ASYMMETRIC ORGANOCATALYTIC HENRY REACTION OF β-SUBSTITUTED α-KETO ESTERS VIA DYNAMIC KINETIC RESOLUTION

LIU GUANNAN

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LIU GUANNAN

(BSc, Nanjing Univ.)

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Thesis Declaration

The work in this thesis is the original work of Liu Guannan, performed independently under the supervision of A/P Lu Yixin, Chemistry Department, National University of Singapore, between 08/2010 and 07/2012.

Name	Signature	Date

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Summary

This thesis describes the development of diastereo- and enantioselective Henry reaction of β-substituted α-keto esters using cinchona alkaloid derived bifunctional catalyst via dynamic kinetic resolution.

Chapter 1 presents a brief historical background and development of asymmetric catalysis. Particularly, the asymmetric organocatalysis is introduced in detail. Then the historical background and development of dynamic kinetic resolution are summarized, especially, those organocatalytic methods are introduced in detail.

In Chapter 2, the diastereo- and enantioselective Henry reactions of β-substituted α-keto esters via dynamic kinetic resolution are investigated by using cinchona alkaloid derived bifunctional catalysts. Our approach combines organocatalytic Henry reaction and concept of dynamic kinetic resolution, and it also provides an access to biologically important and medicinal useful pyrrolidine derivatives.

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List of Abbreviations

^{o}C	degrees Celsius
Ac	acteyl
Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1’-bi-2-naphthol
Boc	*tert*-butoxycarbonyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1, 4-diazabicyclo-[2.2.2] octane
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DDQ	2,3-dichlro-5,6-dicyano-1,4-benzoquinone
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethylsulfoxide
d	doublet
dr	diastereomeric ratio
de	diastereomeric excesses
EA	ethyl acetate
ee	enantiomeric excesses
ESI	electrospray ionization
Et	ethyl
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
i-Pr	isopropyl
IPA	isopropanol
LiHMDS	Lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectra
m	multiplet
m/z	mass-to-charge ratio
mmol	millimole

Me	methyl
Ph	phenyl
PMP	*p*-methoxyphenyl
q	quartet
rac	*racemic*
rt	room temperature
s	singlet
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
Tr	trityl
t	triplet
t-Bu	*tert*-butyl
t_R	retention time

Chapter 1 introduction

1.1 Asymmetric catalysis

1.1.1 Molecular chirality

Chiral molecules are optically active compounds that lack an internal plane of symmetry and have a non-super imposable mirror image.[1] Most of natural products and pharmaceutical compounds are chiral molecules. About 80% of the natural products have at least one chiral center, and 15% of them have 11 or more stereocenters.[2] Therefore, nowadays asymmetric organic synthesis is becoming an extraordinarily important field in medicinal chemistry and pharmaceutical industry. Due to the stereoisomers may have different pharmacological effects and activities and the enzymatic processes in the body are extremely chiral-selective, one isomer could have desired drug activities, while the other one may be inefficient or even lead to severe side effects.[3,4] Thus, finding more efficient approaches to synthesize optically pure compounds is an important target for organic chemists.

1.1.2 Asymmetric synthesis

There are two main approaches to adopt in asymmetric synthesis: chiral auxiliaries based method and asymmetric catalysis. Chiral auxiliaries used to be the main method in asymmetric synthesis[5]. Some excellent examples include Evan's oxazolidinones[6], sulfinamides[7], sulfoxids[8] and carbohydrate derivatives[9]. However, compared with asymmetric catalysis, chiral auxiliary-based approaches

are less efficient due to the post-processing of auxiliaries.

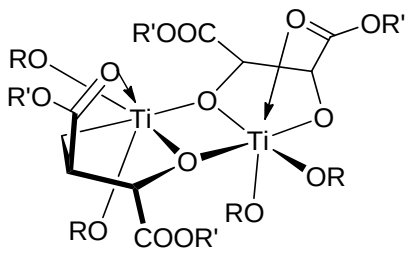
The advantage of asymmetric catalysis is apparent. As catalytic reactions, the catalysts could be regenerated during the reaction. There are three common approaches to perform asymmetric catalysis: enzyme catalysis, transition metal mediated catalysis and asymmetric organocatalysis.

Enzymes are highly efficient and specific biocatalysts in nature, excellent enantioselectivies and high reaction rates are commonplace for enzymatic reactions. Traditionally, enzyme catalysis has been utilized for the preparation of chiral molecules.[10] However, the sensitivity of enzymes to acid, base and temperature, as well as the difficulty of generating specific stereoisomers limit their applications in asymmetric synthesis.

Transition metal mediated catalysis has been widely used to obtain excellent chiral molecules in the past few decades. For instance, Sharpless and Katsuki pioneered enantioselective epoxidation of allylic alcohols with a titanium-tartrate complex **1-1** as catalyst.[11] Noyori and co-workers greatly advanced asymmetric hydrogenation reaction by introducing BINAP **1-2** in metal catalysis.[12] Many previliged ligands are well-established, including chiral salen Mn complexes **1-3** for asymmetric epoxidation of alkenes[13] and chiral copper complexes **1-4** for asymmetric cyclopropanation[14].

Although transition metal mediated catalysis has undoubtedly become the

most important approach to obtain optically pure compounds, it still suffers from some severe drawbacks, such as toxicity and expensive nature of the metals involved, user-unfriendly reaction conditions necessary for carrying out metal catalysis.



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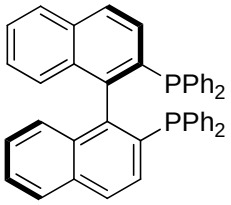
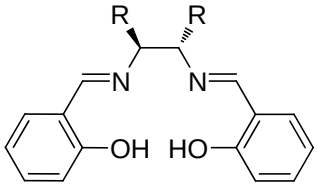
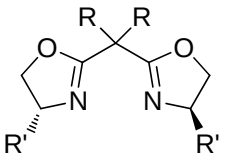


1-2
(R)-BINAP



1-3
Salen ligand



1-4

Scheme 1.1 Structures of some representative ligands.

1.1.3 Asymmetric organocatalysis

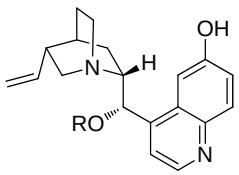
Compared with transition metal mediated process, organocatalysis relies on small chiral molecules without involving metal in the catalytic process. Although this emerging field only drew attention from synthetic community in 2000, it actually has a long history. In 1908, Breding reported the first decarboxylation

reaction with only organic catalysts.[15] Subsequently, a kinetic resolution (KR) approach of this reaction with chiral alkaloids was published.[16] In 1912, Breding presented the crucial work of hydrocynation reaction of benzaldehyde. Although employment of cinchona alkaloid only led to poor enantioselectities, this work was considered as a milestone in the organocatalysis[17]. In 1929 and 1932, Vavon and Vegler reported the acylation of secondary alcohols via kinetic resolution (KR), respectively.[18]

The next breakthrough of organocatalysis came in 1950s when Stork and co-workers introduced the utilization of enamines as nucleophiles.[19] In 1970s the so-called Hajos-Parrish-Eder-Sauer-Wiechert reaction was reported, which has a key intramolecular aldol reaction catalyzed by L-proline via enamine intermediates.[20]

In 1960, Pracejus reported the addition of methanol to methyl phenyl ketene catalyzed by O-acetylquinine.[21] Wynberg and co-workers did a series of modification on the C-9 hydroxyl group of cinchona alkaloids, by employing such catalysts, they were able to perform asymmetric 1,2- and 1,4- nucleophilic additions of carbonyl compounds.[22]

The main development of this field in next two decades is ion-pairing mediated approach, which includes phase-transfer catalysis[23] and Bronsted acids catalyzed processes[24].



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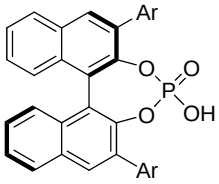

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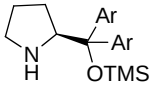

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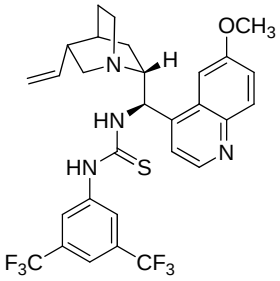

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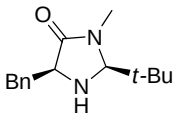

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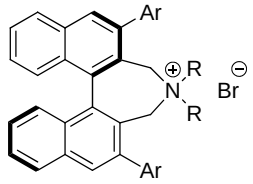

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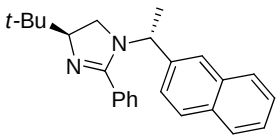

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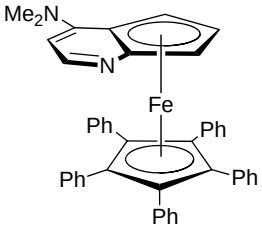

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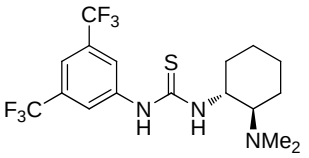


1-13

Scheme 1.2 Selected representative organocatalysts.

The year 2000 saw the rebirth of modern organocatalysis. In the past decade, significant contributions from the groups of Jacobsen[25-27], List[28-33], MacMillan[34-36], Maruoka[37-41] and Denmark[42-45] greatly advanced the field. Some representative catalysts are shown in Scheme 1.2, which includes cinchona alkaloid derivatives **1-5** and **1-8**, chiral BINOL derivative **1-6**, L-proline derivative **1-7**, oxazolidinone **1-9**, phase-transfer catalyst **1-10**, chiral imidazole derivative **1-11**, chiral DMAP

derivative **1-12** and thiourea derivatives **1-8** and **1-13**.

Compared with transition metal catalysts, organocatalysts are often more stable to moisture and air. Moreover, they are typically inexpensive, easy to prepare and less toxic. Thus, organocatalysis not only gained popularity in academic research, but also have a bright future in industrial applications.

1.2 Dynamic Kinetic Resolution (DKR)

1.2.1 Introduction

Resolution of racemates is the most important industrial approach to the synthesis of optically pure compounds. The traditional kinetic resolution is defined as the two enantiomes of a racemate are transformed to products in different rates.[46]

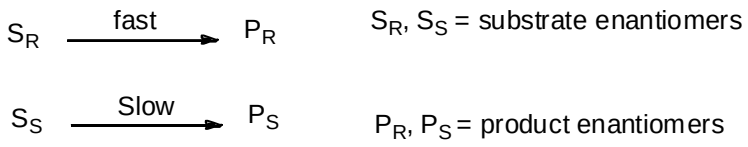


Figure 1.1 Traditional kinetic resolution.

As shown in Figure 1.1, an efficient kinetic resolution could be described as one of the enantiomers is fully transformed to the desired product while the other is retained. Thus, kinetic resolution has the maximum theoretical yield of 50%.

To overcome the limitation of yield without lose enantioselectivity, dynamic kinetic resolution (DKR) was introduced. As shown in Figure 1.2, with an *in situ* equilibration or racemization of the chirally-labile substrate, one of the

enantiomers can be obtained in a theoretical yield of 100%. [47]

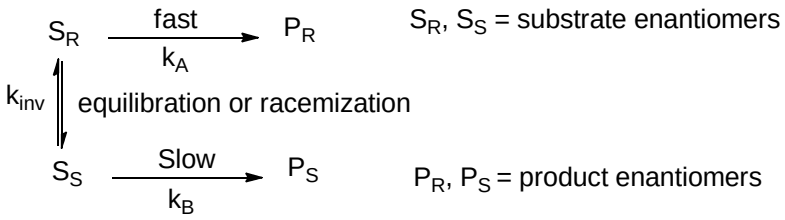
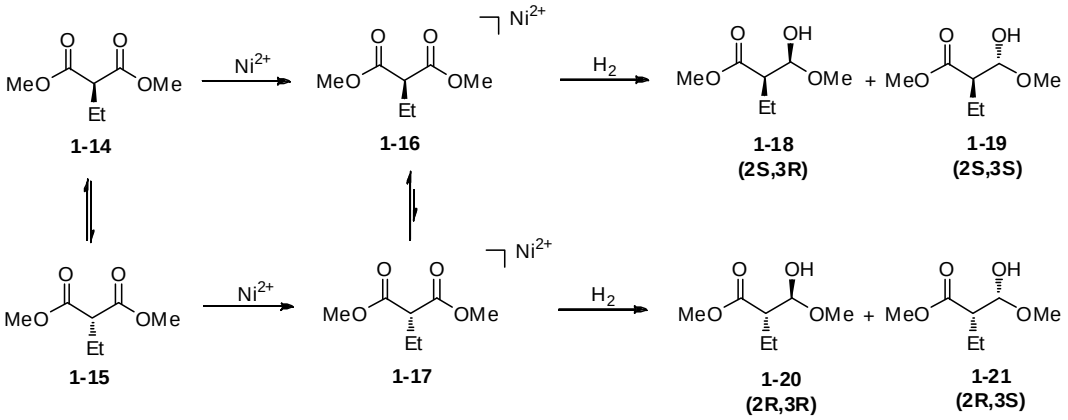


Figure 1.2 Dynamic kinetic resolution.

Harada and co-workers presented the first chemical dynamic kinetic resolution of β-keto ester reduction in 1979[48], as shown in Scheme 1.3. For an efficient DKR, the product could not racemize under the reaction conditions and the selectivity (k_A/k_B) of the resolution step should be at least 20.



Scheme 1.3 Asymmetric hydrogenation of β-keto ester via DKR

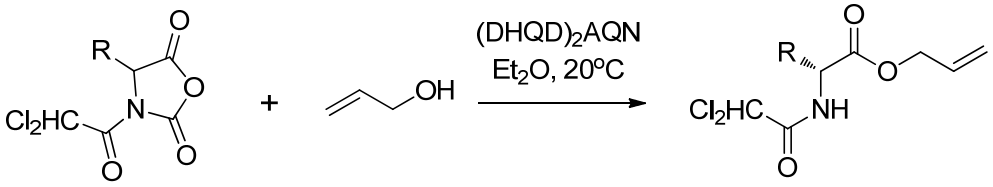
Moreover, the rate constant for the racemization (k_{inv}) should be faster than that of resolution step (k_A), otherwise a high selectivity must be ensured. Racemization of the substrate can be performed chemically, biocatalytically or spontaneously.[47] DKR is not limited to synthesis an enantiomer with only one new chiral center, when the reaction occurs along with the creation of a new

stereogenic center, an enantioselective synthesis of a diastereoisomer is also possible.[49]

Organocatalysts have some important advantages, such as stable, inexpensive, readily available and non-toxic. Recently, organocatalytic DKR has received more and more attention. Some recent examples will be illustrated in the following section.

