additional raising of the reaction temperature to 45ºC leads to similar result as room temperature (entry 8).

Table 4.1 Optimization of Reaction Condition of 1,6-Addition between (*E*)-5-Phenylpent-2-en-4-ynal **1a** and Phenol[a]



Entry	Temp. (^{o}C)	Time (h)	Additive(eq)	Yield (%)
1	r.t.	116 (5d)	None	28[c]
2	r.t.	116 (5d)	K_2CO_3 (0.1eq)	36[c]
3	r.t.	45.5	K_2CO_3 (1eq)	54[b]
4	r.t.	69.5	Cs_2CO_3 (1eq)	37[c]
5	r.t.	65	LiOH (1eq)	23[c]
6	r.t.	65	NaH (1eq)	32[c]
7	r.t.	65	*t*-BuOK (1eq)	29[c]
8	45	22.5	K_2CO_3 (1eq)	50

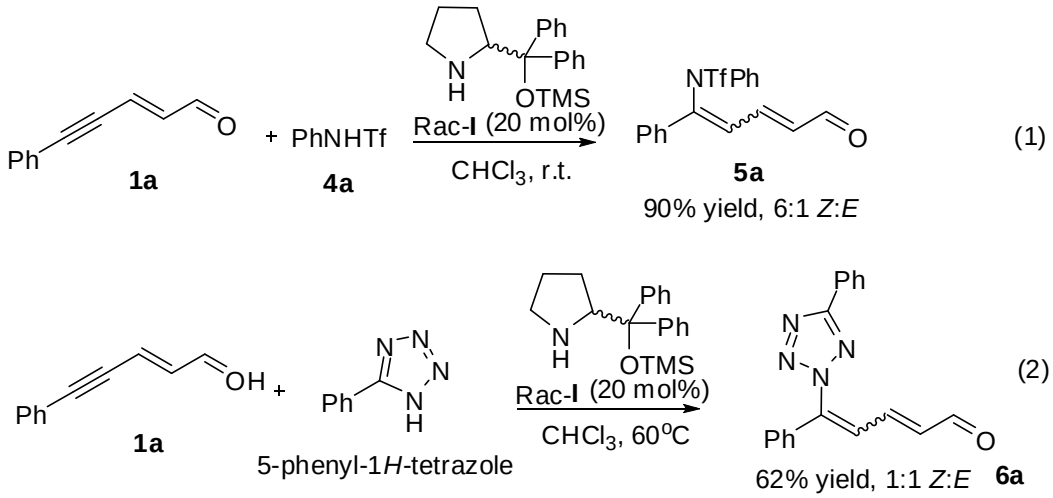
[a] Reaction conditions: unless specified, a mixture of (*E*)-5-phenylpent-2-en-4-ynal **1a** (0.05mmol), phenol (0.10mmol), catalyst (0.01mmol) and additive in $CHCl_3$ was stirred at rt for a specified time. [b] Isolated yields. [c] Calculated yield based on crude ^{1}HNMR.

Crude ^{1}H NMR was conducted during the reaction process in the presence of 3 mol% of organocatalyst **I**, no 1,4-addition intermediate was observed at all. A controlled study is also performed without catalyst **I**. No reaction occurs even heating for 60 h at 66 ^{o}C, indicating that the reaction indeed involves an iminium catalysis.

3) Investigation of nitrogen-based nucleophiles

As for the nitrogen nucleophile, I tried aniline with various electron-withdrawing protection groups such as *para*-methoxysulfonyl, 2,4-dinitrobenzenesulfonyl and trifluoromethanesulfonyl protected aniline. Among those, only trifluoromethanesulfonyl protected aniline **4a** that has the strongest electron-withdrawing electronic property and smallest size act as excellent Michael donor. Gratifyingly, the reaction between (*E*)-5-phenylpent-2-en-4-ynal **1a** and trifluoromethanesulfonyl protected aniline **4a** in chloroform at room temperature in the presence of 20 mol% of organocatalyst **I** give the 1,6-addition product **5a** in 90% yield with 6:1 *Z*/*E* selectivity (Scheme 4.6, eq (1)). However, in sharp contrast, K_2CO_3 base additive would retard the reaction process which is totally opposite with phenol nucleophile (only 50% conversion was observed in the presence of additional 0.5eq of K_2CO_3 base additive). Besides that, triazole and tetrazole heterocycles were studied. Generally speaking, the nucleophilicity of tetrazole is better than that of triazole. For the 5-phenyl-1*H*-tetrazole nucleophile, in the presence of 20 mol% of organocatalyst **I** in chloroform at room temperature, the reaction proceeded slowly. As expected, conducting the reaction at elevated temperature (60 ºC) gave the desired 1,6-addition product **6a** in 62% yield (Scheme 4.6, eq (2)).

