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Doctor of Philosophy

Amine Catalyzed Functionalization of Enolizable Ketones

by

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Declaration of Original and Sole Authorship

I, **Dongxin Zhang**, declare that this thesis entitled "**Amine Catalyzed Functionalization of Enolizable Ketones**" and the data presented in it are original and my own work.

I confirm that:

● No part of this work has previously been submitted for a degree at this or any other university.

● References to the work of others have been clearly acknowledged. Quotations from the work of others have been clearly indicated, and attributed to them.

● In cases where others have contributed to part of this work, such contribution has been clearly acknowledged and distinguished from my own work.

● None of this work has been previously published elsewhere, with the exception of the following:

1. **Dongxin Zhang**, Sherida Johnson, Hai-Lei Cui, Fujie Tanaka. *Asian Journal of Organic Chemistry*, **3**, 391-394, 2014.
2. **Dongxin Zhang**, Fujie Tanaka. *Advanced Synthesis and Catalysis*, **357**, 3458-3462, 2015.
3. **Dongxin Zhang**, Fujie Tanaka. *RSC Advances*, **6**, 61454-61457, 2016.

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Abstract

Amine Catalyzed Functionalization of Enolizable Ketones

Development of efficient methods for the synthesis of biologically important molecules in safe, atom economical, and environmentally friendly ways is a significant goal of modern organic chemistry. In this thesis, efficient methods using amines as catalysts for functionalization of enolizable ketones and synthesis of potential biofunctional molecules have been developed. First, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was indentified to be an efficient catalyst for fast regioselective aldol reactions. Molecules containing tertiary alcohols were concisely obtained through the aldol reactions. The developed DBU-catalysis was applied for the synthesis of spirooxindoles and trifluoromethyl-substituted alcohols. Although the DBU-catalyzed aldol reactions are not enantioselective, the enantiomerically pure forms of the aldol products derived from β-keto esters were obtained by the resolution of the enamines of the aldol products with a homochiral amine. Second, deuteration studies were carried out to elucidate the mechanism of the regioselective formation of the products in the aldol reactions catalyzed by DBU and to understand the relationship between the carbanion formation and the bond-formation. Finally, enantioselective oxa-hetero-Diels-Alder reaction of enones with aryl trifluoromethyl ketones catalyzed by a novel amine catalyst system was developed. Tetrasubstituted carbon centers bearing a trifluoromethyl group were concisely constructed with the formation of the tetrahydropyranone ring. The hetero-Diels-Alder products were further transformed to various trifluoromethyl-substituted tetrahydropyran derivatives.

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List of Abbreviations and Acronyms

[α]	specific rotation
Å	angstrom(s)
Ac	acetyl
Ar	aryl
br	broad (spectral)
Bn	benzyl
t-Bu/ ^{t}Bu	*tert*-butyl
ºC	degrees Celsius
calcd	calculated
compd	compound
δ	chemical shift in parts per million
d	day(s); doublet (spectral)
DABCO	1,4-diazabicyclo[2.2.2]octane
DA reaction	Diels-Alder reaction
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
equiv/eq	equivalent
Et	ethyl
ee	enantiomeric excess

er	enantiomeric ratio
ESI	electrospray ionization
g	gram(s)
h	hour(s)
HPLC	high-performance liquid chromatography
hDA reaction	heter-Diels-Alder reaction
HRMS	high resolution mass spectrometry
LDA	lithium diisopropylamide
m	milli; multiplet (spectral)
Me	methyl
μ	micro
mp	melting point
min	minute(s)
MHz	megahertz
MS	mass spectrometry
ND	not determined
NMP	*N*-methyl-2-pyrrolidone
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
i-Pr/ ^{i}Pr	isopropyl
q	quartet (spectral)

R_f	retention factor
RT/rt	room temperature
s	second(s); singlet (spectral)
t	triplet (spectral)
TLC	thin-layer chromatography
TMS	trimethylsiyl; tetramethylsilane
Ts	*para*-toluenesulfonyl
t_R	retention time
TS	transition state

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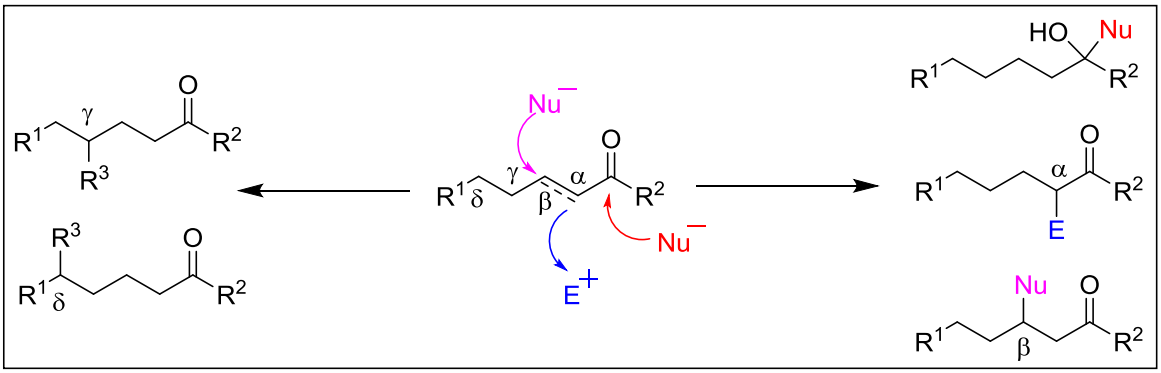
Chapter 1

Introduction

The development of efficient synthetic routes and synthesis of functional molecules are always the main task of organic chemists since functional molecules are often required for drug discovery, creation of biofunctional molecules, biological probes, etc. Particularly, introduction of substituents to carbonyl compounds has been one of the most important reactions used to synthesize molecules of interest.[1,2,3,4,5,6,7,8] Ketone and aldehydes can react with nucleophiles at the carbonyl carbon. They can also react with electrophiles and nucleophiles at the α- and β-positions,[1,2,3,4,5] depending on the structure of the ketones and aldehydes, reacting partner, and activation reagent and/or catalyst. While simple functionalization of γ- and δ- positions is more difficult, some recent advances made the γ- and even δ-functionalization possible.[6,7,8] These reactions have been of great interest in the field of synthetic chemistry (**Scheme 1.1**).



Scheme 1.1. Introduction of substituents to carbonyl compounds.

A great number of methods about functionalization of carbonyl compounds have been reported. Highly reactive bases and metal-based reagents such as lithium diisopropylamide (LDA) and related lithium amides have made a great contribution to this area.[9,10,11] However, reactions with excellent results by these bases and reagents often require absolute conditions, because they are sensitive to air and moisture. For a simple example, LDA is a widely used base for deprotonation of α-position of carbonyl compounds, forming enolates that act as nucleophiles. However, the reaction with LDA often needs to be executed at low temperature with the use of completely dehydrated solvents and reactants under inert gas such as argon and nitrogen. Because LDA is highly reactive, protection of functional groups with highly acidic protons, protection of hydroxyl groups for instance, is usually required, leading long non-economical synthetic routes. In addition, production and delivery as well as the use in laboratories of highly reactive, moisture and oxygen sensitive reagents could possibly pollute the environment if handled improperly.