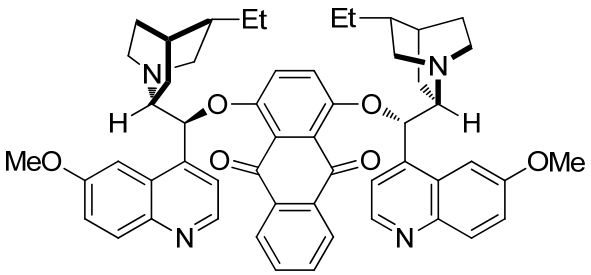
1.2.2 Organocatalytic DKR

In 2001, Deng and co-workers reported an organocatalytic DKR reaction[50], as shown in Scheme 1.4. The asymmetric alkylation of N-carboxyanhydrides was achieved by using cinchona alkaloid derivatives as catalysts. In this process, $(DHQD)_2AQN$ **1-25** acts as a bifunctional catalyst to catalyze both racemization and alcoholytic kinetic resolution of alkyl N-carboxyanhydrides with an electron-withdrawing N-protecting group, leading to the generation of the corresponding amino esters in good yields and high enantioselectivities.



1-22 **1-23** **1-24**

R = Bn:yield 81% ee = 66%
R = *p*-$FC_6H_4CH_2$:yield 82% ee = 67%
R = *p*-$ClC_6H_4CH_2$: yield 82% ee = 67%
R = *p*-$BrC_6H_4CH_2$: yield 82% ee = 70%
R = 2-Thio-CH_2:yield 87% ee = 75%
R = $BnCH_2$:yield 77% ee = 59%

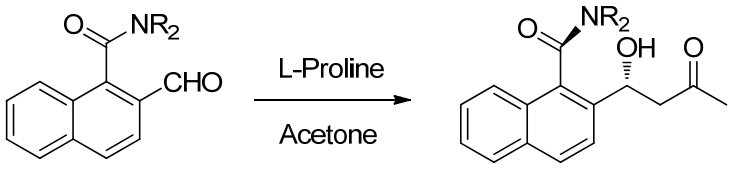


$(DHQD)_2AQN$

1-25

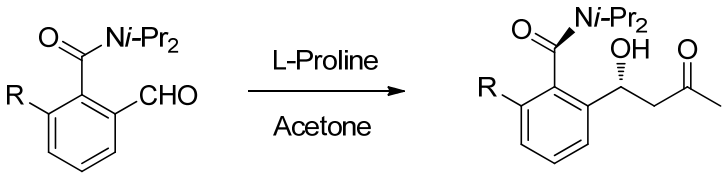
Scheme 1.4 DKR process of N-carboxyanhydrides catalyzed by Cinchona alkaloid derivatives.

In 2004, Walsh and co-workers developed L-proline catalyzed aldol reactions of atropisomeric amides. As shown in Scheme 1.5, the DKR process simultaneously established the stereoselectivies of the atropisomeric amide chiral axis and also a new stereogenic center was formed from the asymmetric aldol reaction.[51]



1-26 **1-27**

R = *i*-Pr: yield 87% de = 70% ee = 91%
R = *c*-Hex: yield 89% de = 66% ee = 92%

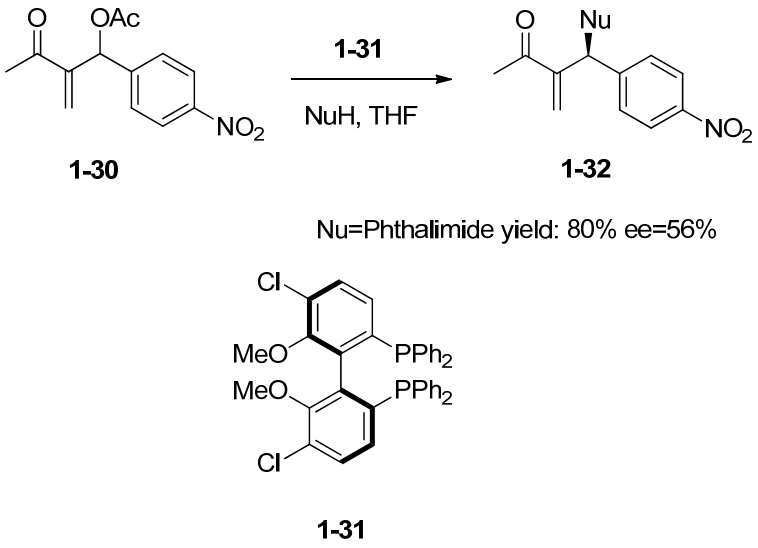


1-28 **1-29**

R = NMe_2: yield 92% de = 56% ee = 94%
R = CF_3: yield 86% de = 75% ee = 82%
R = Ph: yield 100% de = 50% ee = 90%
R = OMe: yield 80% de = 36% ee = 95%
R = TMS: yield 79% de = 78% ee = 89%

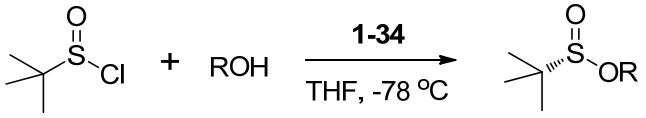
Scheme 1.5 L-Proline catalyzed DKR process of atropisomeric amides.

In 2004, Krische and co-workers employed tertiary phosphine catalyst **1-31** in the reactions of Morita-Baylis-Hillman acetates and phthalimide (Scheme 1.6), the reaction was believed to proceed through a tandem S_N2'- S_N2' mechanism and moderate enantioselectivities were obtained.[52]



Scheme 1.6 Tertiary phosphine catalyzed Morita-Baylis-Hillman reaction via DKR.

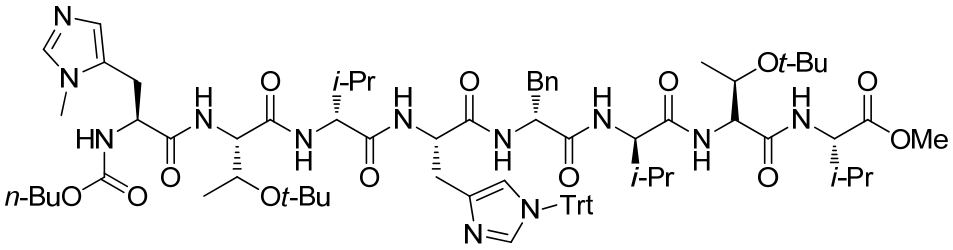
The first catalytic asymmetric synthesis of sulfinate esters through DKR was reported by Ellman and co-workers in 2004. The N-methyl imidazole-containing octapeptide **1-34** was introduced as the catalyst, and high enantioselectivities were achieved from racemic tert-butanesulfinyl chloride.[53] By employing cinchona alkaloid derivatives as the catalyst, Toru and co-workers obtained good results in similar reactions (Scheme 1.7).[54] Sulfone enolates were considered as the racemization intermediates in this reaction in the presence of organic base. In 2009, Ellman and co-workers employed quinidine as the catalyst to extend the scope of this reaction to include various alcohols, and high yields and enantioselectivities were obtained (Scheme 1.8).[55]



1-33 **1-35**

R = Bn: yield 99% ee = 80%

R = 2-Naph: yield 61% ee > 99%



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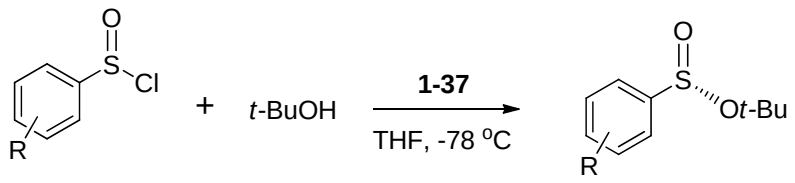


1-36 **1-38**

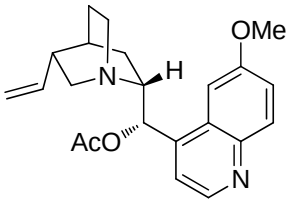
R = Ph: yield 93% ee = 88%

R = p-ClC_6H_4: yield 78% ee = 88%

R = p-$MeOC_6H_4$: yield 70% ee = 99%

R = 4-MeO-3-MeC_6H_4: yield 78% ee = 93%

R = 2,4,6-$(Me)_3C_6H_2$: yield 68% ee = 92%



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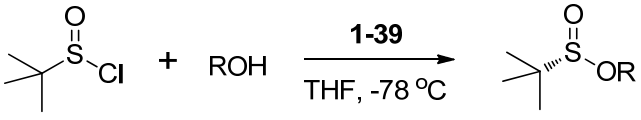
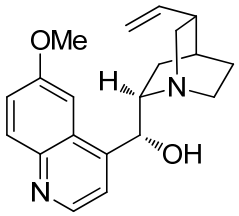
Scheme 1.7 Organocatalyzed DKRs of sulfinyl chlorides.



1-33 **1-35**

R = Et: yield >99% ee = 87%
R = *n*-Pr: yield 98% ee = 89%
R = *n*-Bu: yield 95% ee = 88%
R = *i*-Bu: yield 85% ee = 88%
R = $(CH_2)_2F$: yield >99% ee = 89%



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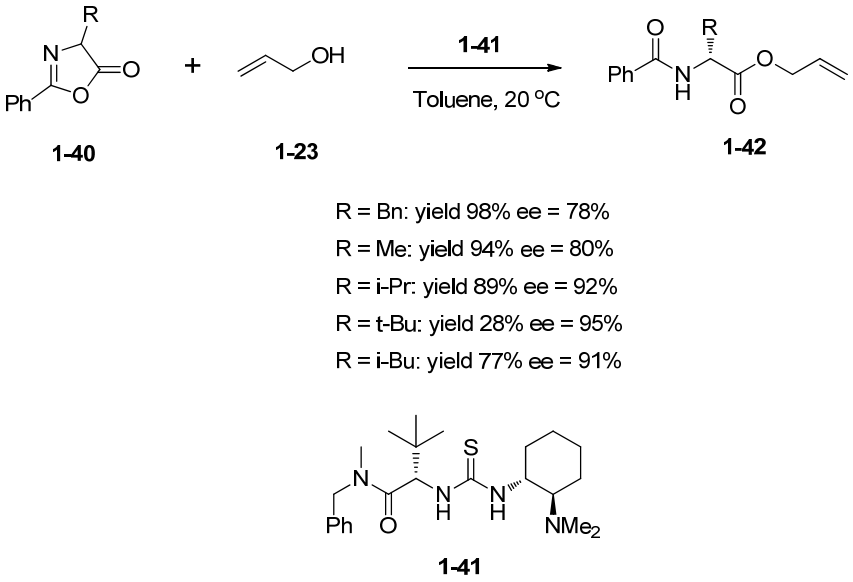
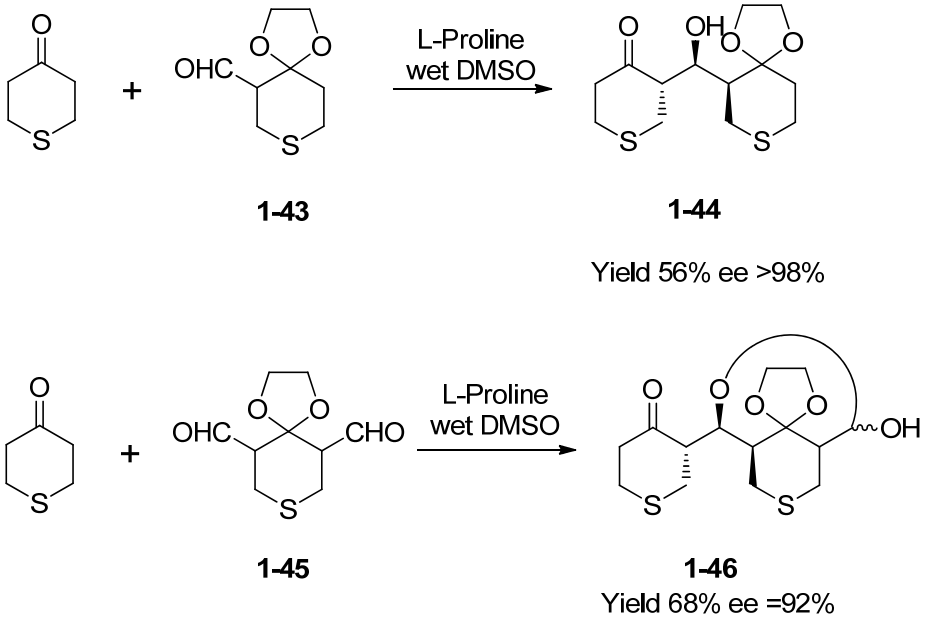
Scheme 1.8 DKRs of *tert*-butanesulfinyl chlorides.

In 2005, Berkessel and co-workers reported a highly enantioselective DKR alcoholysis of azlactones catalysed by thiourea bifunctional catalysts. As shown in Scheme 1.9, this work provided a direct method to synthesis a wide range of protected natural and non-natural α-amino acids with high enantioselectivities.[56] In 2006, the same group also explored various bifunctional thiourea catalysts and extended the substrate scope of this DKR process.[57]



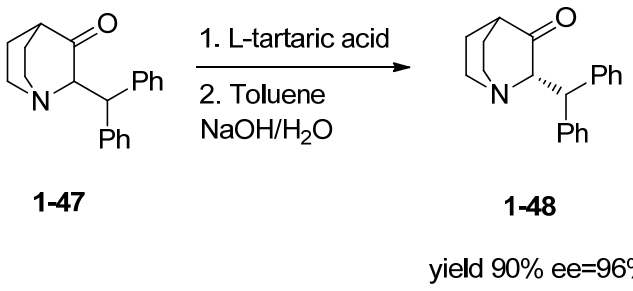
Scheme 1.9 Thiourea catalyzed DKR processes of azlactones

An asymmetric direct aldol reaction was reported by Ward and co-workers in 2005. As shown in Scheme 1.10, they introduced that L-proline-catalyzed aldol reaction of tetrahydro thiopyranone with racemic aldehyde **1-43** and **1-45** generated single adducts with excellent enantioselectivities.[58] With the more soluble L-proline derivatives as the catalyst, the results of these reactions could be further improved to 75% yield and >98% ee, and the key intermediate for the total synthesis of a sex hormone serricornin was prepared.[59]



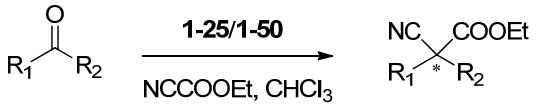
Scheme 1.10 L-Proline catalyzed direct asymmetric aldol reactions via DKR.

Substance P is an undecapeptide that functions as a neurotransmitter and as a neuromodulator which belongs to the tachykinin neuropeptide family.[60] Substance P antagonists are used to treat many ailments ranging from gastrointestinal and central nervous system disorders to inflammatory diseases, pain, and migraine. An efficient synthesis of a pivotal precursor to substance P antagonists had been developed by Seemayer and co-workers in 2006[61], in which L-tartaric acid was used to achieve the DKR of benzhydryl quinuclidinone (Scheme 1.11).



Scheme 1.11 DKR of benzhydryl quinuclidinone catalysed by L-tartaric acid.