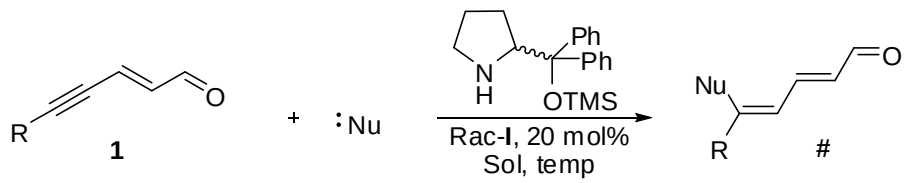
Scheme 4.6 1,6-Addition of Nitrogen Nucleophiles to (*E*)-5-Phenylpent-2-en-4-ynal **1a**



4) Substrate scope of 1,6-addition to yenals

The generality of the 1,6-addition was subsequently investigated. A diverse range of aryl-substituted S, O, N nucleophiles and (*E*)-5-phenylpent-2-en-4-ynals **1** were selected to evaluate the scope of the process. As revealed in Table 4.2, the 1,6-addition processes were tolerant of Michael acceptors **1** with significant structural variations. Remarkably, the aromatic moieties bearing electron-withdrawing (entries 6, 10, 12), -neutral (entries 1-3, 5, 9, 11) and –donating (entry 7) substituents could efficiently participate in the process with high efficiency. Furthermore, heteroaromatic yenals also effectively engaged in the 1,6-addition process (entry4, 8).

Table 4.2 Scope of 1,6-Addition Process [a]



Entry	R	Nu	Solvent	T(^{o}C)	*t*(h)	#	*Z*:*E*	% yield[b]
1	Ph	PhSH	DCM	25	5	**2a**	5:3	87
2	Ph	4-Methylbenzenethiol	DCM	25	7	**2b**	5:4	92
3	Ph	2-Chlorobenzenethiol	DCM	25	7	**2c**	5:3	84
4	2-Thienyl	PhSH	DCM	25	7	**2d**	3:1	84
5	Ph	PhNHTf	$CHCl_3$	25	24	**5a**	6:1	90
6	4-BrC_6H_4	PhNHTf	$CHCl_3$	25	24	**5b**	7:1	85
7	3-$CH_3C_6H_4$	PhNHTf	$CHCl_3$	25	24	**5c**	7:1	91
8	2-Thienyl	PhNHTf	$CHCl_3$	25	24	**5d**	5:4	95
9	Ph	5-Phenyl-1*H*-tetrazole	$CHCl_3$	60	7	**6a**	1:1	62
10	4-BrC_6H_4	5-Phenyl-1*H*-tetrazole	$CHCl_3$	60	4.5	**6b**	1:1	65
11[c]	Ph	Phenol	$CHCl_3$	25	45	**3a**	6:1	54
12[c]	4-ClC_6H_4	Phenol	$CHCl_3$	25	24	**3b**	10:1	60

[a] Unless specified, see the Supporting Information section for reaction conditions. [b] Isolated yield [c] 2eq of phenol and 1eq of K_2CO_3 were applied.

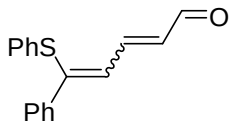
4.4 Conclusions

In conclusion, we have discovered an unprecedented organocatalytic 1,6-addition to yenals with exclusive δ-regioselectivity to generate synthetically useful dienic aldehydes. This chemistry can be extended to "O", "S" and "N" based nucleophiles. The cascade reactions initiated by the organocatalytic 1,6-addition to yenals will be further developed in our lab.