Mukaiyama aldol reactions are also great methods for functionalization of carbonyl compounds.[4,12] However, the Mukaiyama methods require formation of silyl enol ether and related compounds before the reactions and deprotection of the silyl groups after the reactions.[4,12]

As a comparison, functionalization of carbonyl compounds can be performed under mild conditions at ambient temperature without special care for exposing to air and moisture by using organocatalysts.[2,5,13,14,15,16,17,18,19,20] The organocatalytic reactions are safe and environmentally friendly. More importantly, most organocatalytic reactions do not affect functional groups such as hydroxyl groups, and thus protection of these groups is often not necessary. Accordingly, organocatalytic reactions are atom economical and operationally simple. As we all know, it is important that target compounds are synthesized in high yields and high selectivities, avoiding the production of waste, in safe, resource-efficient, and

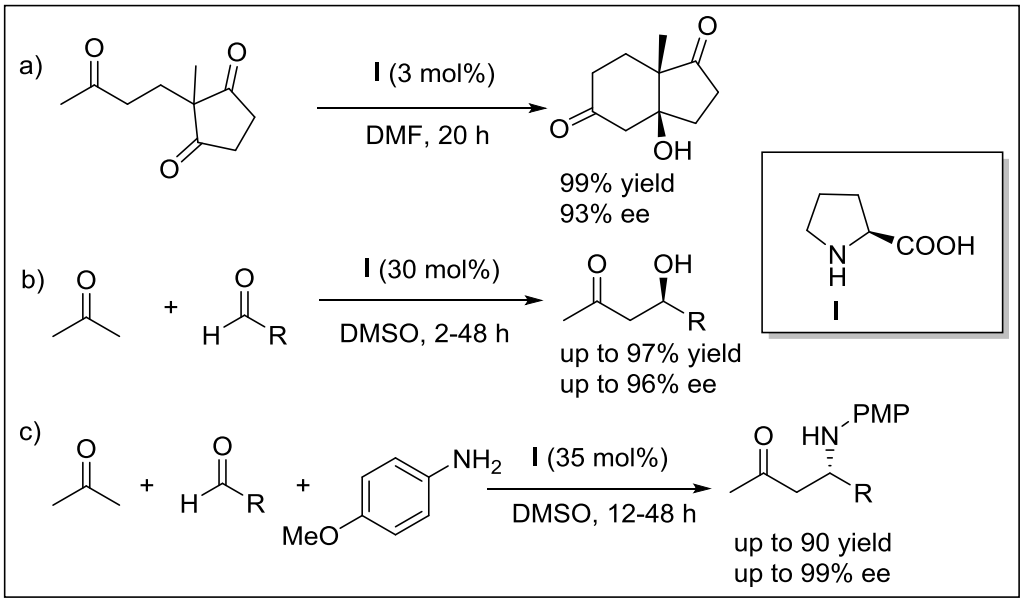
environmentally friendly ways.[21] Due to the great advantages of organocatalysis, the field has quickly grown all over the world.

For functionalization of carbonyl compounds, organocatalytic methods including the use of aminocatalysts have brought fruitful results.[22,23,24] However, there is still a high demand for new and improved organocatalytic methods to synthesize molecules of interest. Here, in the thesis study, I concentrated on the development of amine-catalyzed new chemical transformation methods for functionalization of carbonyl compounds, particularly unactivated enolizable ketones, and on the synthesis of functionalized molecules using the developed methods.

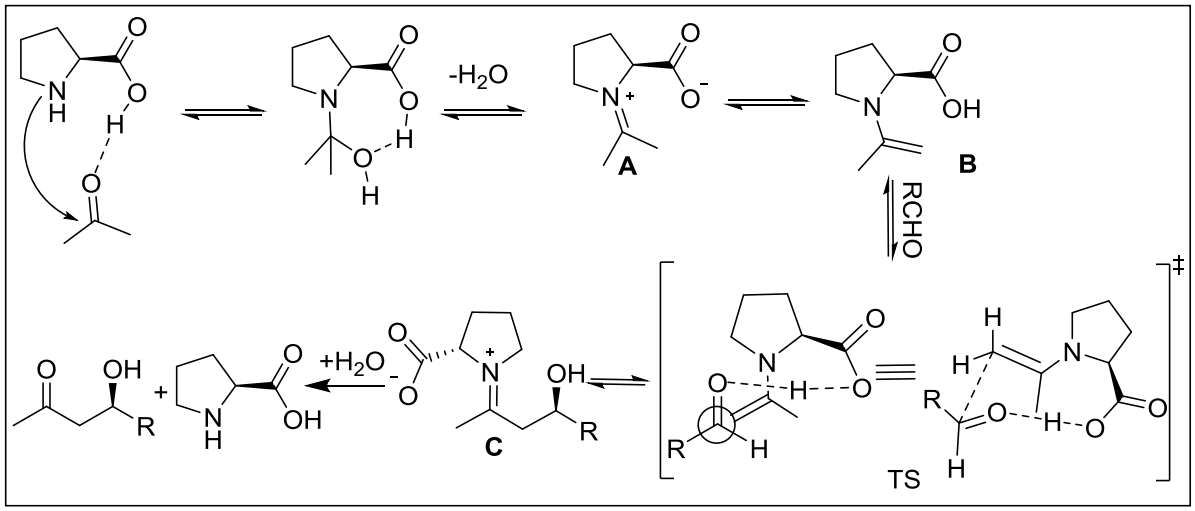
For functionalization of enolizable ketones and aldehydes, it is important to find effective ways for the formation of nucleophiles (i.e. enolates or enamines, etc.) from these ketones or aldehydes. Before discussing the results of the thesis study, reported amine-catalyzed functionalization methods via the formation of enol/enolate and enamine nucleophiles *in situ* are summarized here.[15,25,26,27,28,29]

Preformed enamines have been used as efficient reactants for functionalization of ketones since 1950s.[30,31] First enantioselective reactions involving *in situ*-formed enamine as nucleophiles were reported in early 1970s (**Scheme 1.2**a).[32,33] The reactions were performed using proline and other amino acids as catalysts. The intramolecular reactions were well recognized and used for the synthesis of steroids.[34] In recent years, safe and environmentally benign methods are preferred and amino acid-catalyzed intra- and intermolecular reactions via *in situ*-formed enamines have become popular (**Scheme 1.2**b).[35-48] Based on experimental evidence and theoretical studies, it is suggested that in proline catalysis, both the amine and acid functionalities of the proline are responsible for the catalysis and high enantioselectivity (**Scheme 1.3**).[35,36] The mechanism of proline-catalyzed reaction of acetone and an aldehyde is suggested as following:[35,36] First, the nitrogen atom of proline attacks the carbonyl group of

acetone. With the elimination of water, intermediate iminium ion **A** is formed, further evolving to enamine intermediate **B**. Then, intermediate **B** as a nucleophile reacts with the carbonyl group of the aldehyde, directed by the carboxylic acid group originated from proline in the enamine **B** via the formation of a hydrogen bond. A highly structured Zimmerman-Traxler type transition state (TS) is suggested for the C-C bond formation step. In the transition state, the aldehyde is attacked on the *re*-face when L-proline is used as a catalyst, by placing the R group in the energetically favored pseudoequatorial position. After the C-C bond formation, iminium ion **C** forms. With the hydrolysis of the iminium ion **C**, the desired aldol product is obtained and the proline is turned over to act in another catalytic cycle.