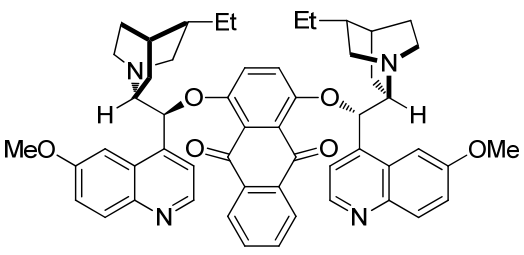
The first highly enantioselective cyanocarbonation of prochiral ketones catalyzed by cinchona alkaloid derivatives was reported by Deng and co-workers[62]. As shown in Scheme 1.12, the reported method employed sterically hindered simple dialkyl ketones and generated corresponding cyano esters with high yield and enantioselectivites, which complemented the known substrate scope of enzymatic and transition metal mediated methods. In the proposed mechanism, as shown in Figure 1.3, the enantioselectivity determination step in the cyanocarbonation was the DKR of the proposed intermediates **1-55** and **1-56** via asymmetric transfer of the alkoxycarbonyl group. The racemization of **1-55** and **1-56** is due to that the cyanide addition to ketone is a reversible reaction.



1-49 **1-51**

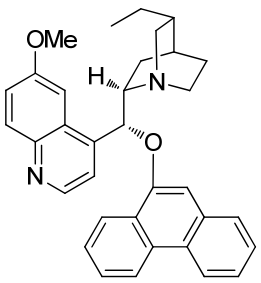
With catalyst 1-25
R1= *n*-Pent, R2=Me: yield 53% ee=64%
R1= *i*-Pr, R2=Me: yield 51% ee=76%
R1= CH(allyl)$_2$, R2=Me: yield 54% ee=81%
R1,2= (CH$_2$)$_5$: yield 52% ee=87%
R1= *t*-Bu, R2=Me: yield 55% ee=88%
R1,2= (Me)$_2$C-(CH$_2$)$_4$: yield 62% ee=91%

With catalyst 1-50
R1= CH(*n*-Pr)$_2$, R2=Me: yield 86% ee=96%
R1= CMe(OMe)$_2$, R2=Me: yield 63% ee=85%
R1= CMe(OEt)$_2$, R2=Me: yield 65% ee=90%
R1,2= (Me)$_2$C-(CH$_2$)$_3$: yield 80% ee=95%
R1,2= (EtO)$_2$C-(CH$_2$)$_3$: yield 99% ee=94%
R1,2= (EtO)$_2$C-(CH$_2$)$_4$: yield 78% ee=96%



(DHQD)$_2$AQN

1-25



DHQD-PHN

1-50

Scheme 1.12 Cyanocarbonation of ketones via DKR.

The catalytic asymmetric reductive amination of carbonyl compounds is a classic and powerful C-N bond formation reaction. However, literature reports on this topic are rather limited.[63] In 2006, List et al. employed BINOL phosphoric acid for the asymmetric reductive aminations of aldehydes using a BINOL phosphoric acid catalyst **1-52** and Hantzsch esters **1-53** (Scheme 1.13).[64]

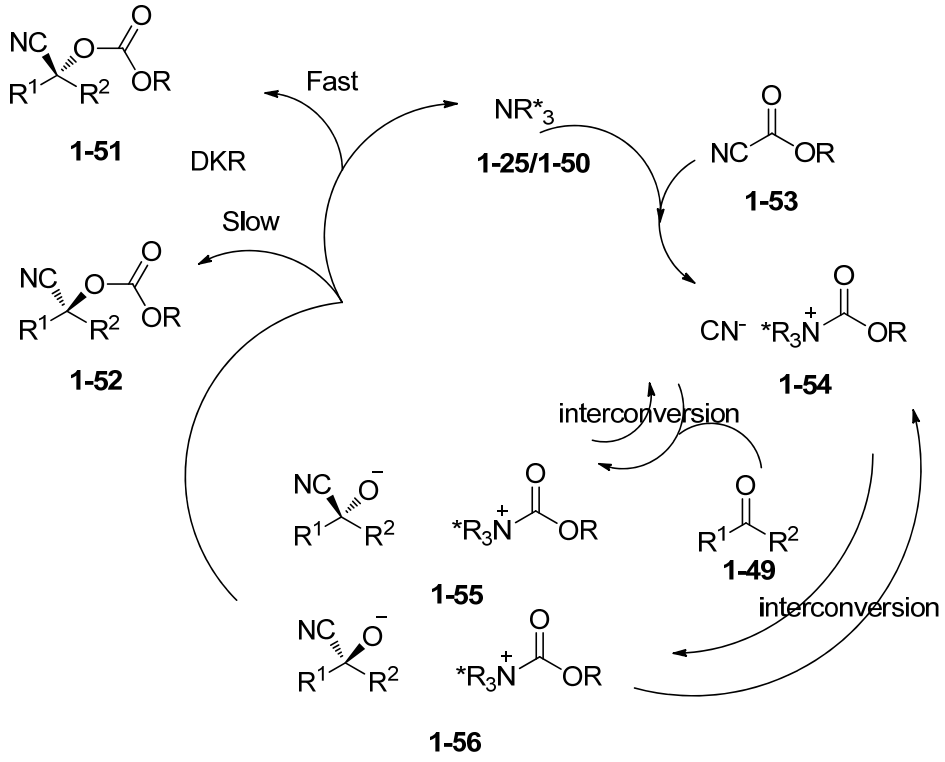
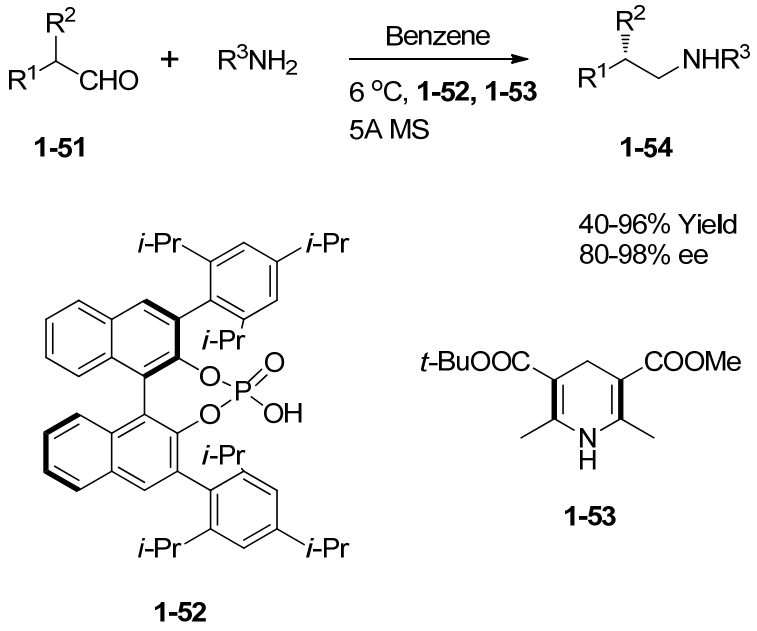
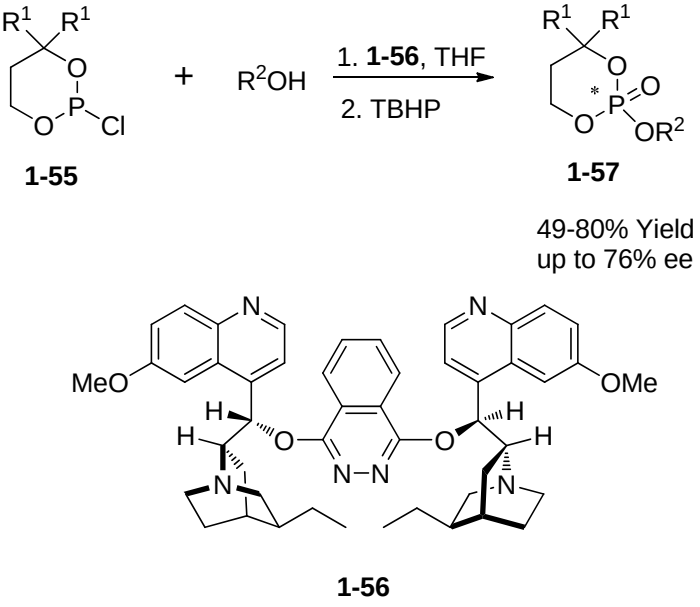


Figure 1.3 Proposed mechanism of cyanocarbonation of ketones via DKR.



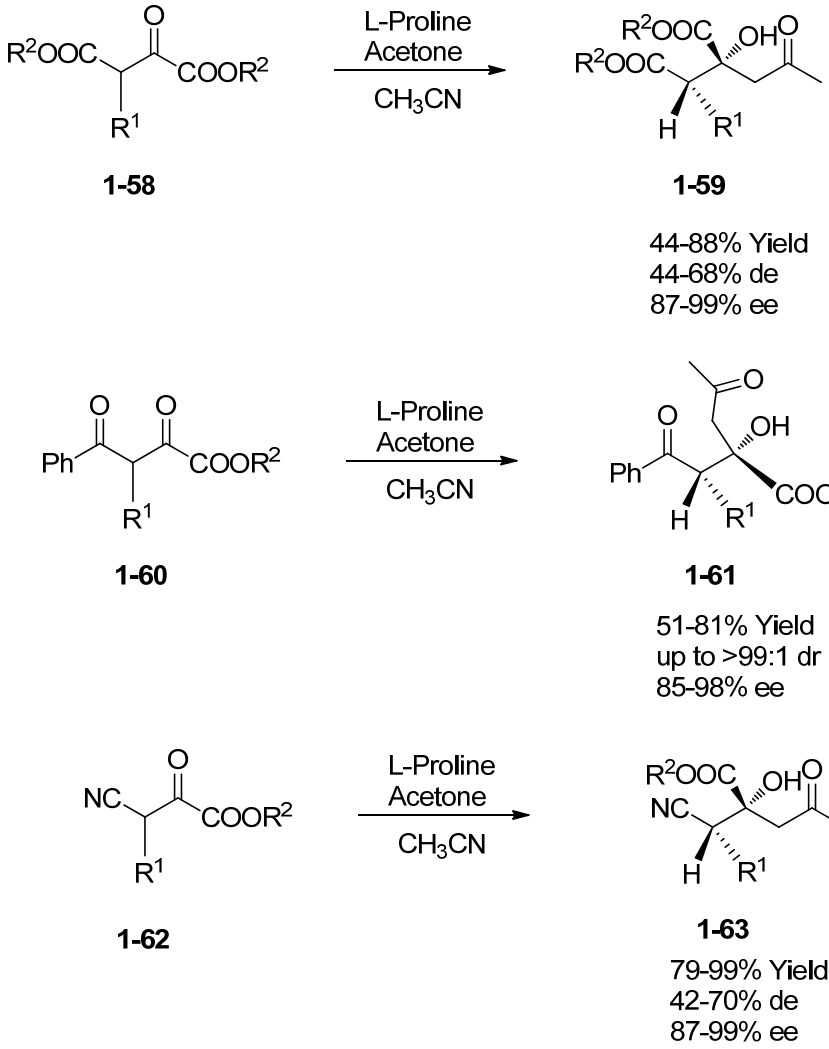
Scheme 1.13 Reductive amination of aldehydes via DKR.

Hayakawa and co-workers have reported the first asymmetric synthesis of a *P*-chiral trialkyl phosphate from a trialkyl phosphite.[65] As shown in Scheme 1.14, the key step of this reaction was the DKR in the condensation between the dialkyl phosphorochloridite and hydroxyl group catalyzed by cinchona alkaloid derivatives.



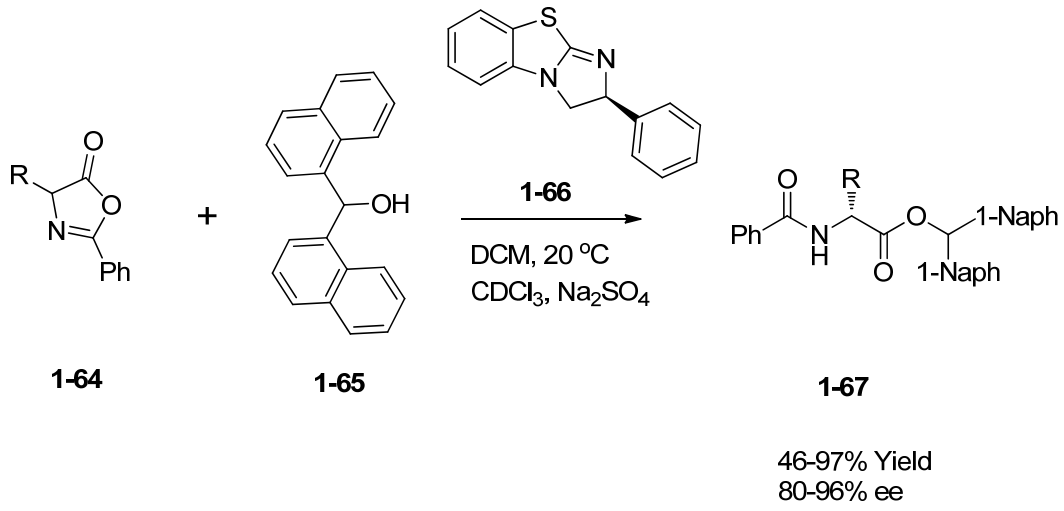
Scheme 1.14 Cinchona alkaloid catalyzed DKR of phosphorochloridite.

In 2007, Zhang and co-workers reported a L-proline-catalyzed DKR of asymmetric aldol reaction between β-substituted α-keto esters and acetone and the desired aldol products were obtained in good yields, low diastereoselectivity and up to 99% ee.[66] In 2009, the same group reported a similar work with employment of different substrates, and more than 99:1 diastereomeric ratio with high enantioselectivties was obtained.[67] In 2010, they further extended the substrate scope by including β-cyano α-keto ester in the asymmetric aldol reaction through DKR (Scheme 1.15).



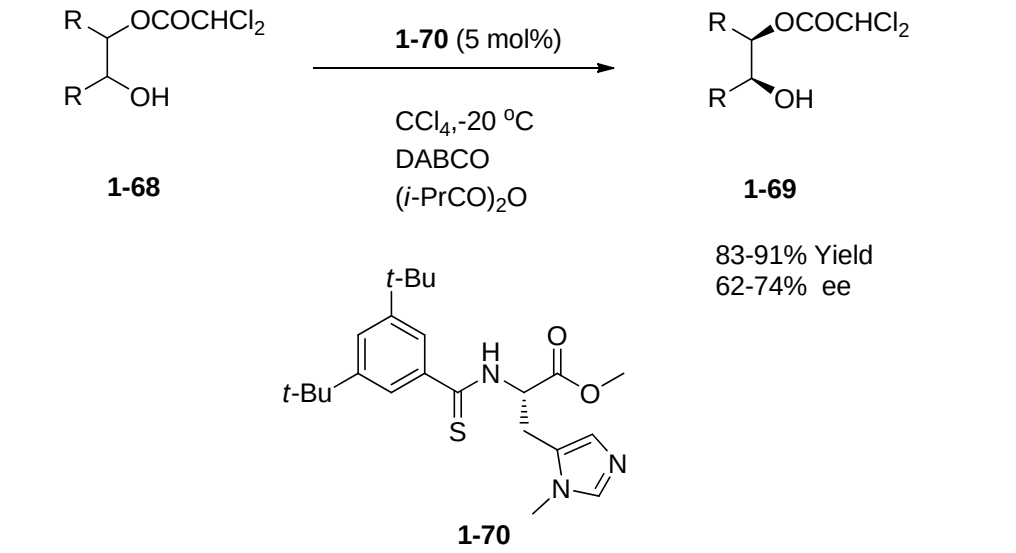
Scheme 1.15 Asymmetric aldol reactions of α-keto esters via DKR.