4.5 Supporting Information

General procedure for the 1,6-addition reactions:

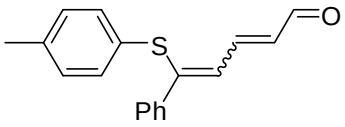
A solution of yenal **1** (0.10 mmol), organocatalyst ***Rac*-I** (6.5 mg, 0.02 mmol) in a solvent (0.1 mL) was added nucleophile (0.12 mmol). The resulting solution was stirred at specific temperature for a specified time as described in Table 4.2. Then the reaction solution was directly purified by running column chromatography to give the desired product.



(2*E*)-5-phenyl-5-(phenylthio)penta-2,4-dienal (2a) (Table 4.2, Entry 1):

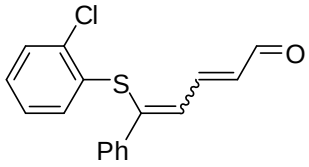
The title compound was prepared according to the general procedure, as described above in 87% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.68 (d, J = 8.1 Hz, 1H), 9.34 (d, J = 8.1 Hz, 0.6H), 8.00 (dd, J_1 = 11.1 Hz, J_2 = 15.3 Hz, 1H), 7.62~7.59 (m, 2H), 7.54~7.51 (m, 1.6H),

7.44~7.39 (m, 5.6H), 7.28~7.25 (m, 3H), 7.20~7.08 (m, 6H), 7.04~6.98 (m, 1.6H), 6.41~6.33 (m, 1H), 6.13~6.09 (m, 0.6H), 5.97~5.89 (m, 0.6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ193.8, 193.6, 154.4, 148.1, 147.7, 138.3, 136.0, 134.7, 133.7, 133.3, 131.3, 130.4, 130.0, 129.6, 129.53, 129.46, 128.9, 128.6, 128.42, 128.38, 128.1, 126.8, 122.0.



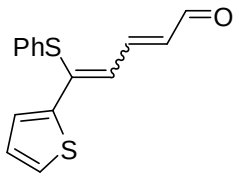
(2*E*)-5-phenyl-5-(p-tolylthio)penta-2,4-dienal (2b) (Table 4.2, Entry 2)

The title compound was prepared according to the general procedure, as described above in 92% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ9.67 (d, J = 8.0 Hz, 1H), 9.32 (d, J = 8.5 Hz, 0.8H), 8.00 (dd, J_1 = 11.0 Hz, J_2 = 15.5 Hz, 1H), 7.583~7.576 (m, 2H), 7.43~7.42 (m, 7H), 7.26~7.22 (m, 6H), 7.08 (d, J = 8.0 Hz, 2H), 7.02 (dd, J_1 = 11.5 Hz, J_2 = 15.0 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.35 (dd, J_1 = 8.0 Hz, J_2 = 15.5 Hz, 1H), 6.03 (d, J = 11.5 Hz, 1H), 5.90 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 0.8H), 2.39 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ193.8, 193.6, 155.2, 148.4, 148.2, 147.8, 139.9, 138.4, 136.9, 136.1, 134.8, 133.0, 130.7, 130.5, 130.3, 129.9, 129.7, 129.4, 129.3, 129.2, 128.5, 128.4, 128.3, 128.0, 126.6, 121.2, 21.3, 20.9.



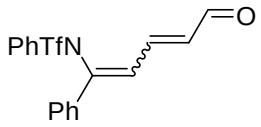
(2*E*)-5-(2-chlorophenylthio)-5-phenylpenta-2,4-dienal (2c) (Table 4.2, Entry 3):

The title compound was prepared according to the general procedure, as described above in 84% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.69 (d, J = 8.0 Hz, 1H), 9.36 (d, J = 8.0 Hz, 0.6H), 7.99 (dd, J_1 = 11Hz, J_2 = 15.0 Hz, 1H), 7.61~7.60 (m, 2H), 7.56 (d, J = 7.5 Hz, 0.6H), 7.49~7.46 (m, 2H), 7.41~7.40 (m, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.30~7.27 (m, 5H), 7.08~7.02 (m, 4H), 6.99~6.96 (m, 1H), 6.38 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 1H), 6.12 (d, J = 11.5 Hz, 0.6H), 5.98 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 0.6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ193.8, 193.6, 151.6, 147.9, 147.5, 146.4, 138.5, 138.0, 136.7, 135.6, 134.1, 133.7, 133.0, 132.2, 131.6, 130.9, 130.5, 130.2, 129.8, 129.6, 128.5, 128.1, 127.9, 127.6, 127.0, 122.9.