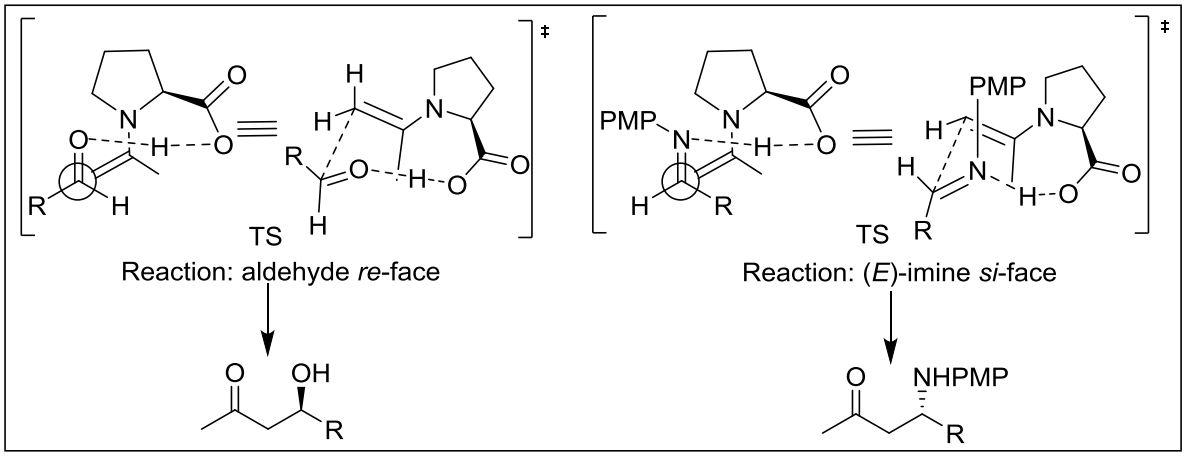


Scheme 1.2. a) L-Proline-catalyzed intramolecular aldol reaction.[32,33] b) L-Proline-catalyzed intermolecular aldol reaction between acetone and aldehydes.[35] c) L-Proline-catalyzed three-component Mannich reaction (PMP = *p*-methoxyphenyl). [37]



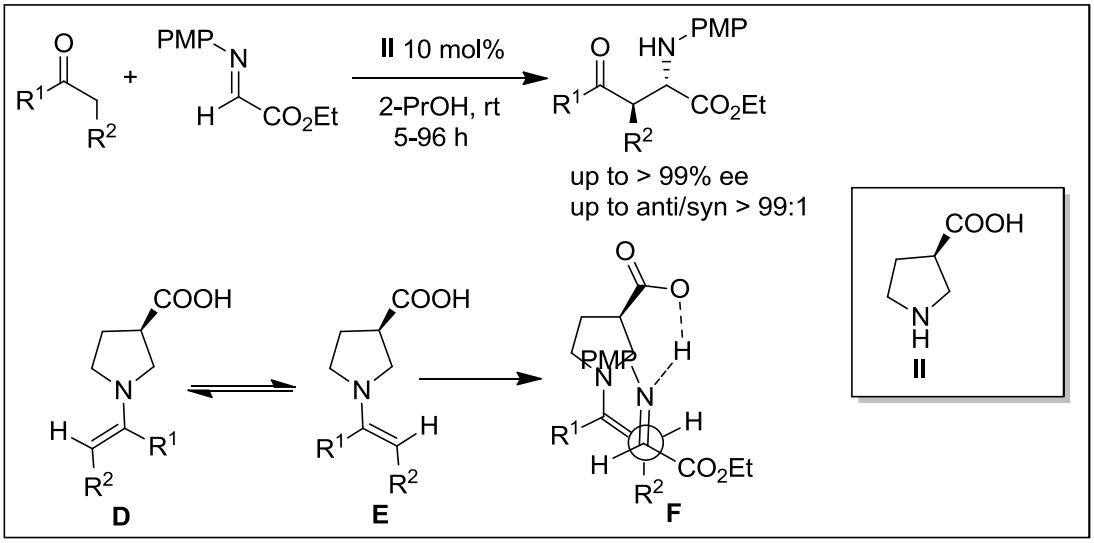
Scheme 1.3. A proposed mechanism for L-proline-catalyzed aldol reaction of acetone and aldehydes.[35,36]

For the L-proline-catalyzed Mannich reaction of acetone and *in situ*-formed imines between *p*-methoxyaniline and aldehydes, the product stereochemistry is different from that obtained in the L-proline-catalyzed aldol reactions (**Scheme 1.2**b vs. **Scheme 1.2**c).[35,36,37,38,39] In the Mannich reaction, the *in situ*-formed aldimines are attacked on the *si*-face. In the transition state, the (*E*)-imine forced the substituent R into the pseudoaxial position (**Scheme 1.4**).



Scheme 1.4. Reversal of stereochemistry of L-proline-catalyzed aldol and Mannich reactions.[35,36,37,38,39] PMP = *p*-methoxyphenyl.

Whereas proline is widely used as catalyst in huge numbers of chemical transformations involving *in situ*-formed enamine nucleophiles, limitations of the proline catalysis have also been reported. For example, because of the α-substituent on the pyrrolidine ring, ketones larger than acetone such as 3-pentanone, are difficult to give desired products in proline-catalyzed reactions. To catalyze reactions of bulky ketones, β-proline (**II**) has been used as catalyst. Catalyst **II** catalyzes Mannich reactions between bulky ketones and imines as well as those between aldehydes and imines.[40,41,42] The stereochemistry of the Mannich products using β-proline as the catalyst is altered compared to that of proline catalysis (**Scheme 1.5**). For the β-proline-catalyzed reactions, both conformations **D** and **E** of enamine nucleophiles may be present, but only conformation **E** can take part in the reaction with the imine because the reacting carbon atoms can be positioned for the C-C bond formation under the interaction between the carboxylic acid and the imine (i.e. proton transfers from the carboxylic acid to the imine).[40,41,42,] In conformation D, the reaction sites are too far apart under the carboxylic acid-imine interaction (i.e. no reaction). The formation of the Mannich product in the β-proline catalysis has been explained by transition state **F**.