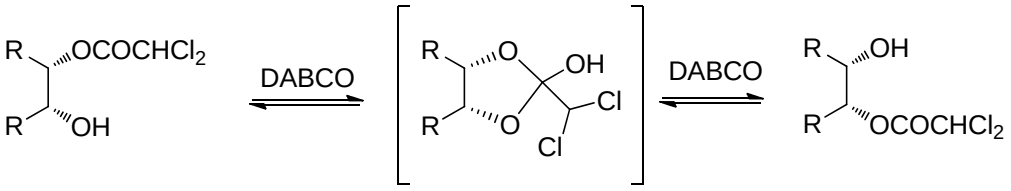
Recently, the Birman group disclosed an organocatalytic DKR reaction between azlactones **1-64** and bis(1-naphthyl)methanol **1-65**.[68] An array of chiral amidine-based catalysts was investigated, among which the best one was chiral benzotetramizole **1-66** (Scheme 1.16).



Scheme 1.16 Benzotetramizole catalyzed DKR of azlactones.

In 2010, Qu and co-workers showed that an enantioselective acylation catalyzed by **1-70**, in combination with a DABCO-mediated racemization of the substrates, led to the efficient DKR process (Scheme 1.17).[69] Both cyclic and acyclic *meso*-1,2-diol monodichloroacetates **1-68** could be transformed to the corresponding enantiomerically enriched diol esters **1-69**. The authors proposed the DKR on the basis of racemization of the unreacted **1-68** via an intramolecular chloroacetoxy migration process.



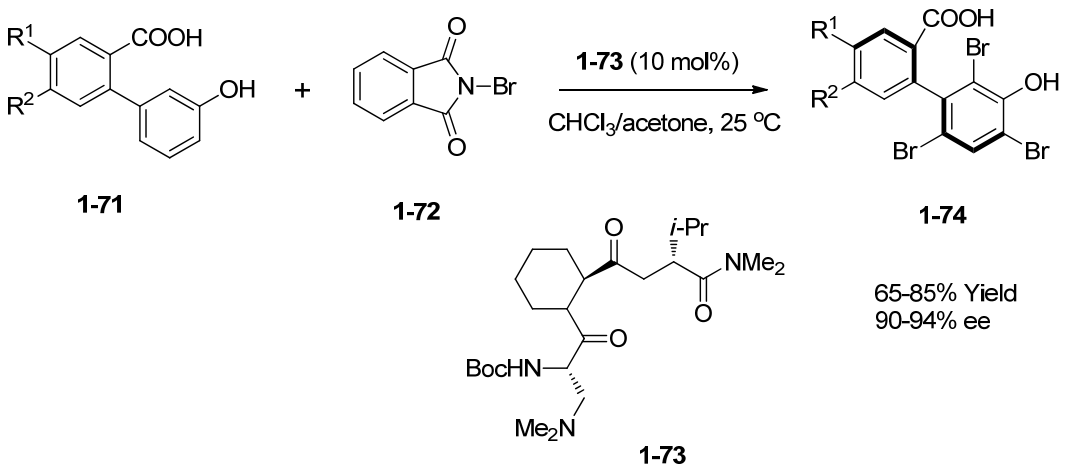


racemizing intramolecular transesterification

Scheme 1.17 Thioamide catalyzed DKR of *meso*-1,2-diol monodichloroacetates.

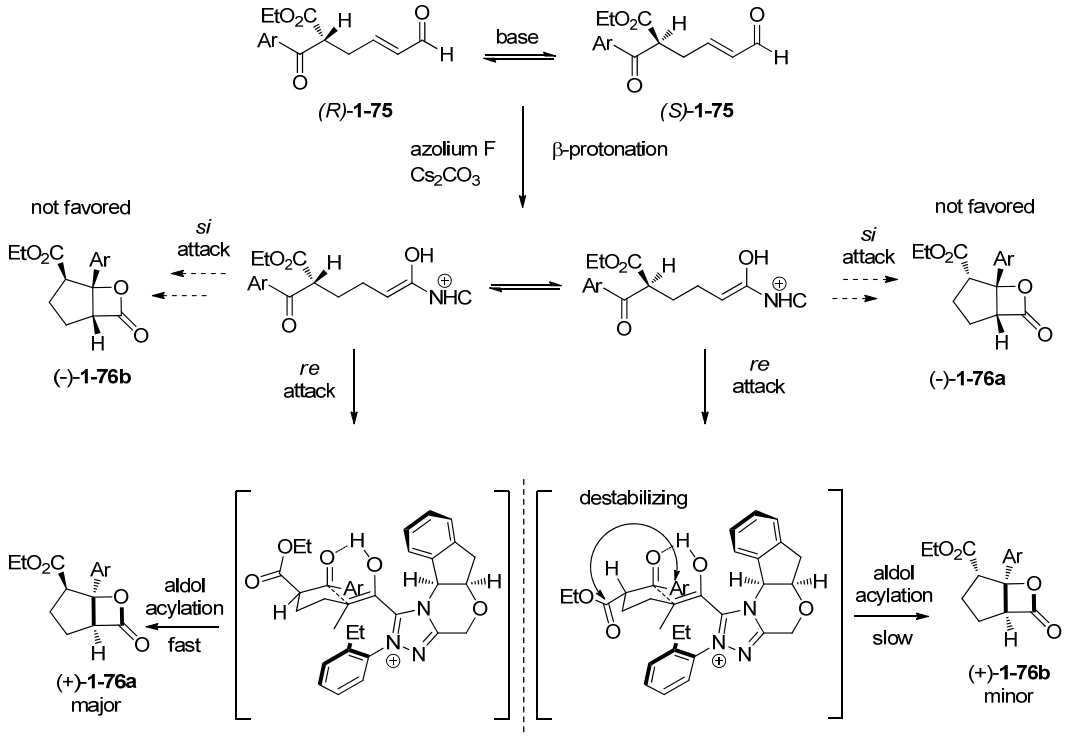
Recently, peptide-catalyzed asymmetric bromination of biaryl atropisomers via DKR was reported by Miller and co-workers.[70] The reaction proceeded via an atropisomer selective electrophilic aromatic substitution reaction using N-bromophthalimide. As shown in Scheme 1.18, the chiral brominated biaryl products **1-74** could be obtained with excellent enantioselectivites. In a rationale of the observed high enantioselectivity, it was proposed that starting atropisomers rapidly interconverted with a barrier to atropisomer interconversion estimated to be ~30 kcal mol^{-1} (for R^1=R^2=H), whereas the corresponding triply bromiated

product **1-74** exhibited much more restricted rotation.



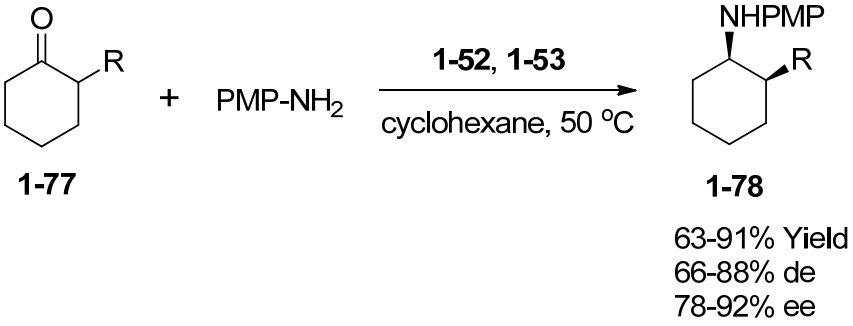
Scheme 1.18 Tripeptide catalyzed bromination via DKR.

Scheidt and co-workers described a new catalytic DKR with N-heterocyclic carbenes (NHC) as an efficient approach to synthesize highly substituted β-lactones.[71] As shown in Scheme 1.19, this reported process leveraged the basic conditions necessary to generate the NHC catalyst from the azolium salt to promote racemization of the β-keto ester substrates.



Scheme 1.19 NHC catalyzed dynamic kinetic resolution.

The scope of reductive amination of α-substituted ketones via DKR was extended by List and co-workers in 2010.[72] They showed substituted cyclohexanones **1-77** were ideal substrates for this reaction, and both aromatic and aliphatic substituents allow the corresponding products **1-78** to be obtained with high yields, diastereoselectivites and enantioselectivities (Scheme 1.20).



Scheme 1.20 Reductive aminations of cyclohexanones via DKR.

1.3 Project objectives

Dynamic kinetic resolution (DKR) is an efficient tool in asymmetric synthesis and at the outset of our work, there was no report on asymmetric Henry reaction via DKR.

The main aim of this project was to utilize DKR in Henry reaction between β-substituted α-keto ester and nitromethane to develop a diastereoselective and enantioselective process. Given the important synthetic applications of nitroalkane compounds, we anticipate our approach will provide easy access to a range of biologically important molecules, particularly those containing nitrogen atoms.

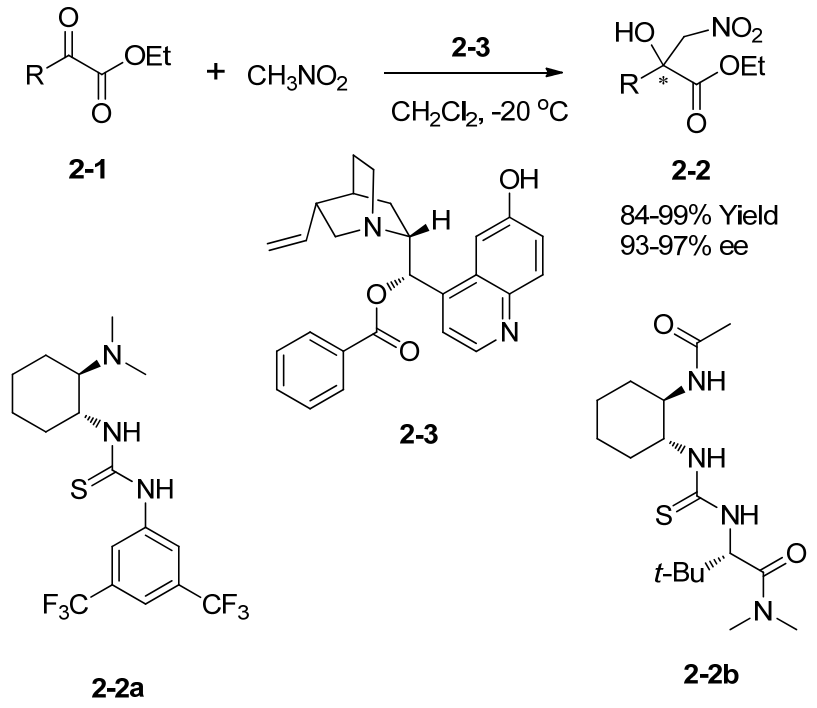
In chapter 2, diastereo- and enantioselective organocatalytic Henry reactions of β-substituted α-keto esters via DKR will be described in detail.

Chapter 2 Asymmetric organocatalytic Henry reactions of β–substituted α-keto esters via dynamic kinetic resolution.

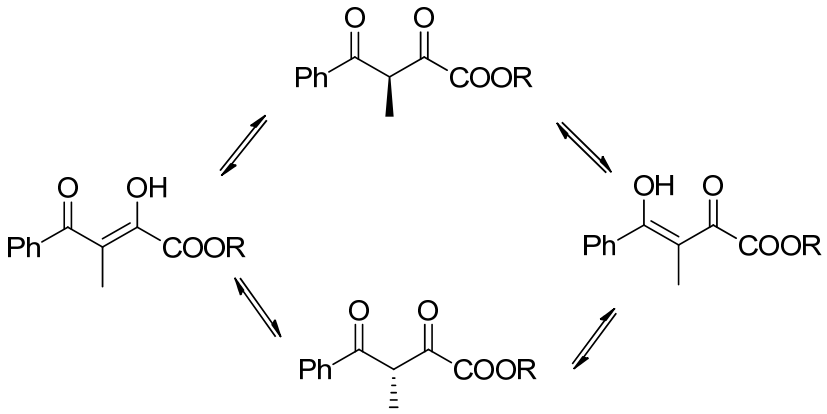
2.1 Introduction

Dynamic kinetic resolution (DKR) is a powerful approach to obtain highly enantioselective products from racemic starting materials, which avoids the shortages of kinetic resolution. DKR needs the *in situ* equilibration or racemization of the starting materials in the process and the products cannot racemize in such conditions. Theoretically, quantitative yield with 100% enantiomeric excess (ee) can be achieved.[46, 47] If the second chiral center is generated in the reaction, high enantioselectivity of one diastereoisomer is also possible[49]. Recently, increasing attentions has been focused on the acquisition of highly enantio-rich reactions via this effective resolution.

As a classic carbon–carbon bond formation reaction in organic chemistry, Henry reaction or nitroaldol reaction yield nitroalkances, which are important synthetic intermediates.[73] Typically, aldehydes react with nitromethane in the presence of chiral metal complexes or chiral phase transfer catalysts.[74-79] Deng and co-workers employed cinchona alkaloid derivatives as catalysts for the Henry reaction of nitroalkanes with ketoesters (Scheme 2.1).[80] Takemoto's group[81] and Jacobsen's group[82] also employed thiourea derivatives **2-4a** and **2-4b** as catalysts in the asymmetric Henry reaction. Prior to these reports, enantioselectivity of Henry reaction was very poor (<54% ee). [83]



Scheme 2.1 Asymmetric catalytic Henry reaction of α-keto esters.