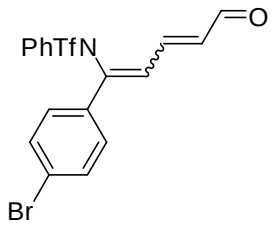
(2*E*)-5-(phenylthio)-5-(thiophen-2-yl)penta-2,4-dienal (2d) (Table 4.2, Entry 4):

The title compound was prepared according to the general procedure, as described above in 84% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.63 (d, J = 8.0 Hz, 1H), 9.47 (d, J = 8.0 Hz, 0.3H), 7.93 (dd, J_1 = 11.0 Hz, J_2 = 15.0 Hz, 1H), 7.50~7.46 (m, 1H), 7.41~7.39 (m, 2H), 7.29 (d, J = 5.0 Hz, 1H), 7.26~7.14 (m, 6H), 7.09 (t, J = 4.5 Hz, 0.3H), 6.94 (t, J = 4.5 Hz, 1H), 6.36 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 1H), 6.19 (d, J = 11.5 Hz, 0.3H), 6.01 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 0.3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ193.6, 147.7, 145.2, 143.7, 138.3, 137.9, 134.7, 134.0, 133.3, 131.1, 130.54, 130.49, 129.9, 129.6, 129.3, 129.2, 128.8, 128.7, 128.3, 128.0, 127.6, 126.7, 123.6.



1,1,1-trifluoro-*N*-((1*Z*)-5-oxo-1-phenylpenta-1,3-dienyl)-*N*-phenylmethanesulfonamide (5a) (Table 4.2, Entry 5):

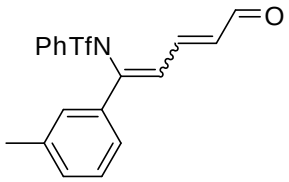
The title compound was prepared according to the general procedure, as described above in 90% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (d, J = 8.0 Hz, 1H), 9.47 (d, J = 8.0 Hz, 0.15H), 7.60~7.59 (m, 2H), 7.54~7.37 (m, 9H), 7.31~7.29 (m, 2H), 7.14~7.03 (m, 1.2H), 6.91 (d, J = 11.0 Hz, 0.15H), 6.42 (dd, J_1= 8.0 Hz, J_2 = 15.5 Hz, 1H), 6.38~6.36 (m, 0.12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ193.1, 192.9, 146.8, 146.6, 144.0, 143.7, 139.4, 136.9, 135.43, 135.35, 134.6, 133.2, 130.4, 130.2, 129.8, 129.4, 129.3, 129.1, 129.0, 128.7, 128.5, 127.7, 127.0, 126.5, 123.9, 122.0, 117.7.



***N*-((1*Z*)-1-(4-bromophenyl)-5-oxopenta-1,3-dienyl)-1,1,1-trifluoro-*N*-phenylmethanesulfonamide (5b) (Table 4.2, Entry 6):**

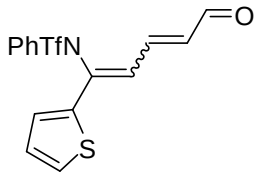
The title compound was prepared according to the general procedure, as described above in 85% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (d, J = 7.5 Hz, 1H), 9.48 (d, J = 7.5 Hz, 0.1H), 7.54~7.51 (m, 3H), 7.48~7.38 (m, 6H), 7.32~7.28 (m, 1.8H), 7.18 (d, J = 8.5 Hz, 0.4H), 7.11 (d, J = 11.0 Hz, 1H), 7.02~6.96 (m, 0.15H), 6.90 (d, J = 11.5 Hz, 0.15H),

6.43 (dd, J_1 = 8.0 Hz, J_2 = 15.5 Hz, 1H), 6.38~6.35 (m, 0.1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.9, 192.7, 145.7, 145.4, 143.5, 142.5, 139.1, 135.7, 135.1, 134.4, 132.2, 132.1, 131.3, 129.9, 129.6, 129.5, 128.93, 128.87, 128.4, 127.8, 127.0, 124.9, 124.8, 123.8, 121.1, 118.5.