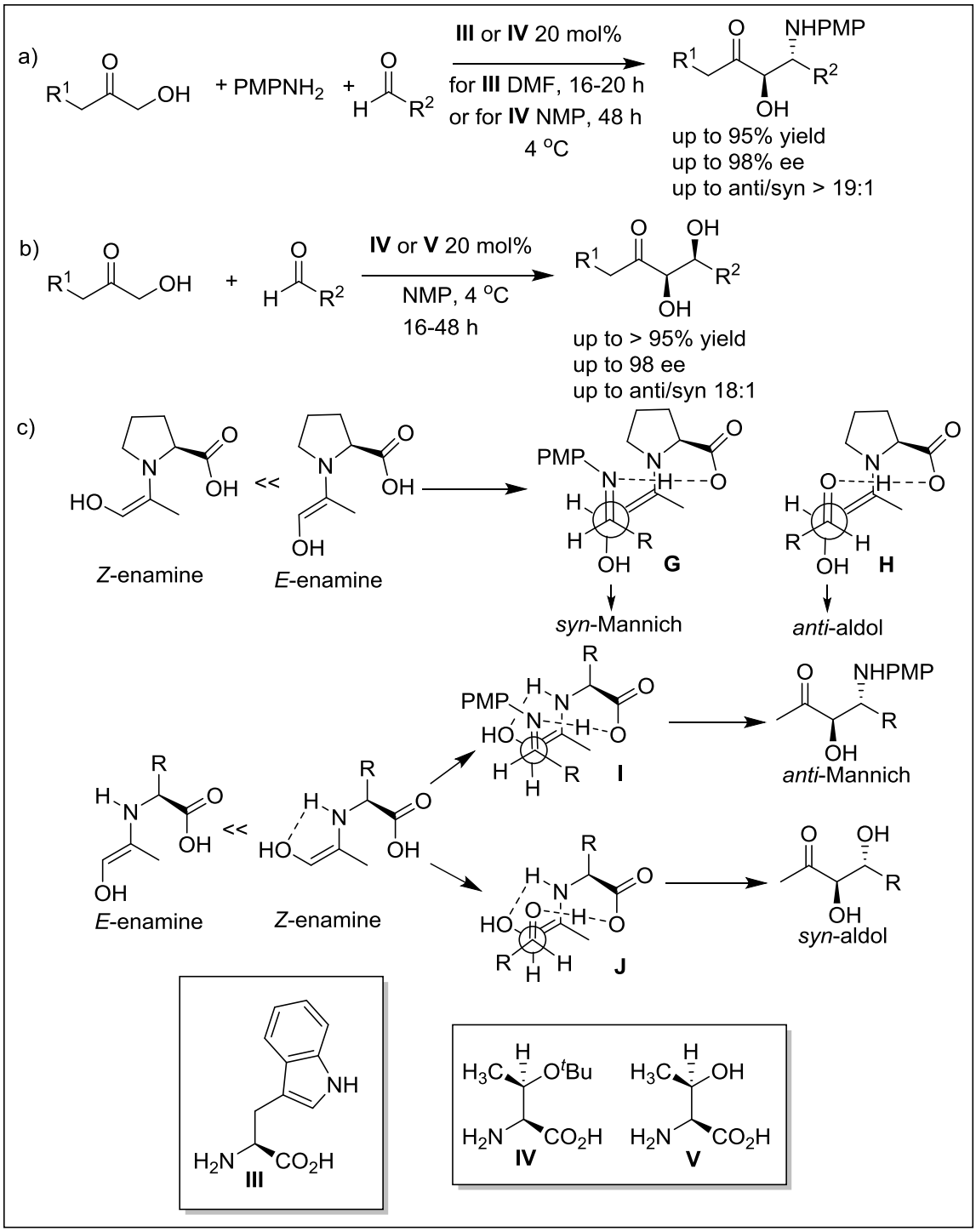


Scheme 1.5. β-Proline catalyzed anti-Mannich reactions (PMP = *p*-methoxyphenyl).[40,41,42]

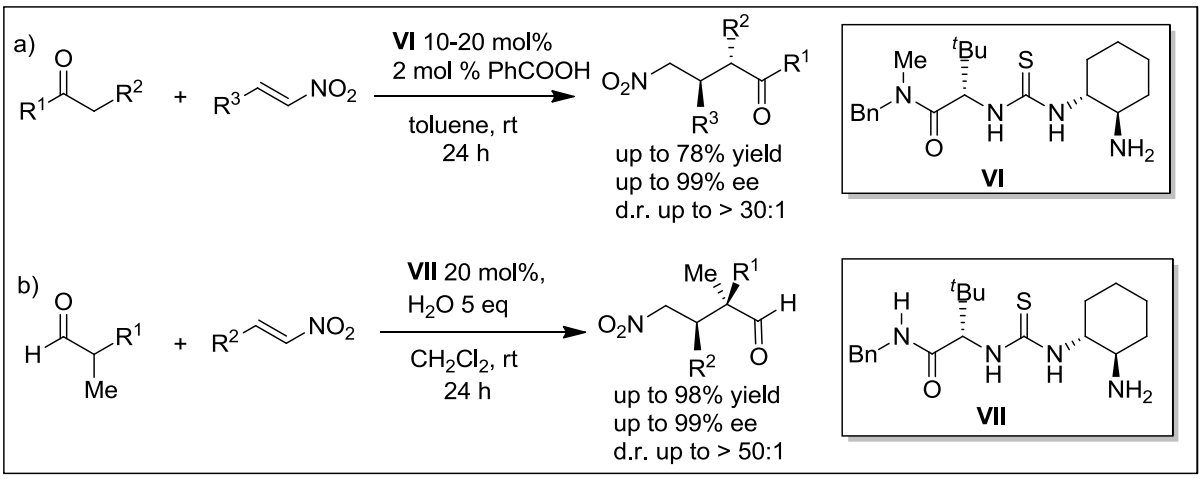
Product stereochemistry has also been altered by using primary amine-containing amino acids from those catalyzed by proline (**Scheme 1.6**a,b).[43,44,45] When α-hydroxyl ketones are applied as substrates, 1,2-amino alcohols and 1,2-diols are synthesized through Mannich and aldol reactions catalyzed by proline or primary amine-containing amino acids.[43,44,46] In the reactions of hydroxyacetone catalyzed by proline, products are formed via a reaction involving an (*E*)-enamine because of steric interactions in (*Z*)-enamine.[44,46,47,48] The stereochemistry of the product has been explained by transition state **G** or **H**. However, when primary amine containing amino acids are used as catalysts, (*Z*)-enamines are formed predominantly because of the hydrogen bonding between the oxygen of the hydroxyl group and the amine proton of the enamine. Then, *anti*-Mannich and *syn*-aldol products are formed via transition states **I** and **J** respectively (**Scheme 1.6**c).[44]

Besides aldol and Mannich reactions, conjugate additions involving enamine nucleophiles have also been reported. For example, primary amine-thiourea bifunctional catalysts have been used for the conjugate additions of acyclic ketones and α,α-disubstituted aldehydes to nitroolefins to generate a series of chiral nitroalkanes (**Scheme 1.7**a,b).[49,50] It has been suggested that the bifunctional catalysts activate the carbonyl group by the formation of enamine and the nitroolefins by hydrogen-bonding.[49,50,51] Although the thiourea moiety possibly interacts with the nitro group, the exact mode of thiourea binding to nitroolefins is unknown. Some theoretical studies have been performed and suggested that only one of the nitro oxygen is engaged in the interaction with the thiourea.[49,50,51]

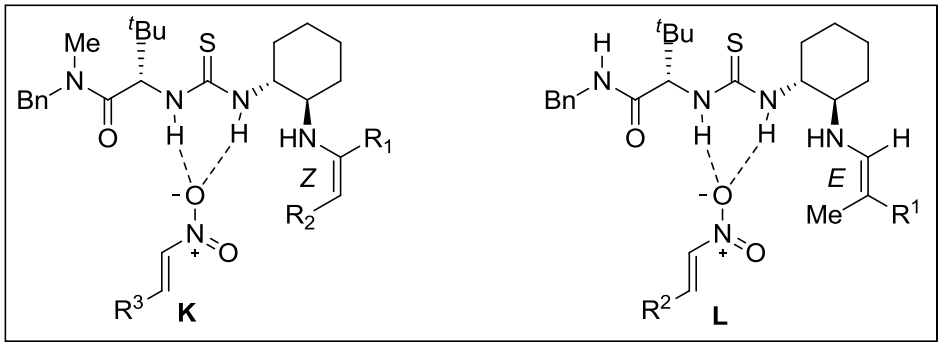
For ketone cases, the reaction favors formation of *anti*-diastereomers and it has been suggested that (*Z*)-enamine intermediate **K** participated in the transition state (**Scheme 1.8**).[49] For the reactions of aldehydes, *syn*-diastereomers are mainly obtained and this is explained by the involvement of (*E*)-enamine intermediates in the transition state **L**.[50]



Scheme 1.6. Primary amine-containing amino acid-catalyzed a) Mannich reactions with *anti*-selectivity[44] and b) aldol reactions with *syn*-selectivity.[43,44] c) Proposed transition states to lead the products in the proline and primary amine-containing amino acid catalysis.[44]