Scheme 2.2 The racemization of selected β-substituted α-keto esters

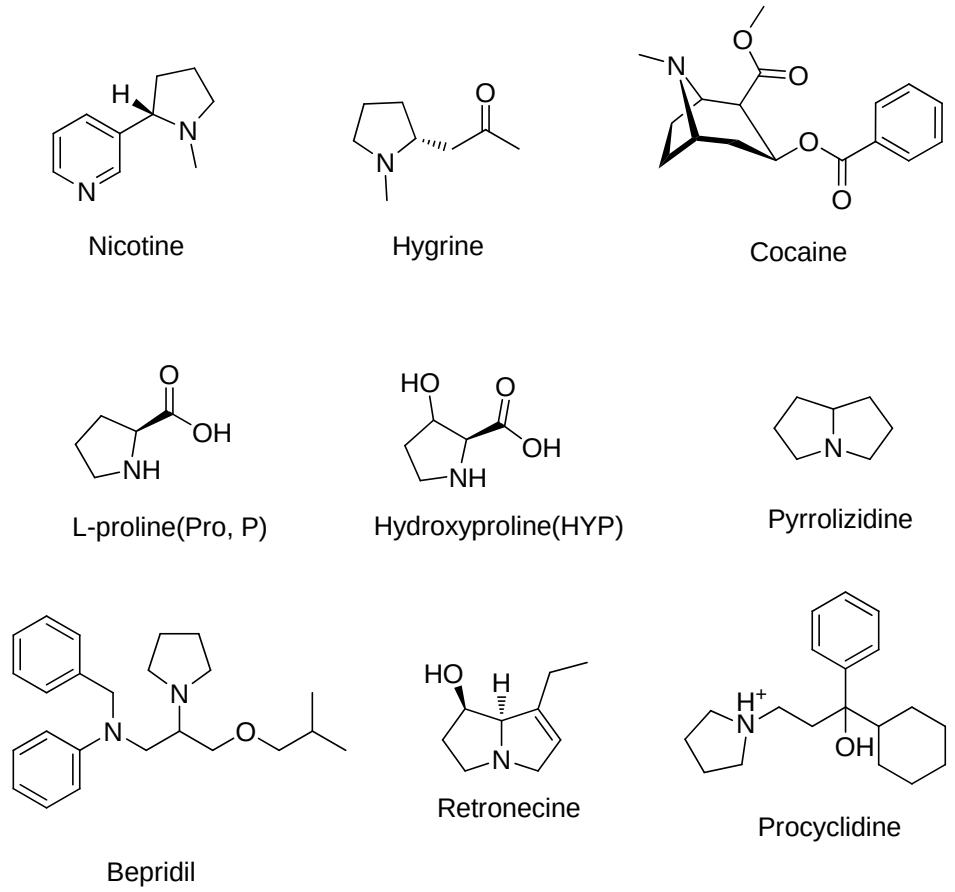
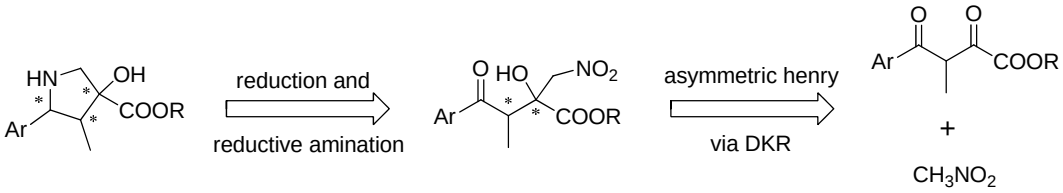


Figure 2.1 Some useful pyrrolidine derivatives.

Till now, the Henry reactions through DKR process still have not been reported. The ester group activates the ketone as an electron-withdrawing group. Thus, α-keto ester is more active for Henry reaction than normal ketone. With next to a configurationally labile stereogenic center, the activate carbonyl group could participate Henry reaction via DKR. With β-aroyl and methyl di-substituted, the α-keto ester could establish the fast *in situ* equilibrium of keto-enol tautomerism. Therefore, by using well-designed catalyst, DKR process could be achieved for good diastereoselectivies[67]. There exist two enol forms of this series of our selected substrates (Scheme 2.2)[84]. As shown in Scheme 2.3, due to the good

performance of cinchona alkaloid derivatives in asymmetric Henry reactions for α-keto esters[80] ,we intend to use corresponding derivatives to catalyze the desired asymmetric Henry reaction, of which the desired products could be converted to natural products and significant biologically molecules of pyrrolidine derivatives. Some useful pyrrolidine derivatives are shown in Figure 2.1.

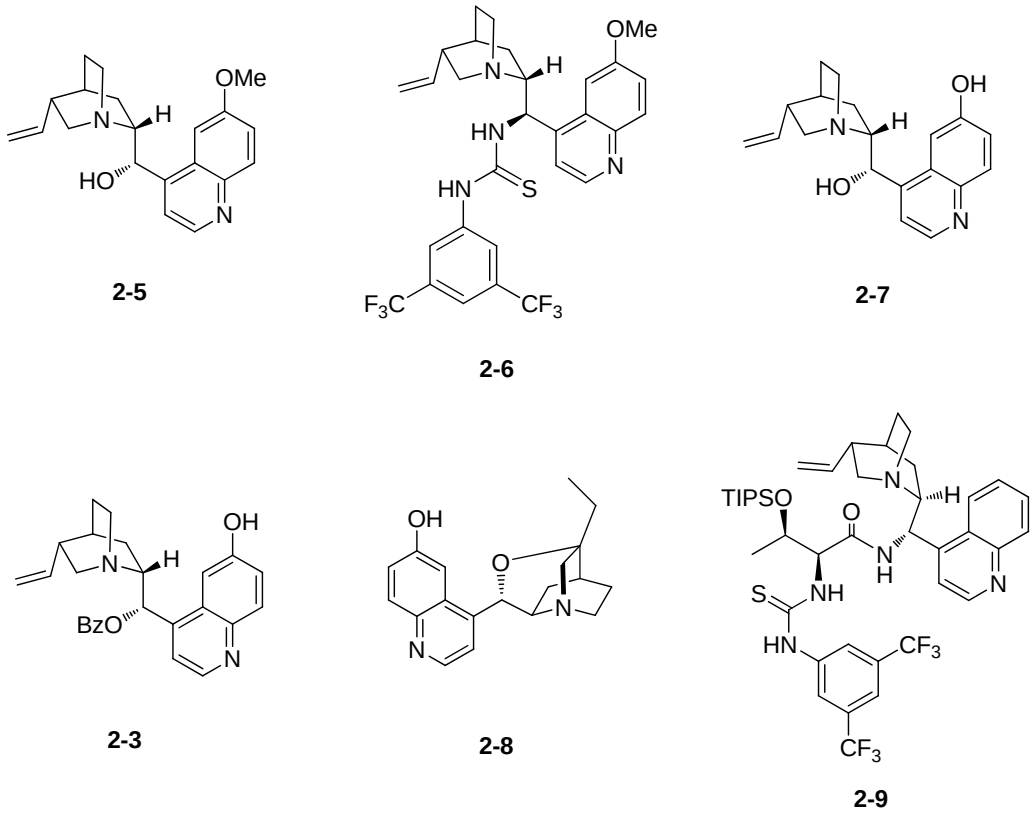


Scheme 2.3 Reaction design for the asymmetric Henry reaction via DKR.

2.2 Results and discussions

2.2.1 Reaction optimization

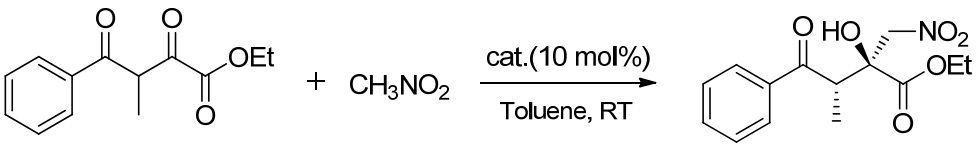
We selected the Henry reaction of β-substituted α-keto ester **2-10** and nitromethane as the model reaction, some bifunctional catalysts were screened (Scheme 2.4), and the results are shown in Table 2.1



Scheme 2.4 List of preliminary bifunction catalysts screened.

The thiourea bifunctional catalysts **2-6** (entry 2) and **2-9** (entry 6) were not effective. Whereas, C6'-OH cinchona alkaloid derivates catalysts **2-3** (entry 4) and **2-7** (entry 3) provided moderate enantioselectives, which indicated C6'-OH group is crucial in cinchona alkaloid scaffold for enantiocontrol in this reaction. β-ICD **2-8** (entry 5) with C6'-OH group only led to the product with 19% ee, demonstrating the importance of quinidine or quinine scaffold in stereochemical control.

Table 2.1 Preliminary catalyst screening for asymmetric Henry reaction[a].



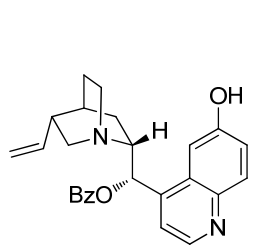
2-10 **2-11**

Entry	Catalyst	Time	Yield[b]	dr[c]	ee/%[d]
1	**2-5**	48h	52	>10:1	13
2	**2-6**	48h	55	>10:1	16
3	**2-7**	72h	63	>10:1	45
4	**2-3**	78h	61	>10:1	67
5	**2-8**	85h	49	>10:1	19
6	**2-9**	48h	70	>10:1	20

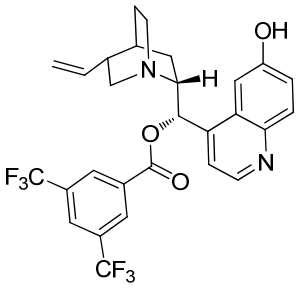
[a] Reactions were carried out using **2-10** (0.05 mmol), CH_3NO_2 (0.5 mmol), catalyst (0.005 mmol) in 0.125 ml Toluene at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC analysis.

With the demonstrated importance of the C6'-OH group in cinchona alkaloid derivatives, a comprehensive catalyst screening was performed (Scheme 2.5), and the results are summarized in Table 2.2

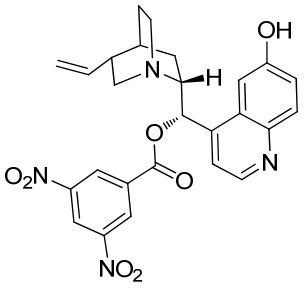
The electron withdrawing groups on aromatic ring (**2-12** and **2-13**) can increase enantioselectivity slightly (entry 2 and 3), however, longer reaction time was required. Esters **2-15** and **2-16** (entry 5 and 6) gave less satisfactory results. Therefore, we chose catalyst **2-3** (entry 1) as the best catalyst for the subsequent.



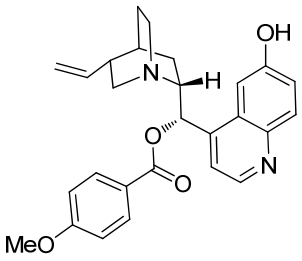
2-3



2-12



2-13



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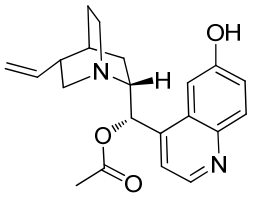
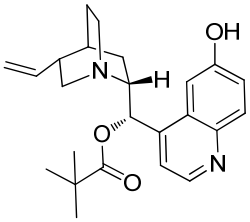


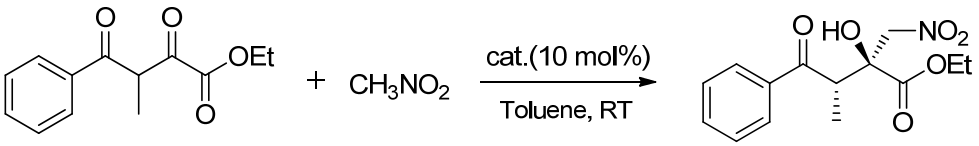
2-15



2-16

Scheme 2.5 List of comprehensive bifunctional catalysts screened

Table 2.2 Comprehensive catalyst screening for asymmetric Henry reaction[a].



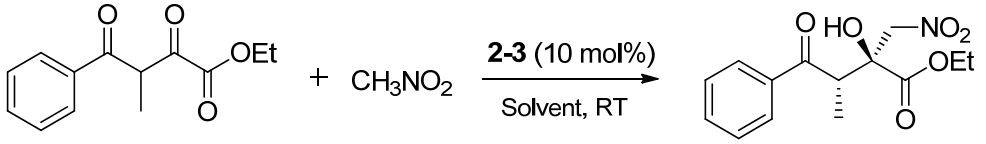
2-10 2-11

Entry	Catalyst	Time	Yield[b]	dr[c]	ee/%[d]
1	**2-3**	72h	61	>95:5	67
2	**2-12**	108h	55	>95:5	67
3	**2-13**	96h	53	>95:5	70
4	**2-14**	36h	68	>95:5	64
5	**2-15**	18h	79	>95:5	56

6	**2-16**	96h	42	>95:5	61

[a] Reactions were carried out using **2-10** (0.05 mmol), CH_3NO_2 (0.5 mmol), catalyst (0.005 mmol) in 0.125 ml solvent at room temperature. [b] Isolated yield. [c] Determined by ^{1}HNMR analysis. [d] Determined by chiral HPLC analysis.

Table 2.3 Solvent screening for asymmetric Henry reaction[a].



2-10 **2-11**

Entry	Solvent	Time	Yield[b]	dr[c]	ee/%[d]
1	THF	72h	72	>95:5	67
2	CH_2Cl_2	24h	51	>95:5	59
3	$CHCl_3$	24h	59	>95:5	67
4	Acetone	72h	70	>95:5	66
5	Toluene	72h	61	>95:5	67
6	Et_2O	96h	52	>95:5	66
7	Dioxane	80h	56	>95:5	67
8	CH_3CN	60h	33	>95:5	51
9	CH_3OH	96h	-	-	-
10	CH_3NO_2	36h	85	>95:5	56
11[e]	Toluene	72h	70	>95:5	73
12[f]	Toluene	72h	76	>95:5	76
13[g]	Toluene	72h	75	>95:5	75

14[f]	CH_2Cl_2	60h	86	>95:5	68
15[f]	Xylene	72h	82	>95:5	75

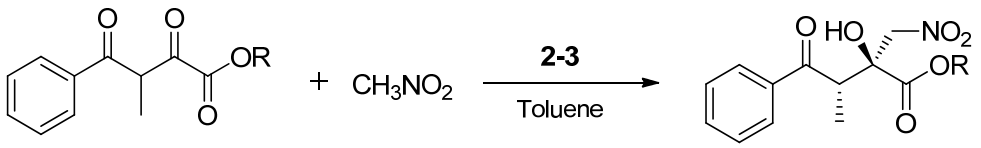
[a] Reactions were carried out using **2-10** (0.05 mmol), CH_3NO_2 (0.5 mmol), **2-3** (0.005 mmol) in 0.125 ml solvent at room temperature. [b] Isolated yield. [c] Determined by ^{1}HNMR analysis. [d] Determined by chiral HPLC analysis. [e] With 3Å molecular sieve. [f] With 4Å molecular sieve. [g] With 5Å molecular sieve.

We performed the Henry reaction between **2-10** and nitromethane catalyzed by bifunctional cinchona alkaloid **2-3** in a number of common organic solvents, and the results are summarized in Table 2.3. When the Henry reaction carried out in protic solvent CH_3OH (entry 9), messy results were obtained. For aprotic solvents, the decrease of solvent polarity favored the enantioselectivity of the Henry product **2-11**. Addition of 4Å molecular sieve to toluene (entry 12) led to the best result of 76% yield and 76% ee, which seems to indicate the importance of hydrogen bonding interactions in our reaction system.