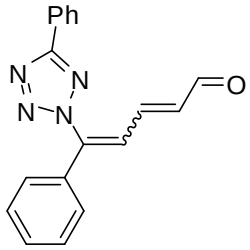
1,1,1-trifluoro-*N*-((1*Z*)-5-oxo-1-m-tolylpenta-1,3-dienyl)-*N*-phenylmethanesulfonamide (5c) (Table 4.2, Entry 7):

The title compound was prepared according to the general procedure, as described above in 91% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.64 (d, J = 7.5 Hz, 1H), 9.47 (d, J = 8.0 Hz, 0.14H), 7.53~7.50 (m, 1H), 7.47~7.45 (m, 2H), 7.42~7.37 (m, 4H), 7.31~7.28 (m, 3H), 7.23~7.18 (m, 1.5H), 7.13~7.07 (m, 1.5H), 6.88 (d, J = 11.0 Hz, 0.14H), 6.41 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 1H), 6.37~6.34 (m, 0.1H), 2.37 (s, 3H), 2.35 (s, 0.4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.1, 193.0, 147.0, 146.9, 144.1, 143.9, 139.5, 138.8, 138.5, 136.9, 135.4, 135.2, 134.4, 133.1, 131.3, 131.0, 130.2, 129.8, 129.6, 129.4, 129.3, 129.1, 128.8, 128.5, 128.2, 127.6, 127.2, 126.3, 124.3, 123.9, 123.4, 122.0, 117.7, 113.4, 21.4, 21.3.



1,1,1-trifluoro-*N*-((1*Z*)-5-oxo-1-(thiophen-2-yl)penta-1,3-dienyl)-*N*-phenylmethanesulfonamide (5d) (Table 4.2, Entry 8):

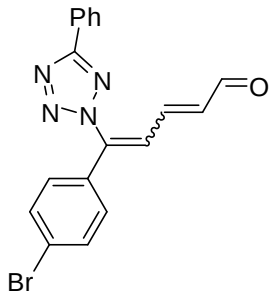
The title compound was prepared according to the general procedure, as described above in 95% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.69 (d, J = 7.8 Hz, 1H), 9.58 (d, J = 7.8 Hz, 0.8H), 7.58~7.46 (m, 4H), 7.43~7.31 (m, 9.8H), 7.18~7.17 (m, 0.8H), 7.08 (d, J = 11.4 Hz, 1H), 7.05~7.01 (m, 1.8H), 6.95 (d, J = 11.1 Hz, 0.8H), 6.47~6.39 (m, 1.8H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.0, 192.9, 146.0, 143.9, 139.9, 139.5, 138.8, 137.6, 137.2, 135.8, 135.2, 134.8, 132.0, 130.0, 129.9, 129.5, 129.3, 128.9, 128.8, 128.5, 128.34, 128.26, 128.1, 127.7, 127.2, 124.4, 123.9, 121.3, 121.0, 118.7, 118.5.



(2*E*)-5-phenyl-5-(5-phenyl-2*H*-tetrazol-2-yl)penta-2,4-dienal (6a) (Table 4.2, Entry 9):

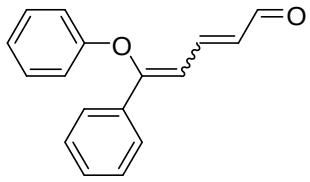
The title compound was prepared according to the general procedure, as described above in 62% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.58 (d, J = 7.8 Hz, 1H), 9.56 (d, J = 7.8 Hz, 1H), 8.26~8.19 (m, 4H), 7.60~7.43 (m, 16H), 7.31~7.27 (m, 2H), 7.23~7.15 (m, 2H), 7.07 (d, J = 11.4 Hz, 1H), 6.51 (dd, J_1 = 7.8 Hz, J_2 = 12.9 Hz, 1H), 6.46 (dd, J_1 = 7.8 Hz, J_2 = 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.1, 192.8, 165.6, 165.1, 145.4,

143.5, 142.9, 141.5, 135.9, 135.7, 133.7, 131.0, 130.9, 130.9, 130.6, 130.1, 129.03, 128.95, 128.8, 127.19, 127.15, 127.1, 126.55, 126.47, 123.8, 120.7.