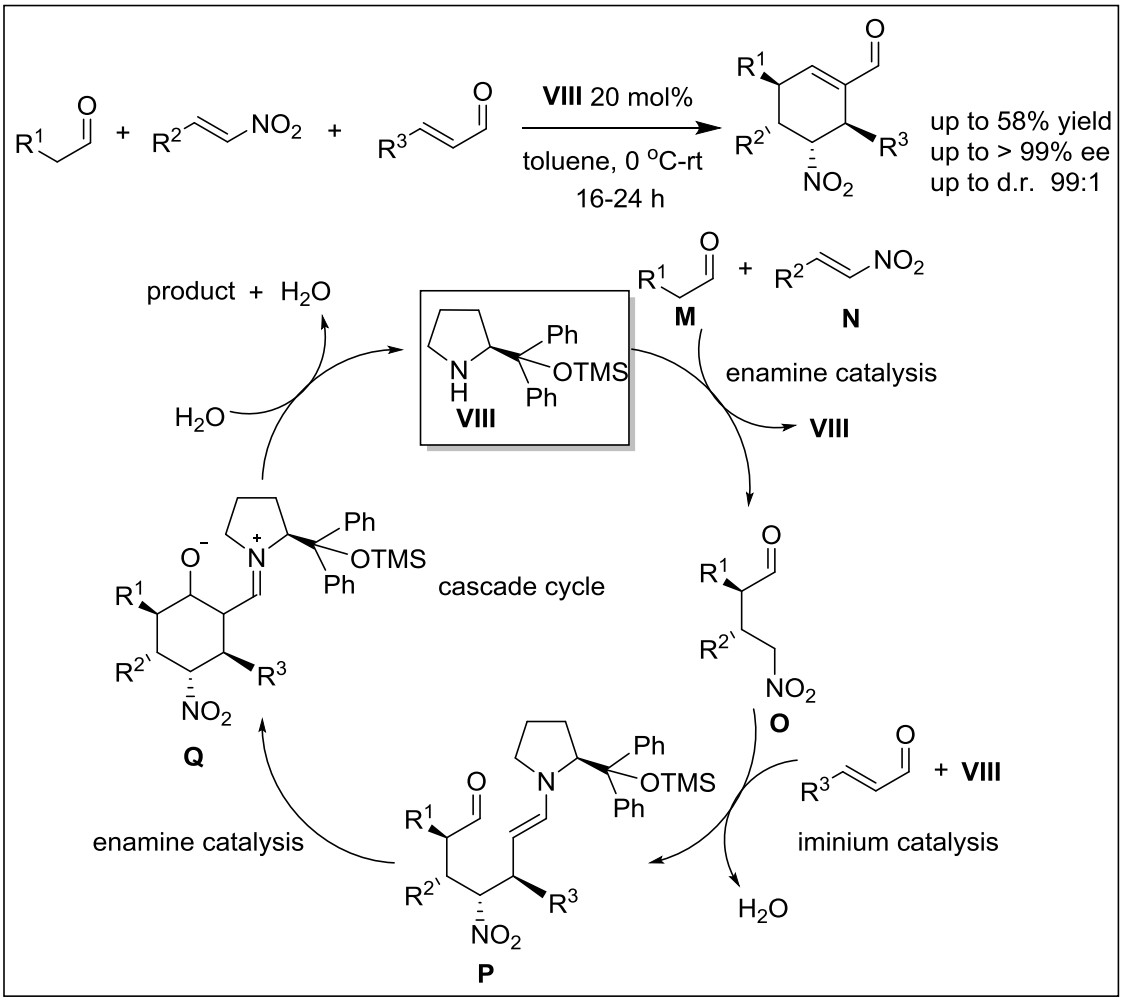


Scheme 1.7. Enantioselective Michael additions of a) ketones[49] and b) aldehydes[50] to nitroolefins catalyzed by primary amine and thiourea based bifunctional catalysts.

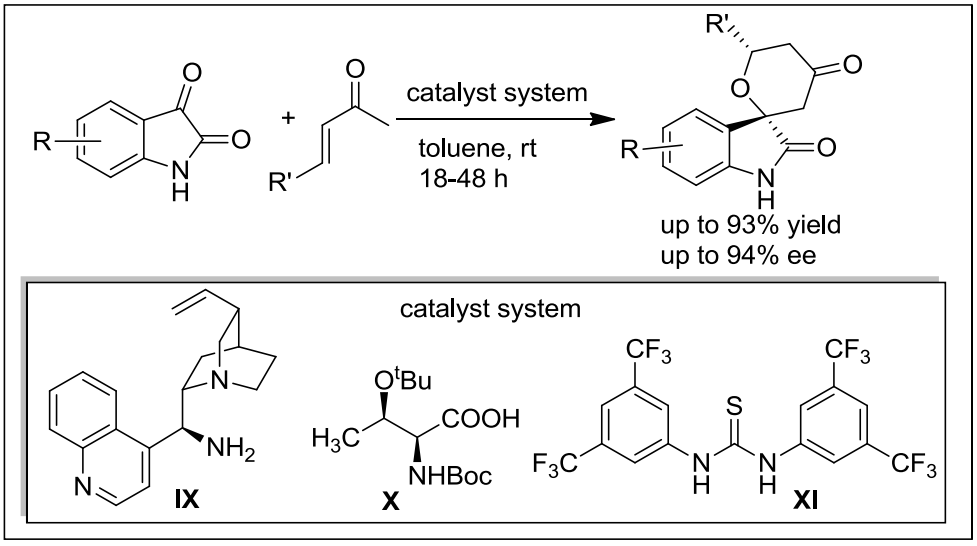


Scheme 1.8. Proposed intermediates in Michael reactions catalyzed by **VI** and **VII**.[49,50]

With the combination of enamine and iminium catalysis,[5] formation of more than one bond to generate products in one pot has also been widely applied. For instance, a triple cascade organocatalytic reaction by way of a Michael/Michael/aldol condensation sequence has been reported to afford the products with four stereogenic centers (**Scheme 1.9**).[52] Firstly, catalyst **VIII** forms enamine with aldehyde **M**; this enamine reacts as a nucleophile with nitroolefin **N** to afford the Michael adduct **O**. Then, **O** acts as a donor for the conjugate additions to the iminium ion formed from the enals and catalyst **VIII**, giving intermediate **P**. In the last step, intermediate **P** is used for an intramolecular aldol condensation, leading to **Q**, which is hydrolyzed to give tetra-substituted cyclohexene carbaldehyde.



Scheme 1.9. A triple cascade reaction and its proposed catalytic cycle.[52]



Scheme 1.10. Hetero-Diels-Alder reactions of enones with isatins.[53]

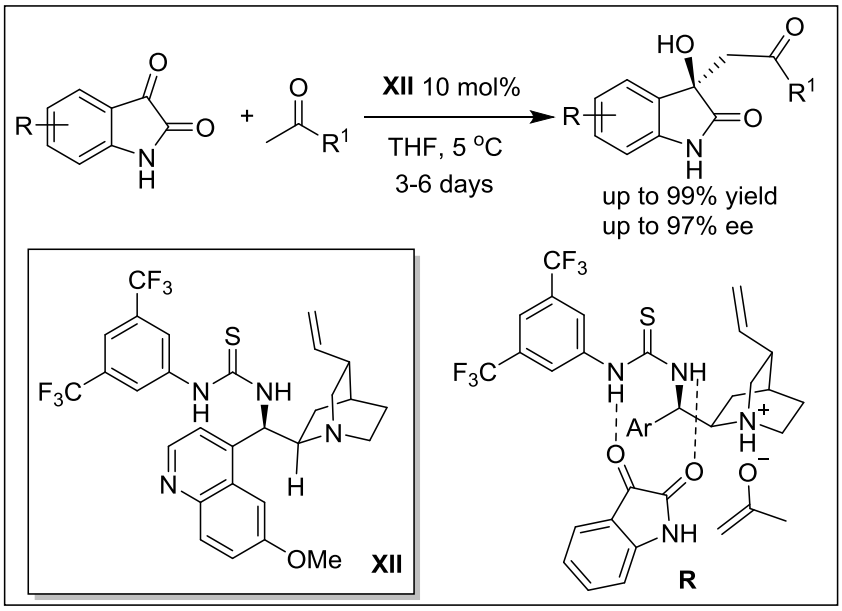
Recently, organocatalytic hetero-Diels-Alder reactions of enones with isatins have been reported to afford spirooxindole tetrahydropyranones using amine-based catalyst systems composed of the primary amine **IX**, a chiral acid **X**, and a thiourea derivative **XI** (**Scheme 1.10**).[53,54,55] In this reaction, enamines of enones are involved.