Further optimizations on reaction temperature, catalyst loading and different esters were performed (Table 2.4). Under the optimized reaction conditions at 0 ^oC, the increased ee of 84% was obtained of Henry product **2-11** (entry 3). Decreased the concentration to 0.2 M slightly decreased the enantioselectivity as well prolong the reaction apparently (entry 4). In the presence of 5 mol % **2-3**, **2-11** was obtained with decreased ee of 73% (entry 5). From entry 1 and 6 - 8, a significant improvement of enantioselectity was observed by replaced R group of substrate from methyl ester to *t*-Bu ester. Thus, the best condition was 0.4 M

concentration at 0 °C with 10% catalyst loading and 4Å molecular sieve in toluene and using *t*-Bu esters as substrates.

Table 2.4 Optimization of reaction temperature, catalyst loading and different esters[a].



2-10 **2-11**

Entry	R	Time	Yield[b]	dr[c]	ee/%[d]
1	Et	48h	76	>95:5	76
2[e]	Et	72h	73	>95:5	84
3[f]	Et	96h	75	>95:5	82
4[g]	Et	96h	80	>95:5	75
5[h]	Et	96h	80	>95:5	73
6[e]	Me	96h	79	>95:5	73
7[e]	*i*-Pr	68h	95	>95:5	82
8[e]	*t*-Bu	60h	97	>95:5	86

[a] Reactions were carried out using **2-10** (0.05 mmol), CH_3NO_2 (0.5 mmol), **2-3** (0.005 mmol) in 0.125 ml Toluene with 10 mg 4Å molecular sieve. [b] Isolated yield. [c] Determined by ^{1}HNMR analysis. [d] Determined by chiral HPLC analysis. [e] The temperature was 0 °C [f] The temperature was -10 °C [g] The concentration was 0.2M. [h] Catalyst loading was 5 mol%.

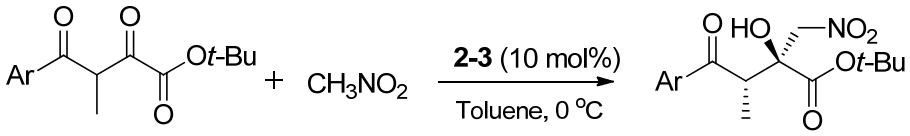
2.2.2 Substrate scope

With the established best reaction conditions, we next studied the scope of

the asymmetric Henry reaction via DKR with an array of different β-substituted α-keto esters (Table 2.5).

Consistently high diastereoselectivities and enantioselectivities were observed for a wide range of β-aromatic methyl di-substituted α-keto esters (entries 1 and 3-13). In this substrate scope, we observed good enantioselectivities for β-methyl substituate α-keto *t*-butyl esters with around 80% ee for all the relevant entries (entry 1 and 3-13). All the reactions proceeded with 80% ee besides the one with ethyl group as a β-substituent, ee dropped to 55% (entry 2). In particular, high diastereoselectivities (between 28:1 to >99:1) were attainable for β-methyl substituted α-ketoester substrates (entry 1 and 3-13). With ethyl group as a β-substituent, diastereoselectivity dropped to 18:1 (entry 2).

Table 2.5 Substrate scope of **2-3** catalyzed asymmetric Henry reaction via DKR[a].



2-10a - 2-10n **2-11a - 2-11n**

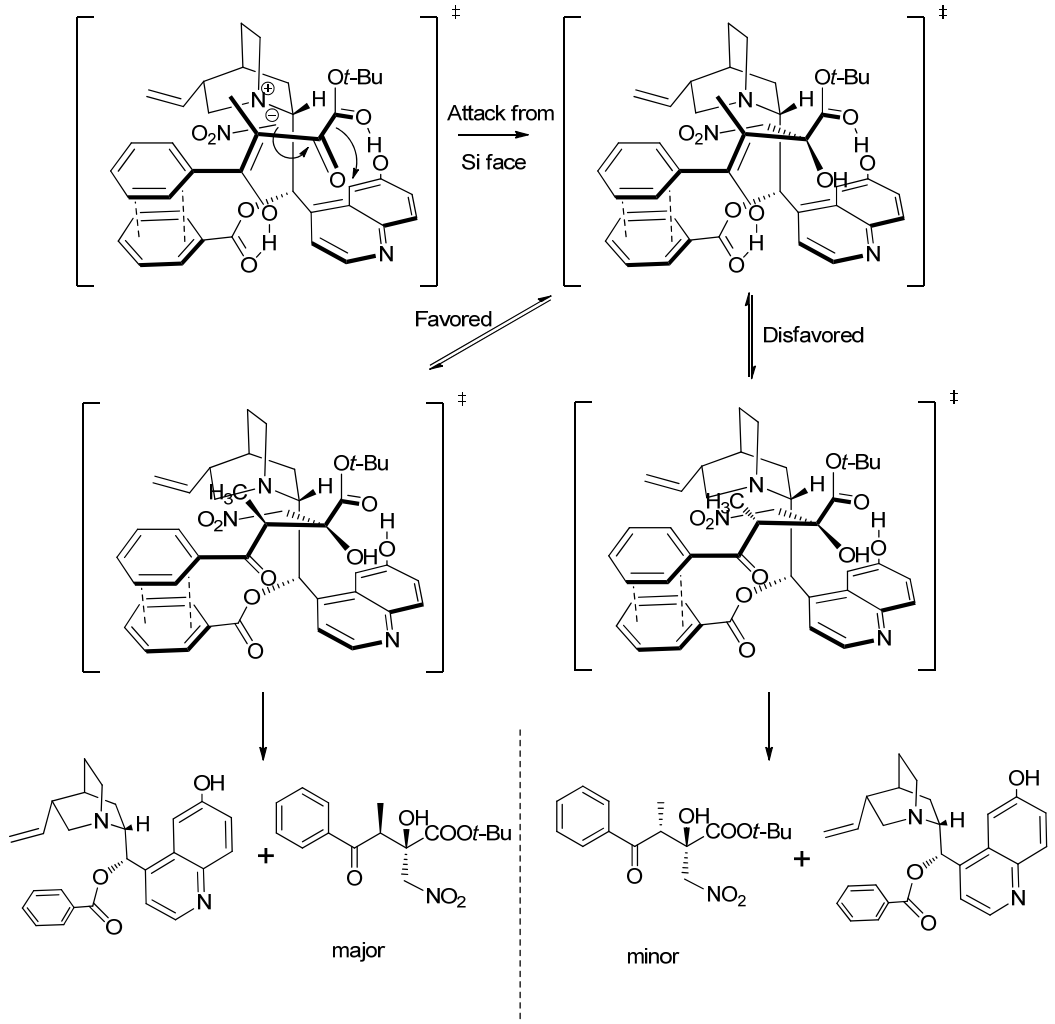
Entry	**2-10**	Ar	**2-11**	Time	Yield[b]	dr[c]	ee/%[d]
1	**2-10a**	Ph	**2-11a**	48h	97	53:1	86
2[e]	**2-10b**	Ph	**2-11b**	72h	89	18:1	55
3	**2-10c**	3-ClC_6H_4	**2-11c**	72h	96	28:1	85
4	**2-10d**	3-$MeOC_6H_4$	**2-11d**	48h	96	>99:1	81
5	**2-10e**	3-$CF_3C_6H_4$	**2-11e**	48h	90	37:1	81

6	**2-10f**	4-ClC_6H_4	**2-11f**	72h	95	70:1	83
7	**2-10g**	4-BrC_6H_4	**2-11g**	72h	93	>99:1	81
8	**2-10h**	4-MeC_6H_4	**2-11h**	48h	95	>99:1	84
9	**2-10i**	4-$MeOC_6H_4$	**2-11i**	60h	96	>99:1	80
10	**2-10j**	4-$BnOC_6H_4$	**2-11j**	72h	95	52:1	82
11	**2-10k**	2-$MeOC_6H_4$	**2-11k**	72h	88	>99:1	77
12	**2-10l**	1-Naphenyl	**2-11l**	36h	91	>99:1	88
13	**2-10m**	2-thiophenyl	**2-11m**	24h	96	56:1	77

[a] Reactions were carried out using **2-10** (0.05 mmol), CH_3NO_2 (0.5 mmol), **2-3** (0.005 mmol) in 0.125 ml Toluene with 10 mg 4Å molecular sieve at 0 ^oC. [b] Isolated yield. [c] Determined by ^1HNMR analysis. [d] Determined by chiral HPLC analysis. [e] Ethyl as the β-substituted group.

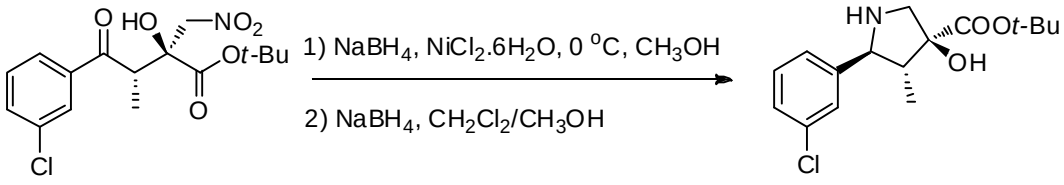
2.2.3 Proposed transition state models

To offer a stereochemical reasoning, transition state model as shown in Scheme 2.6. The tertiary amine moiety of **2-3** first deprotonates the α-proton of nitromethane to generate an ammonium ion and carbanion ion pair. At the same time, the enol form of substrate α-ketoester interacts with catalyst **2-3** through hydrogen bonding and maybe π-π interaction. The subsequent attack of carbanion at the carbonyl group from Si face leads to the formation of major enantiomer. Due to the steric hindrance of quinuclidine ring, the *4S* configuration was favored when the enol transforms to ketone of keto-enol tautomerism.



Scheme 2.6 Proposed transition states models.

2.2.4 Product manipulation



2-11c **2-17**

Scheme 2.7 Coversion of **2-11c** to pyrrolidine derivative **2-17**.

The Henry product can be easily converted to pyrrolidine derivative via reductive amination (Scheme 2.7). Treated with $NaBH_4$ and $NiCl_2{\cdot}6H_2O$, **2-11c**

was converted to **2-17** in 75% yield without losing enantioselectivity.

2.3 Conclusion

In summary, the first highly diastereo- and enantioselective organocatalytic Henry reaction between β-substituted α-keto esters and nitromethane catalyzed by cinchona alkaloid derivatives via DKR was developed. The resulting compounds could be readily converted to biologically important pyrrolidine derivatives.

2.4 Experimental section

2.4.1 General information

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or DPX300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Flash chromatography separation was performed on Merck 60 (0.040 – 0.063 mm) mesh silica gel.

The enantiomeric excesses of products were determined by chiral-phase HPLC analysis, using a Daicel Chiralcel AD-H column (250 x 4.6 mm), or Daicel

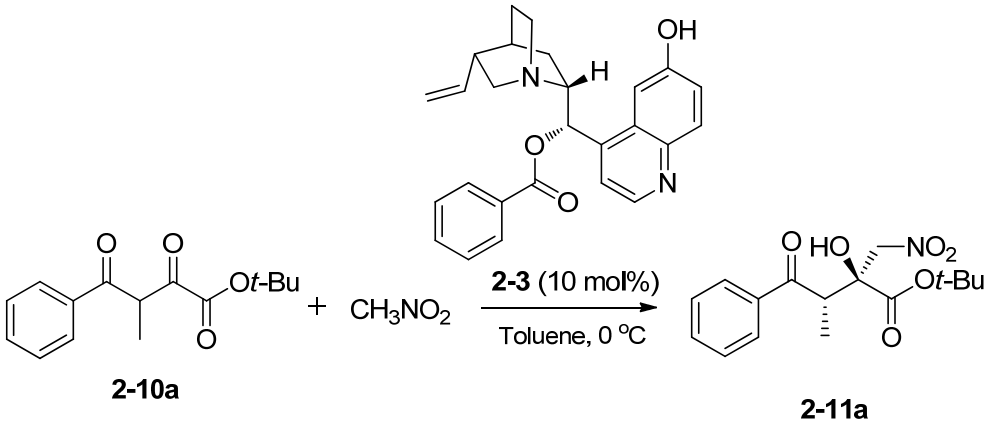
Chiralpak IC column or ID column (250 x 4.6 mm). The diastereomeric ratios of products were determined by crude ^{1}H NMR on a Bruker ACF300 or DPX300 (300 MHz) or AMX500 (500 MHz) spectrometer.

Catalysts 2-5 was commercial available, **2-3**, **2-7**, **2-12** to **2-16** were prepared according to the literature procedures[73,85]. Catalysts **2-6**[86], **2-8**[87], **2-9**[88] were prepared following the literature procedures. Substrate **2-10**[89] was prepared according to the literature procedures. For all the Henry reaction products **2-11** and **2-11a-m**, the two diastereomers were cannot separated.

The absolute configuration of **2-11c** was assigned by X-ray crystallographic analysis, and configurations of other Henry reaction products were assigned by analogy. Due to the quite high diastereoselectivies of Henry reaction products **2-11a** to **2-11m**, the minor diastereomers are unnecessary to separate out, which are also cannot be separated by column in experiments.

2.4.2 Representative procedure for the Henry reaction

Asymmetric Henry reaction of *tert*-butyl 3-methyl-2,4-dioxo-4-phenylbutanoate

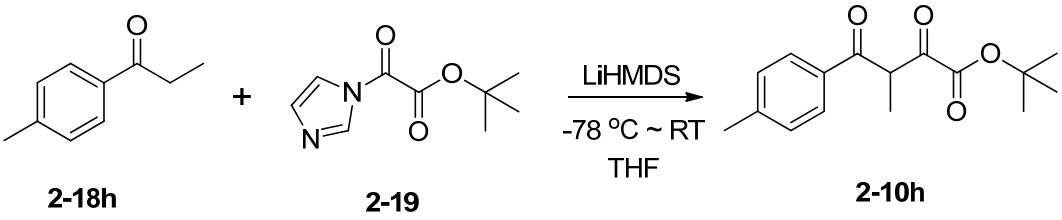


2-10a **2-11a**

To a solution of *tert*-butyl 3-methyl-2,4-dioxo-4-phenylbutanoate **2-10a** (13.1 mg, 0.05 mmol), nitromethane (31 mg, 0.5 mmol) and 4Å molecular sieve (10 mg) in toluene (0.125 mL) was added **2-3** (2.2 mg, 0.005 mmol). The resulting mixture was stirred for 48h at 0 ^{o}C. After removal of the solvent, the residue was purified by flash column chromatography (hexane/EtOAc = 8/1 as an eluent) to afford Henry product **2-11a** (15.7 mg, 97% yield) as a white solid. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude mixture, and the enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

2.4.3 Representative procedure for synthesizing the substrates.

Synthesis of *tert*-butyl-3-methyl-2,4-dioxo-4-(p-tolyl)butanoate

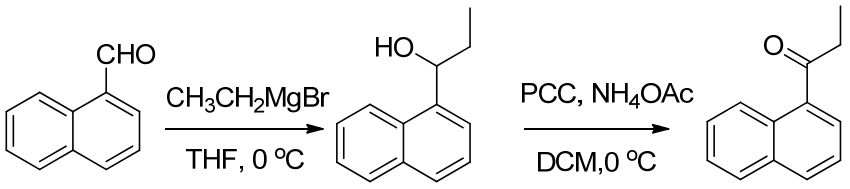


To a solution of **2-18h** (0.48 mL, 3 mmol) in THF (10 mL) was slowly added a solution of lithium bis(trimethylsilyl)amide (1 mol/L in THF, 4.5 mL, 4.5 mmol) in THF (10 mL) via syringe under nitrogen atmosphere at -78 ^{o}C (dry ice/acetone bath). After stirred for 0.5 h, a solution of imidazol-1-yl-oxo-acetic acid *t*-butyl ester **2-19** (588 mg, 3 mmol) in THF (10 mL) was added via syringe. After that

reaction mixture was allowed to warm to room temperature. The obtained mixture was stirred for overnight then saturated solution of NH_4Cl was added to quench the reaction. Then added 20 mL EA and 15 mL H_2O, the organic layer was separated, dried over anhydrate Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography (hexane/EtOAc = 12/1 as an eluent) to afford product (0.59 g, 71% yield) as a white solid.