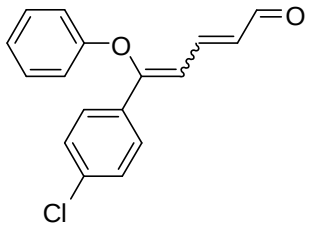
(2*E*)-5-(4-bromophenyl)-5-(5-phenyl-2*H*-tetrazol-2-yl)penta-2,4-dienal (6b) (Table 4.2, Entry 10):

The title compound was prepared according to the general procedure, as described above in 65% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.58 (d, J = 7.8 Hz, 1H), 9.58 (d, J = 7.8 Hz, 1H), 8.24~8.17 (m, 4H), 7.75~7.66 (m, 3H), 7.61~7.50 (m, 9H), 7.39~7.33 (m, 2H), 7.22~7.13 (m, 3H), 7.04 (d, J = 11.4 Hz, 1H), 6.52 (dd, J_1 = 7.8 Hz, J_2 = 13.8 Hz, 1H), 6.47 (dd, J_1 = 7.8 Hz, J_2 = 13.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.0, 192.7, 165.7, 165.2, 144.6, 143.2, 141.6, 140.3, 136.3, 136.1, 132.7, 132.3, 132.2, 132.1, 131.1, 131.0, 129.1, 129.0, 128.6, 127.2, 126.4, 126.3, 125.6, 125.5, 124.0, 121.0.



(2*E*)-5-phenoxy-5-phenylpenta-2,4-dienal (3a) (Table 4.2, Entry 11):

The title compound was prepared according to the general procedure, as described above in 54% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.55 (d, J = 7.8 Hz, 1H), 9.41 (d, J = 8.1 Hz, 0.15H), 7.62~7.57 (m, 3H), 7.54~7.49 (m, 0.8H), 7.44~7.33 (m, 3.5H), 7.32~7.23 (m, 2.5H), 7.14~7.12 (m, 0.3H), 7.03~6.95 (m, 3H), 6.68 (d, J = 11.4 Hz, 1H), 6.29 (dd, J_1 = 8.1 Hz, J_2 = 15.6 Hz, 1H), 6.02 (dd, J_1 = 8.1 Hz, J_2 = 15.3 Hz, 0.15H), 5.81 (d, J = 11.4 Hz, 0.15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.8, 193.2, 165.6, 157.2, 149.9, 145.7, 133.5, 131.5, 130.4, 130.1, 130.0, 129.8, 129.6, 129.5, 128.8, 128.6, 126.7, 125.2, 122.7, 120.8, 116.3, 114.6, 107.4.



(2*E*)-5-(4-chlorophenyl)-5-phenoxypenta-2,4-dienal (3b) (Table 4.2, Entry 12):

The title compound was prepared according to the general procedure, as described above in 60% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.54 (d, J = 8.1 Hz, 1H), 9.42 (d, J = 7.8 Hz, 0.1H), 7.59~7.46 (m, 3.4H), 7.42~7.39 (m, 0.4H), 7.32~7.20 (m, 4H), 7.12~7.09 (m, 0.2H), 7.05~7.00 (m, 1H), 7.00~6.93 (m, 2H), 6.65 (d, J = 11.1 Hz, 1H), 6.29 (dd, J_1 = 7.8 Hz, J_2 = 15.3 Hz, 1H), 6.03 (dd, J_1 = 8.1 Hz, J_2 = 15.3 Hz, 0.1H), 5.81 (d, J = 11.7 Hz, 0.1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.7, 193.0, 157.0, 156.0, 154.3, 149.0, 145.3, 136.5, 136.1, 132.1, 131.9, 130.7, 130.1, 130.0, 129.9, 129.1, 129.0, 128.0, 125.3, 122.9, 120.7, 116.2, 114.9, 107.7.

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