In the amine catalysis described above, the amine catalysts form covalent bonds with ketones and aldehydes to generate enamines that act as nucleophiles. And during the catalysis, hydrogen bonds and/or ion pairs are also involved to form the enamine and to activate and direct the electrophiles. Hydrogen bonds and ion pairs alone without formation of covalent bonds between reactants and catalysts have also been used for asymmetric organocatalysis.[16,20,56] In these cases, the formation of hydrogen bonds and/or ion pairs are usually used to activate electrophiles; formation of nucleophiles from ketones may be performed by the use of preformed silyl enol ethers[57,58] and related compounds or the use of relatively reactive ketones such as β-keto esters.[59,60]

The use of oganobases as catalysts to form enolates of unactivated ketones has been claimed but these reactions were performed with alkali metals.[61] The alkali metals were important for the reactions, indicating that organic molecules alone were not sufficient.[61,62] In addition, organobases such as guanidine-group-containing bases are used in their protonated forms as acid catalysts.[60,62]

Asymmetric organocatalyzed aldol reaction of unactivated ketones as donors via formation of hydrogen bonds and/or ion pairs is currently difficult. This is probably because the acidity of the α-proton in these ketones is low (p*K*a values are high) to form enol/enolate through interaction with organic molecules that provides only hydrogen bondings. Catalysis by simple hydrogen bonds and/or ion pairs that activate ketone substrates via enol/enolate mechanism for aldol donors is rare but such examples have been reported, for example, enantioselective aldol reaction of unactivated ketones with isatins catalyzed by cinchona

derived thiourea **XII** (**Scheme 1.11**).[63] Transition state **R** is proposed in which the ketone is deprotonated by the tertiary amine and during the approach of the enolate to isatin, the ionic interaction between the enolate and protonated tertiary amine is retained. Simultaneously, it is suggested that the thiourea moiety provides dual hydrogen bonds to activate the isatin carbonyl groups and direct the reaction face for nucleophilic attack of the enolate. Whereas this reaction gave the aldol products in high yields with high enantioselectivities, the reaction was slow and took several days.



Scheme 1.11. Cinchona alkaloids based thiourea derivative catalyzed aldol reaction of unactivated ketones via enolate intermediate and its possible transition state.[63]

As described above, depending on the structures of catalysts, substrate specificity, products, and the product stereochemistries can be altered, indicating that currently difficult chemical transformations may be overcome by the use of new designs and appropriate catalyst systems and conditions. New chemical transformations should also be able to be performed if appropriate development would be made. Whereas many organocatalytic reaction methods for functionalization of unactivated enolizable ketones have been reported, most of the reactions are relatively slow; the reaction time often ranges from a few hours to

several days. Therefore, the development of efficient synthetic methods is necessary to synthesize functionalized molecules from these ketones. At the same time, new methods to efficiently synthesize functionalized molecules in safe and atom economical ways are required.

In this thesis study, efficient chemical transformation methods involved in functionalization unactivated enolizable ketones have been developed and using the methods, functionalized molecules that are relevant to the search of biofunctional molecules have been synthesized.

In **Chapter 2**, the development of efficient and fast aldol reactions with high regioselectivities and the application of these aldol reactions to synthesize functionalized molecules are described.

In **Chapter 3**, deuteration studies of enolizable ketones under aldol reaction catalysis conditions are described.

In **Chapter 4**, the development of catalytic enantioselective hetero-Diels-Alder reactions is described. The use of the hetero-Diels-Alder reactions is demonstrated by the synthesis of tetrahydropyranon and tetrahydropyran derivatives.

In **Chapter 5**, summary and conclusions are provided.

In **Chapter 6**, experimental details and characterization of synthesized compounds are provided.

Chapter 2

Development of DBU-Catalyzed Aldol Reactions

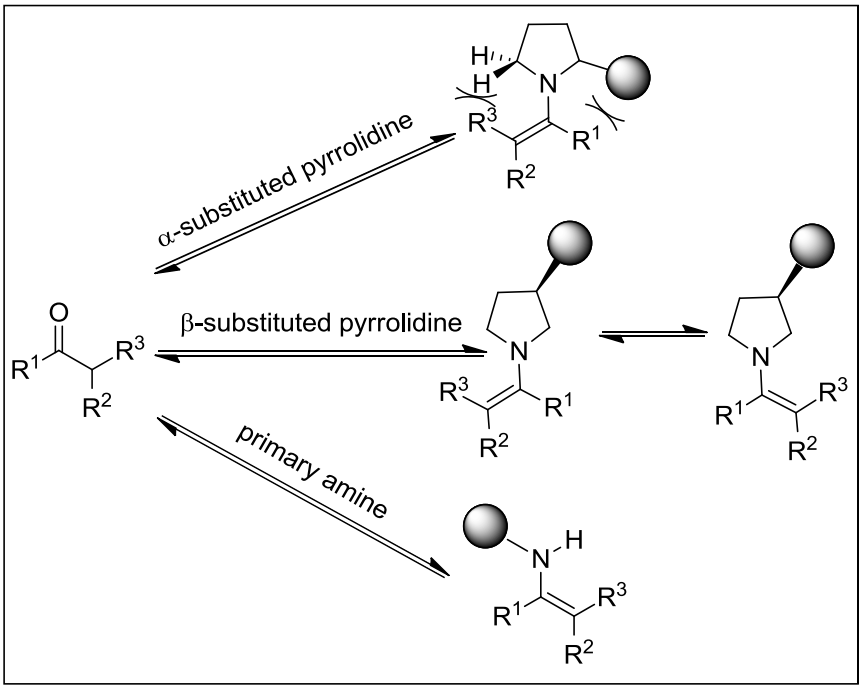
2.1 Introduction for Chapter 2

Functionalization of unactivated enolizable ketones is often performed via enamine formation using secondary and primary amine-based catalysts as explained in **Chapter 1**. However, the reactions of bulky substrates (i.e. bulky ketones, α-branched aldehydes etc.) catalyzed by pyrrolidines with α-substituent, such as proline, usually proceed with slow reaction rates and some reactions cannot even be facilitated, probably due to slow formation or inability to form the enamine intermediates because of the sterical reasons (**Scheme 2.1**). Pyrrolidines bearing substituent at the β-position and primary amine catalysts have been used to effectively functionalize sterically hindered ketones and aldehydes.[40,41,42,43,44,45,64,65] Use of pyrrolidines that do not have substituent at the α-position can lead better formation of enamines with bulky ketones and aldehydes than that of pyrrolidines bearing α-substituent.[40,41,42] Although primary amines helped to solve the issue of bulky substrates to some extent, usually the reaction time needed was still quite long.[43,44,45,64,65] Accordingly, fast reactions yet providing high selectivities (chemo-, regio-, diastereo-, enantio-, etc.) would be useful and essential to be developed.

Because aldol reaction is one of the most important methods for functionalization of ketone or aldehyde, affording β-hydroxy ketone or aldehyde,[66,67] first, the research was

performed to developed efficient aldol reaction methods for unactivated enolizable ketones including ketones used in slow reactions.[68,69] Organocatlytic aldol reactions are often based on the use of secondary and primary amine-based catalysts via enamine catalysis.[35,36,43,44,45,46,70] Reports of tertiary amine-catalyzed aldol reactions of unactivated enolizable ketones via enolate intermediate are rare.[28,63,71] For example, Mlynarski and co-workers reported the asymmetric aldol reaction of hydroxyacetone to various aldehydes catalyzed by quindine while the stereoselectivities were relatively low.[71] Zhao and co-workers reported the quinidine thiourea catalyzed aldol reactions of unactivated ketones to isatins with high enantioselectivities, but the reactions were slow and took several days.[63] Also, DBU had been used as aldol reaction catalyst, but the catalytic efficiency for the formation of aldol products depended on substrates.[28,72]

In this chapter, the development of DBU-catalyzed aldol reaction methods and the applicationof the aldol reactions to synthesize functionalized molecules are described.