2.4.4 Representative Method of synthesizing ketone intermediate (2-18)

Synthesis of 1-(naphthalen-1-yl)propan-1-one



2-21l **2-20l** **2-18l**

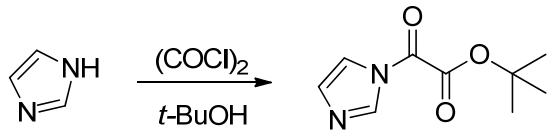
To the solution of 1-naphthaldehyde **2-21l** (0.80 mL, 5.1 mmol) of THF (20 mL) slowly added the fresh prepared CH_3CH_2MgBr (5.5 mmol) solution of THF at 0 ^oC. After stirring for 5 h, saturated NH_4Cl solution (20 mL) and EA (25 mL) was added to quench the reaction. The aqueous layer was extracted by EA (15 mL x 3). Then combined separated organic layer wash by H_2O (20 mL x 2) and brine (20 mL) and dried by Na_2SO_4. After removal of solvent by reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc = 20/1 as an eluent) to afford product alcohol **2-20l** (0.52 g, 54% yield) as a slight yellow

oil.

To the solution of 1-(naphthalen-1-yl)propan-1-ol **2-20l** (0.52 g, 2.8 mmol) of DCM (20 mL), slow added 4Å Molecular sieve (1.6 g) and NH_4OAc (0.56 g, 6.8 mmol), and then slowly added PCC (0.90 g, 4.1 mmol) to the mixture at 0 ^oC with continued stirring. After overnight stirring, added DCM (50 ml) to dilute, the resulted mixture was filtered and the filtrate was washed by H_2O (20 mL x 3) and brine (20 mL) and dried by Na_2SO_4, after the removal of solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc = 15/1 as an eluent) to afford product ketone **2-18l** (0.34 g, 65% yield) as a colorless oil.

2.4.5 Procedure for synthesizing intermediate *t*-butyl ester (2-19).

Synthesis of *tert*-butyl-2-(1H-imidazol-1-yl)-2-oxoacetate (2-19).



2-19

tert-Butyl alcohol (0.28 mL, 3 mmol) was added in one batch to a stirred solution of oxalyl chloride (0.27 mL, 3 mmol) in Et_2O (25 mL) at 0 ^oC under N_2. After 1 h, a solution of imidazole (0.61 g, 9 mmol) in EA (10 mL) was added over 15 min. After an additional 1 h, the stirred reaction mixture was filtered, and the imidazole hydrochloride precipitate was washed with Et_2O (20 mL). The solvent was then removed under reduced pressure from the filtrate and washings. The

residual slight green oil, 536 mg, was checked by 'H NMR analysis pure enough without further purification, which was referred to literature procedure[90] with improvement of our group.

2.4.6 X-ray crystallographic analysis of 2-11c

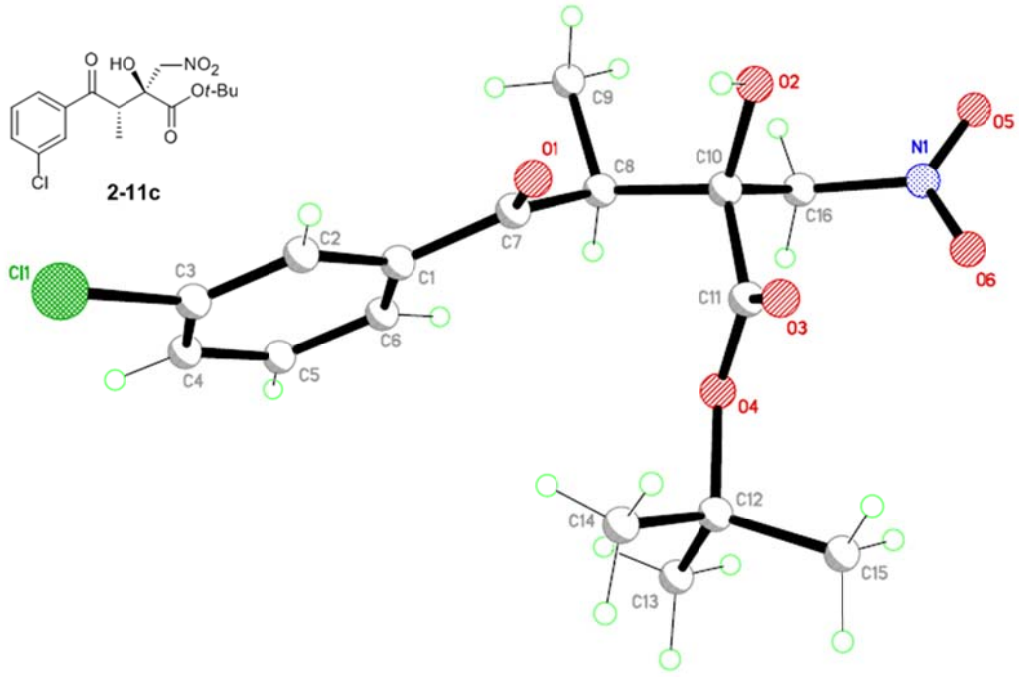


Figure 2.2 ORTEP structure of Henry product 2-11c

Table Crystal data

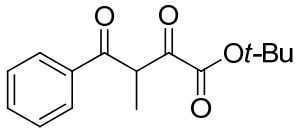
Identification code	c011
Empirical formula	$C_{16}H_{20}ClNO_6$
Formula weight	357.78
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 5.7597(4) Å α= 90°.
	b = 17.0971(11) Å β= 90°.
	c = 17.4304(12) Å γ= 90°.
Volume	1716.4(2) $Å^3$
Z	4
Density (calculated)	1.385 Mg/m^3
Absorption coefficient	0.254 mm^{-1}
F(000)	752
Crystal size	0.40 x 0.24 x 0.12 mm^3
Theta range for data collection	1.67 to 27.48°.
Index ranges	-7<=h<=7, -22<=k<=18, -22<=l<=22
Reflections collected	12203
Independent reflections	3943 [R(int) = 0.0468]
Completeness to theta = 27.48°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9702 and 0.9053

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3943 / 0 / 222
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.0933
R indices (all data)	R1 = 0.0501, wR2 = 0.0968
Absolute structure parameter	0.02(6)
Largest diff. peak and hole	0.260 and -0.199 e.Å^{-3}

2.4.7 Analytical data of substrates

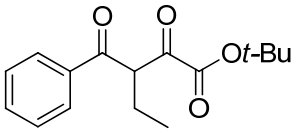
tert-butyl-3-methyl-2,4-dioxo-4-phenylbutanoate **(2-10a)**



2-10a

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 - 7.96 (m, 2H), 7.64 - 7.57 (m, 1H), 7.56 - 7.45 (m, 2H), 4.96 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.41 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.08, 191.62, 159.32, 135.17, 133.73, 128.90, 128.67, 84.54, 51.00, 27.55, 12.69.; HRMS (ESI) *m/z* calcd for $C_{15}H_{18}O_4$ $[M+Na]^+$ 285.1097, found 285.1108.

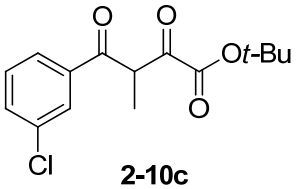
tert-butyl-3-benzoyl-2-oxopentanoate **(2-10b)**



2-10b

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 -7.97 (m, 2H), 7.68 – 7.56 (m, 1H), 7.53 – 7.48 (m, 2H), 4.87 (q, *J* = 7.3 Hz, 1H), 2.11 – 1.86 (m, 2H), 1.41 (s, 9H), 0.97 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.97, 190.98, 159.57, 135.94, 133.65, 128.87, 128.63, 84.57, 57.81, 27.56, 21.43, 12.01.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4$ $[M+Na]^+$ 299.1254, found 299.1258.

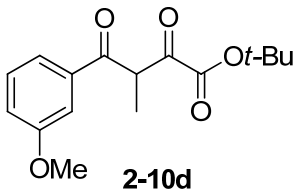
tert-butyl-4-(3-chlorophenyl)-3-methyl-2,4-dioxobutanoate **(2-10c)**



2-10c

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (t, *J* = 1.8 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.63 – 7.55 (m, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 4.90 (q, *J* = 7.1 Hz, 1H), 1.44 (s, 9H), 1.42 (d, *J* = 8.6 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.78, 191.08, 159.34, 136.79, 135.32, 133.66, 130.25, 128.71, 126.75, 84.80, 77.42, 77.00, 76.58, 50.96, 27.61, 12.63.; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}ClO_4$ $[M+Na]^+$ 319.0708, found 319.0712.

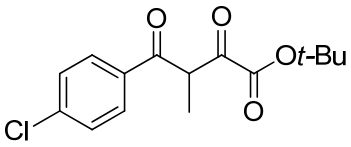
tert-butyl-4-(3-methoxyphenyl)-3-methyl-2,4-dioxobutanoate **(2-10d)**



2-10d

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.93 (q, *J* = 7.1 Hz, 1H), 3.86 (s, 3H), 1.44 (d, *J* = 7.2Hz, 3H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.85, 191.61, 160.06, 159.35, 136.55, 129.88, 121.29, 120.27, 112.84, 84.58, 55.47, 51.15, 27.59, 12.78.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_5$ $[M+Na]^+$ 315.1203, found 315.1205.

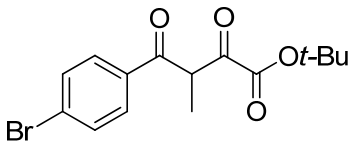
tert-butyl-4-(4-chlorophenyl)-3-methyl-2,4-dioxobutanoate **(2-10f)**



2-10f

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 4.90 (q, *J* = 7.1 Hz, 1H), 1.43 (s, 9H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.81, 191.22, 159.37, 140.31, 133.57, 130.07, 129.27, 84.74, 50.91, 27.60, 12.64.; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}ClO_4$ $[M+Na]^+$ 319.0708, found 319.0716.

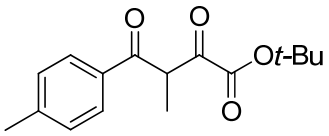
tert-butyl-4-(4-bromophenyl)-3-methyl-2,4-dioxobutanoate **(2-10g)**



2-10g

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 4.89 (q, *J* = 7.1 Hz, 1H), 1.43 (s, 9H), 1.42 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.00, 191.19, 159.36, 133.98, 132.27, 130.14, 129.05, 84.75, 50.88, 27.61, 12.63.; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}{}^{79}BrO_4$ $[M+Na]^+$ 363.0202, found 363.0204; $C_{15}H_{17}{}^{81}BrO_4$ $[M+Na]^+$ 365.0202, found 365.0183.

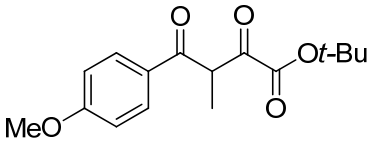
tert-butyl-3-methyl-2,4-dioxo-4-(p-tolyl)butanoate **(2-10h)**



2-10h

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.94 (q, *J* = 7.1 Hz, 1H), 2.43 (s, 3H), 1.43 (d, *J* = 1.6 Hz, 3H), 1.42 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.72, 191.83, 159.43, 144.74, 132.73, 129.61, 128.84, 84.49, 50.99, 27.61, 21.70, 12.78.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4$ $[M+Na]^+$ 299.1254, found 299.1251.

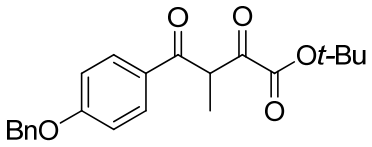
tert-butyl-4-(4-methoxyphenyl)-3-methyl-2,4-dioxobutanoate **(2-10i)**



2-10i

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 4.92 (q, *J* = 7.1 Hz, 1H), 3.89 (s, 3H), 1.43 (d, *J* = 5.4 Hz, 3H), 1.42 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.63, 191.89, 164.02, 159.46, 131.08, 128.14, 114.10, 84.44, 55.55, 50.80, 27.61, 12.86.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_5$ $[M+Na]^+$ 315.1203, found 315.1198.

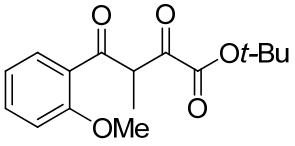
tert-butyl-4-(4-(benzyloxy)phenyl)-3-methyl-2,4-dioxobutanoate **(2-10j)**



2-10j

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.34 – 7.44 (m, 4H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 5.14 (s, 2H), 4.92 (q, *J* = 7.1 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 3H), 1.41 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.57, 191.77, 163.07, 159.31, 135.90, 130.99, 128.60, 128.18, 127.36, 114.86, 84.30, 70.10, 50.70, 27.48, 12.74.; HRMS (ESI) *m/z* calcd for $C_{22}H_{25}O_5$ $[M+Na]^+$ 369.1697, found 369.1699.

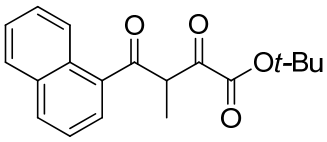
tert-butyl-4-(2-methoxyphenyl)-3-methyl-2,4-dioxobutanoate **(2-10k)**



2-10k

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.89 (q, *J* = 7.1 Hz, 1H), 3.86 (s, 3H), 1.46 (s, 9H), 1.40 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.08, 192.11, 159.62, 158.37, 134.62, 131.50, 125.56, 121.13, 111.58, 84.09, 55.82, 55.16, 27.65, 12.33.HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_5$ $[M+H]^+$ 293.1384, found 293.1384.