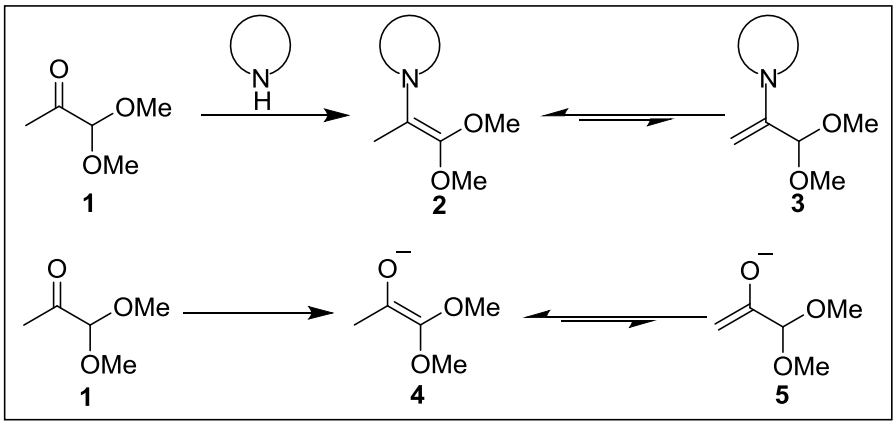
Scheme 2.1. Comparison of α-substituted pyrrolidine, β-substituted pyrrolidine, and primary amine in condensation with sterically hindered ketones and aldehydes.

2.2 Development of DBU-Catalyzed Aldol Reactions for the Synthesis of Spirooxindoles

2.2.1 Development of DBU-Catalyzed Aldol Reactions of a Pyruvic Aldehyde Derivative

Pyruvic aldehyde derivative **1** is one of the useful starting materials for the synthesis of functional molecules because it has an acetal group, a protected aldehyde group, which can be used for further transformations. In spite of the expected usefulness of the aldol reaction of **1**, previously reported aldol reactions of **1** performed under mild conditions are relatively slow. For example, the proline-catalyzed aldol reaction of **1** with α,α-disubstituted alkylaldehydes reported by Enders took 5 to 10 days at room temperature or at 4 °C to obtain the aldol products in up to 53% yield in excellent diastereo- and enantioselectivities.[73] Reactions of **1** using primary amine-based catalysis reported by the group of Luo and Cheng also required up to 3 days.[74] The Chimni group also reported the reaction of **1** with isatins using cinchona-derived amines with acid additives as catalysts at 25 °C, and the time required for completion of these reactions ranged from 16 to 30 h.[75]

The slow reactions of ketone **1** might be explained as shown in **Scheme 2.2** (initial hypotheses). Formation of enamine **2** may be more favored than that of enamine **3**, because the acidity of α-proton at the carbon with the dimethoxy group may be higher than that of the protons of the methyl group and because enamine **2** can be stablized by the dimethoxy group. In addition, the dimethoxy group may act as sterically hindered group for the formation of the enamine. The reactivity of enamine **2** at the carbon with dimethoxy group may be much lower than enamine **3** due to the stabilization and the steric hindrance by the dimethoxyl group. This is matter is further discussed on **Chapter 3**.



Scheme 2.2. Enamine and enolate formation of ketone **1** (initial hypotheses).

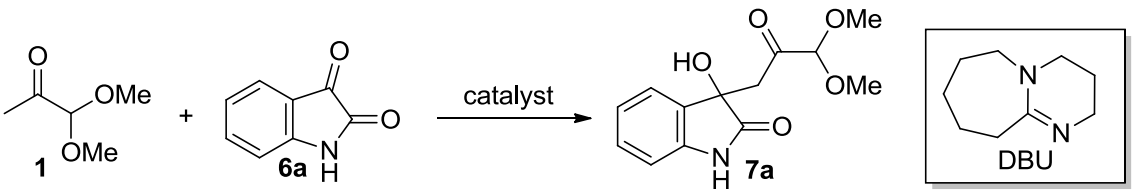
For enolate formation of **1**, it is also considered that enolate **4** is more stable than enolate **5**. Although the stability of the enamine or enolate might be different from the reactivity, formation of **2** or **4** would diminish the reaction at the methyl group of **1** to some degree. For efficient and fast reactions, formation of **3** or **5** should be enhanced or other effective ways should be applied.

To develop a new method for fast aldol reactions of pyruvic aldehyde derivative **1**, first, reaction using isatin **6a** as an acceptor electrophile to form product **7a** was investigated (**Table 2.1**). Isatin **6a** was chosen because oxindole derivatives are important as bioactive molecules, drug leads, and synthons to synthesize bioactive molecules.[76,77] Synthesis of oxindole derivatives is a current topic.[76,77,78,79,80]

The goal was to obtain reasonable product yields for the aldol reaction within 30 min at room temperature (25 ^{o}C). When the reaction was performed using pyrrolidine, pyrrolidine-acetic acid (1:1), or pyrrolidine-Et_3N (1:1) as catalyst (20 mol%) in DME, isatin **6a** was completely consumed in 30 min; but multiple products were formed including a small amount of desired aldol product **7a** (**Table 2.1**, entries 1-3). For these catalysts, neither use of a lower catalyst loading (10 and 5 mol%) nor a shorter reaction time improved the outcome to obtain **7a**. In contrast, the reaction in the presence of pyrrolidine-DBU (1:1, 20 mol%) in DME gave

7a in good yield (entry 4). The reaction using DBU as a sole catalyst in DME also afforded **7a** in similar yield (entry 5). A screen of a small set of solvents for the reaction in the presence of DBU revealed that toluene was the optimal solvent of those tested in terms of cleanness of the reaction (less or no by-product formation) and the yield of **7a** (entry 7). The regioisomer of **7a**, in which a new bond was formed at the acetal carbon, was not obtained. Loading of DBU was able to be reduced; the reaction in the presence of DBU (10 mol%) in toluene afforded **7a** in 80% yield (entry 8). Further testing of the reaction at 0 °C (entry 9) and of the use of NaOMe, DABCO, or DMAP as catalyst (entries 10-12) indicated that the reaction using DBU (20 or 10 mol%) in toluene was optimal (entries 7 and 8). Note that the DBU-catalyzed aldol reaction constructed tetrasubstituted carbon center in short reaction time.

Table 2.1. Screen of catalysts and conditions for the aldol reaction.[a]



Entry	Catalyst[b] (loading relative to **6a**)	Solvent	Time	Yield (%)[c]
1	Pyrrolidine-Et_3N (**XIII**) 1:1 (20 mol%)	DME	30 min	ND
2	Pyrrolidine-CH_3COOH (**XIV**) 1:1 (20 mol%)	DME	30 min	ND
3	Pyrrolidine (20 mol%)	DME	30 min	ND
4	Pyrrolidine-DBU 1:1 (20 mol%)	DME	30 min	72
5	DBU (20 mol%)	DME	30 min	74
6	DBU (10 mol%)	dioxane	30 min	56[d]
7	DBU (20 mol%)	toluene	30 min	79
8	DBU (10 mol%)	toluene	30 min	80
9[e]	DBU (10 mol%)	toluene	30 min	67
10	NaOMe[f] (20 mol%)	toluene	30 min	73
11	DABCO (**XV**) (20 mol%)	toluene	3 h	NR
12	DMAP (**XVI**) (20 mol%)	toluene	3 h	NR

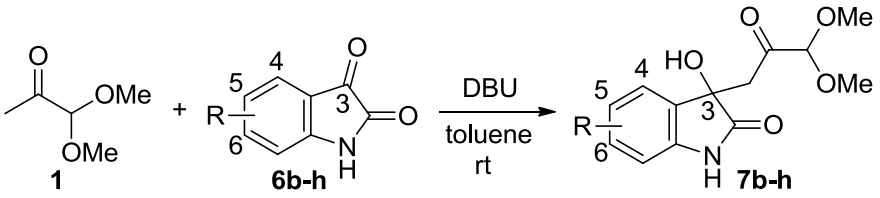
13	Et_3N (**XIII**) (20 mol%)	toluene	3 h	NR
14[g]	DBU (10 mol%)	toluene	30 min	67

[a] Reaction conditions: **1** (5.0 mmol), **6a** (0.50 mmol), and catalyst (0.10 mmol or 0.05 mmol as indicated; i.e., 20 mol% or 10 mol% to **6a**) in solvent (1 mL) at rt (25 °C) except noted; DME: dimethoxyethane. [b] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO: 1,4-diazabicyclo[2.2.2]octane; DMAP: 4-(dimethylamino)pyridine. [c] Isolated yield of **7a**. ND = not determined because of formation of by-products, see text. NR = no reaction. [d] Yield was determined by ^{1}H NMR spectroscopy of the crude mixture. [e] Reaction at 0 °C for 10 min then rt for 20 min. [f] NaOMe 5 M solution in MeOH was used. [g] **1** (2.5 mmol) was used.