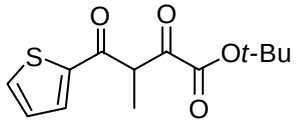
tert-butyl-3-methyl-4-(naphthalen-1-yl)-2,4-dioxobutanoate **(2-10l)**



2-10l

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.89 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.61 – 7.52 (m, 3H), 5.07 (q, *J* = 7.1 Hz, 1H), 1.47 (d, *J* = 7.1 Hz, 3H), 1.43 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.41, 177.42, 163.26, 133.47, 128.42, 128.33, 128.30, 126.75, 125.66, 124.30, 84.53, 54.22, 27.60, 12.60.; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}NO_4$ $[M+Na]^+$ 335.1254, found 335.1254.

tert-butyl-3-methyl-2,4-dioxo-4-(thiophen-2-yl)butanoate **(2-10m)**

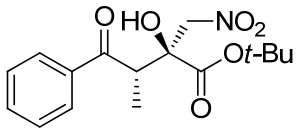


2-10m

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.71 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.18 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.76 (q, *J* = 7.1 Hz, 1H), 1.49 (d, *J* = 7.1 Hz, 3H), 1.44 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.94, 190.06, 159.25, 142.55, 134.82, 133.04, 128.41, 84.74, 52.66, 27.61, 13.12.; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_4S$ $[M+Na]^+$ 291.0662, found 291.0667.

2.4.8 Analytical data of products

(2S,3S)-*tert*-butyl-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxo-4-phenylbutanoate **(2-11a)**

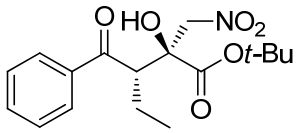


2-11a

A white solid; diastereomeric ratio is 53:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.64 - 7.57 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 4.81 (dd, *J* = 47.7, 12.8, 2H), 4.38 (s, 1H), 3.97 (q, *J* = 7.3 Hz, 1H), 1.38 (s, 9H), 1.34 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.27, 170.69, 133.89, 128.87, 128.53, 84.37, 78.48, 76.47, 44.06, 27.52, 12.66.; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_6$ $[M+Na]^+$ 346.1261, found 346.1262; the ee value of the major isomer was 86%, (determined by Daicel Chiralpak IC column, λ = 254 nm, 5%

i-PrOH/hexanes, flow rate = 1.0 mL/min, t(minor) = 43.69 min, t(major) = 48.50 min).

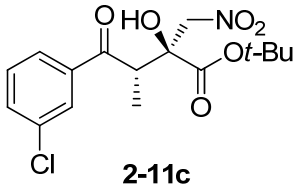
(2S,3S)-*tert*-butyl-3-benzoyl-2-hydroxy-2-(nitromethyl)pentanoate **(2-11b)**



2-11b

A white solid; diastereomeric ratio is 18:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.63 (dd, *J* = 10.4, 4.1 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 5.01 – 4.82 (m, 2H), 4.20 (s, 1H), 3.87 (q, *J* = 10.5 Hz, 1H), 1.95 – 1.83 (m, 2H), 1.40 (s, 9H), 0.87 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.19, 170.73, 128.77, 128.58, 84.62, 78.20, 76.51, 51.22, 27.51, 21.55, 12.38.; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_6$ $[M+Na]^+$ 360.1418, found 360.1410; the ee value of the major isomer was 55%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(minor) = 14.70 min, t(major) = 16.22 min).

(2S,3S)-*tert*-butyl-4-(3-chlorophenyl)-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxo butanoate **(2-11c)**

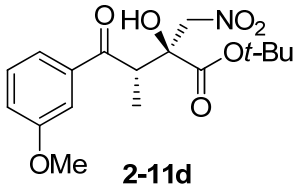


2-11c

A white solid; diastereomeric ratio is 28:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (t,

J = 1.8 Hz, 1H), 7.89 – 7.80 (m, 1H), 7.63 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 4.87 (dd, *J* = 29.5, 13.0 Hz, 2H), 4.31 (s, 1H), 3.94 (q, *J* = 7.3 Hz, 1H), 1.45 (s, 9H), 1.37 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.93, 170.54, 137.58, 135.26, 133.76, 130.19, 128.57, 126.62, 84.68, 78.26, 76.39, 44.47, 27.57, 12.63.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}ClNO_6$ $[M+Na]^+$ 380.0871, found 380.0878; the ee value of the major isomer was 85%, (determined by Daicel Chiralpak IC column, λ = 254 nm, 5% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(minor) = 28.36 min, t(major) = 36.52 min).

(2S,3S)-*tert*-butyl-2-hydroxy-4-(3-methoxyphenyl)-3-methyl-2-(nitromethyl)-4-oxobutanoate **(2-11d)**

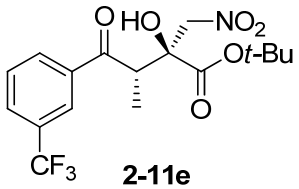


2-11d

A white solid; diastereomeric ratio is >99:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.18 – 7.12 (m, 1H), 4.82 (dd, *J* = 48.7, 12.8 Hz, 2H), 4.34 (s, 1H), 3.93 (q, *J* = 7.3 Hz, 1H), 3.86 (s, 3H), 1.39 (s, 9H), 1.33 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.66, 160.06, 129.83, 121.08, 120.23, 112.92, 84.40, 78.50, 76.47, 55.49, 44.35 27.57, 12.72.; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_7$ $[M+Na]^+$ 376.1367, found 376.1369; the ee value of the major isomer was 81%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min,

t(minor) = 25.63 min, t(major) = 33.49 min).

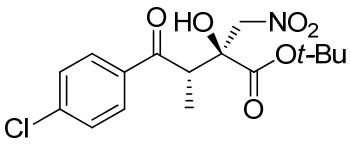
(2S,3S)-*tert*-butyl-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxo-4-(3-(trifluoromethyl)phenyl)butanoate **(2-11e)**



2-11e

A white solid; diastereomeric ratio is 37:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 4.85 (dd, *J* = 41.1, 13.1 Hz, 2H), 4.25 (s, 1H), 3.96 (q, *J* = 7.3 Hz, 1H), 1.41 (s, 9H), 1.35 (d, J = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, CDCl3) δ 200.86, 170.58, 136.76, 131.71, 130.4, 129.58, 125.34, 124.51, 84.81, 78.18, 76.45, 44.58, 27.59, 12.63.; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}F_3NO_6$ $[M+Na]^+$ 414.1135, found 414.1121; the ee value of the major isomer was 81%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 9.14 min, t(minor) = 9.42 min).

(2S,3S)-*tert*-butyl-4-(4-chlorophenyl)-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxobutanoate **(2-11f)**

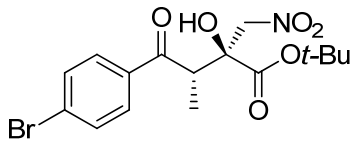


2-11f

A white solid; diastereomeric ratio is 70:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d,

J = 8.7 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 4.82 (dd, *J* = 44.4, 12.9 Hz, 2H), 4.31 (s, 1H), 3.91 (q, *J* = 7.3 Hz, 1H), 1.40 (s, 9H), 1.32 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.03, 170.64, 140.48, 134.25, 129.95, 129.21, 84.55, 78.27, 76.44, 44.17, 27.56, 12.64.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}ClNO_6$ $[M+Na]^+$ 380.0871, found 380.0890; the ee value of the major isomer was 83%, (determined by Daicel Chiralpak IC column, λ = 254 nm, 5% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(minor) = 28.82 min, t(major) = 37.83 min).

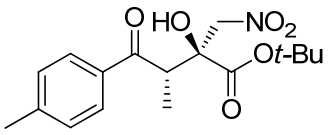
(2S,3S)-*tert*-butyl-4-(4-bromophenyl)-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxo butanoate **(2-11g)**



2-11g

A white solid; diastereomeric ratio is >99:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 4.82 (dd, *J* = 29.1, 13.0 Hz, 2H), 4.30 (s, 1H), 3.90 (q, *J* = 7.3 Hz, 1H), 1.40 (s, 9H), 1.32 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.23, 170.63, 134.69, 132.21, 130.02, 129.25, 84.57, 78.26, 76.43, 44.17, 27.56, 12.63.; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}{}^{79}BrNO_6$ $[M+Na]^+$ 424.0366, found 424.0377; $C_{16}H_{20}{}^{81}BrNO_6$ $[M+Na]^+$ 426.0346, found 426.0351; the ee value of the major isomer was 81%, (determined by Daicel Chiralpak IC column, λ = 254 nm, 5% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(minor) = 32.90 min, t(major) = 43.68 min).

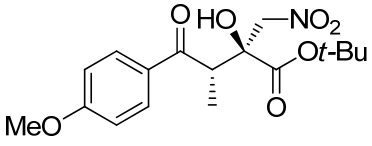
(2S,3S)-*tert*-butyl-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxo-4-(p-tolyl)butanoate **(2-11h)**



2-11h

A white solid; diastereomeric ratio is >99:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.81 (dd, *J* = 45.0, 13.1 Hz, 2H), 4.43 (s, 1H), 3.94 (q, *J* = 7.3 Hz, 1H), 2.43 (s, 3H), 1.37 (s, 9H), 1.33 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.92, 170.72, 144.99, 133.23, 133.9, 128.68, 84.23, 78.54, 76.53, 43.84, 27.53, 21.68, 12.70.; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_6$ $[M+Na]^+$ 360.1418, found 360.1405; the ee value of the major isomer was 84%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 19.58 min, t(minor) = 23.72 min).

(2S,3S)-*tert*-butyl-2-hydroxy-4-(4-methoxyphenyl)-3-methyl-2-(nitromethyl)-4-oxobutanoate **(2-11i)**

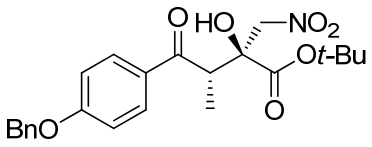


2-11i

A white solid; diastereomeric ratio is >99:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 4.81 (dd, *J* = 41.6, 13.2 Hz, 2H),

4.51 (s, 1H), 3.92 (q, *J* = 7.3 Hz, 1H), 3.88 (s, 3H), 1.37 (s, 9H), 1.33 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.85, 170.77, 164.24, 130.99, 128.72, 114.06, 84.12, 78.52, 76.61, 55.55, 43.43, 27.53, 12.78.; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_7$ $[M+Na]^+$ 376.1367, found 376.1372; the ee value of the major isomer was 80%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 32.21 min, t(minor) = 35.78 min).

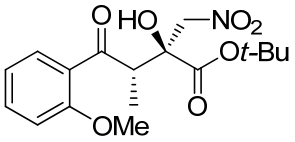
(2S,3S)-*tert*-butyl-4-(4-(benzyloxy)phenyl)-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxobutanoate **(2-11j)**



2-11j

A white solid; diastereomeric ratio is 52:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.46 – 7.38 (m, 4H), 7.36 (d, *J* = 6.8 Hz, 1H), 7.06 – 7.00 (m, 2H), 5.15 (s, 2H), 4.81 (dd, *J* = 43.7, 12.8 Hz, 2H), 4.50 (s, 1H), 3.92 (q, *J* = 7.2 Hz, 1H), 1.37 (s, 9H), 1.33 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.80, 170.76, 163.35, 135.91, 130.99, 128.71, 128.32, 127.45, 114.89, 84.14, 78.49, 76.60, 70.24, 43.44, 27.52, 12.77.; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_7$ $[M+Na]^+$ 452.1680, found 452.1663; the ee value of the major isomer was 82%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 39.91 min, t(minor) = 48.58 min).

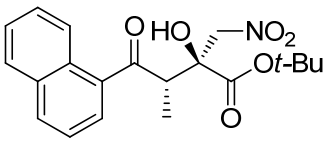
(2S,3S)-*tert*-butyl-2-hydroxy-4-(2-methoxyphenyl)-3-methyl-2-(nitromethyl)-4-oxobutanoate **(2-11k)**



2-11k

A white solid; diastereomeric ratio is >99:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.07 – 6.93 (m, 2H), 4.81 (q, *J* = 12.8 Hz, 2H), 4.21 (s, 1H), 4.07 (q, *J* = 7.2 Hz, 1H), 3.92 (s, 3H), 1.43 (s, 9H), 1.28 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.42, 170.99, 158.21, 134.20, 130.95, 121.04, 111.64, 84.02, 78.80, 76.39, 55.65, 49.31, 27.59, 11.91; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_7$ $[M+Na]^+$ 376.1367, found 376.1351; the ee value of the major isomer was 77%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 27.91 min, t(minor) = 31.76 min).

(2S,3S)-*tert*-butyl-2-hydroxy-3-methyl-4-(naphthalen-1-yl)-2-(nitromethyl)-4-oxobutanoate **(2-11l)**

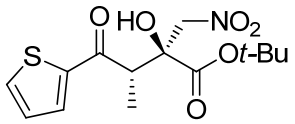


2-11l

A white solid; diastereomeric ratio is >99:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.81 (m, 2H), 7.63 –

7.50 (m, 3H), 4.87 (dd, *J* = 30.6, 12.8 Hz, 2H), 4.36 (s, 1H), 3.97 (q, *J* = 7.3 Hz, 1H), 1.44 (s, 9H), 1.35 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.29, 170.98, 135.37, 133.92, 133.19, 130.33, 128.47, 128.20, 127.50, 126.75, 125.40, 124.27, 84.62, 78.73, 76.45, 48.45, 27.63, 12.28.; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NO_6$ $[M+Na]^+$ 396.1418, found 396.1413; the ee value of the major isomer was 88%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 18.86 min, t(minor) = 24.54 min.

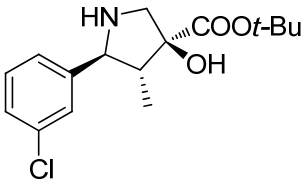
(2S,3S)-*tert*-butyl-2-hydroxy-3-methyl-2-(nitromethyl)-4-oxo-4-(thiophen-2-yl)butanoate **(2-11m)**



2-11m

A white solid; diastereomeric ratio is 56:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 3.8, 0.8 Hz, 1H), 7.72 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.17 (dd, *J* = 4.8, 4.0 Hz, 1H), 4.84 (dd, *J* = 39.9, 13.1 Hz, 2H), 4.28 (s, 1H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.39 (s, 9H), 1.37 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.24, 170.51, 143.23, 135.46, 133.23, 128.47, 84.50, 78.22, 76.34, 46.19, 27.48, 13.02.; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NO_6S$ $[M+Na]^+$ 352.0825, found 352.0826; the ee value of the major isomer was 77%, (determined by Daicel Chiralpak ID column, λ = 254 nm, 15% *i*-PrOH/hexanes, flow rate = 1.0 mL/min, t(major) = 25.94 min,

t(minor) = 32.17 min).



2-17

A slight red solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 3.1 Hz, 1H), 7.38 – 7.36 (m, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.29 – 7.27 (m, 1H), 4.91 (d, *J* = 1.8 Hz, 1H), 4.21 (ddd, *J* = 12.3, 11.7, 7.9 Hz, 2H), 3.45 (q, *J* = 8.0 Hz, 1H), 1.57 (s, 9H), 1.54 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.63, 146.36, 134.66, 129.99, 127.20, 126.86, 125.41, 124.16, 79.68, 77.20, 71.42, 55.46, 50.71, 28.48, 11.18; LRMS (ESI) *m/z* calcd for $C_{16}H_{22}ClNO_3$ $[M+Na]^+$ 334.12, found 334.18.

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