Whereas pyrrolidine with or without acetic acid or Et_3N may form an enamine with **1** as a nucleophile for the aldol reaction, the reaction using DBU as catalyst may proceed via an enolate. Enamine and enolate generated by the deprotonation at the dimethoxy-substituted carbon of **1** may be less reactive than those generated by deprotonation at the methyl group of **1** because of electronic and steric reasons as described above. As a strong base, DBU was an efficient catalyst for the reaction; possibility of the formation of the dianion[81] of **1** is discussed in **Chapter 3**.

With the best conditions identified to form **7a**, a series of aldol products were synthesized from substituted isatins (**Table 2.2**). Reactions utilizing chloro-, bromo-, and methyl- substituted isatin derivatives afforded corresponding aldol products **7b**-**7f** in good to high yields (70-89%). The methoxy and the nitro substituted isatins were less soluble in toluene. Based on this solubility feature, these reactions were performed in DME to increase yields of products **7g** and **7h** (**Table 2.2**, 62-63% in DME versus 45-47% in toluene; entry 8 versus entry 9; entry 10 versus entries 11 and 12).

Table 2.2. Aldol reactions of **1** and **6**.[a]



Entry	R	**7**	DBU (mol%)[b]	Time (min)	Yield (%)
1	4-Cl	**7b**	10	30	70
2	4-Cl	**7b**	20	15	78
3	4-Br	**7c**	10	15	83
4	6-Cl	**7d**	10	15	89
5	5-Br	**7e**	10	30[c]	54
6	5-Br	**7e**	20	15	70
7	5-Me	**7f**	10	30	88
8	5-OMe	**7g**	10	15	45
9[d]	5-OMe	**7g**	10	15	63
10	5-NO_2	**7h**	10	15	47
11[d]	5-NO_2	**7h**	20	15[c]	<10[e]
12[d]	5-NO_2	**7h**	30	15	62

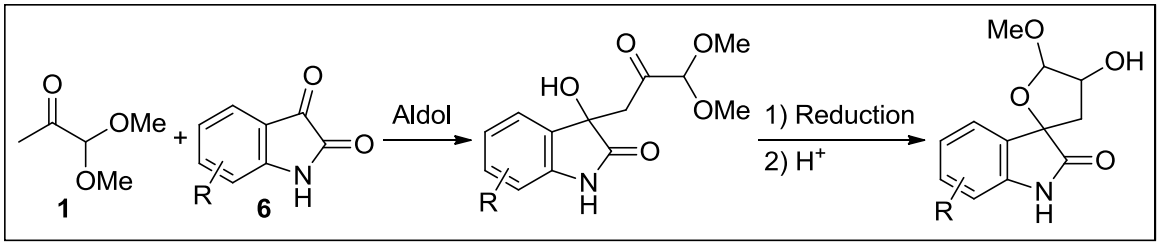
[a] Reaction conditions: **1** (5.0 mmol), **6** (0.50 mmol), and catalyst (0.10 mmol or 0.05 mmol as indicated; i.e., 20 mol% or 10 mol% to **6**) in toluene (1 mL) at rt (25 °C) except noted. [b] DBU loading amount relative to **6**. [c] Reaction was stopped at the indicated time without complete consumption of **6**. [d] Reaction in DME. DME: dimethoxyethane. [e] Estimated by TLC analysis.

2.2.2 Synthesis of Furanose Spirooxindoles from the Aldol Products

Spirooxindoles are common in many natural products and bioactive molecules.[76,77] Thus, to discover therapeutic leads and biofunctional molecules, there is a high demand for new types of spirooxindoles and for the development of efficient, concise synthetic methods to access spirooxindole frameworks.[76,77]

As 5-membered-ring sugars, furanose units, are present in DNA and RNA, hence spirooxindoles with furanose units will likely be biofunctional molecules.[82,83,84] The DBU-

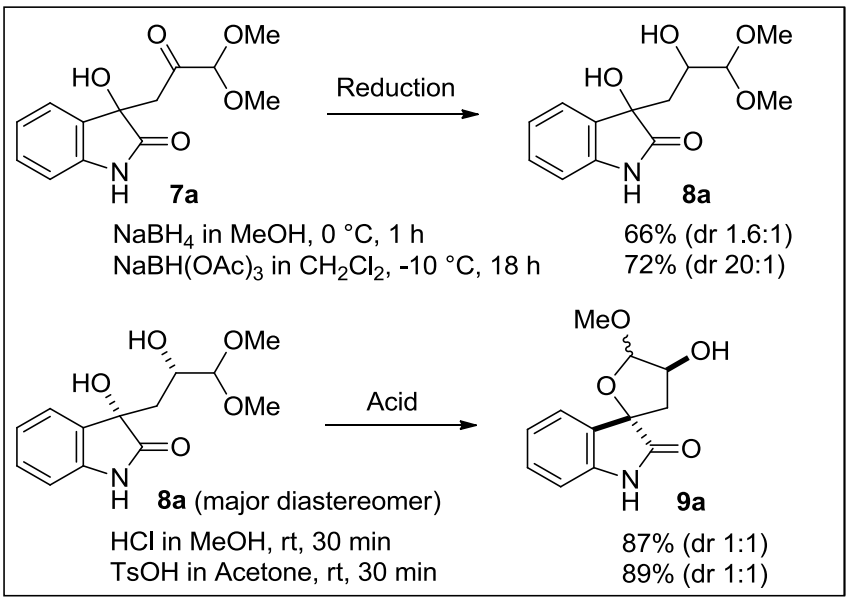
catalyzed aldol reaction of a pyruvic aldehyde derivative (**1**) with isatins (**6**) described in section **2.2.1** was applied to synthesize a furanose-oxindole-spirosystem. The design to synthesize the furanose spirooxindoles was the aldol reaction followed by reduction of the ketone carbonyl group and an acidic workup as shown in **Scheme 2.3**.



Scheme 2.3. A route to furanose-spirooxindoles.

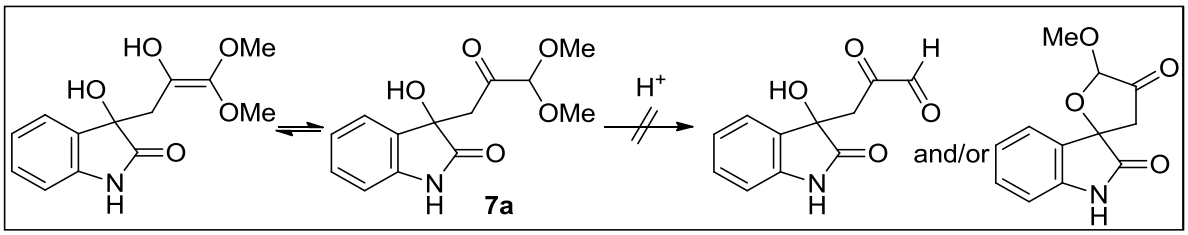
The aldol product **7a** was first reduced using $NaBH_4$ in MeOH at 0 °C; diol **8a** was obtained as a mixture of the two diastereomers (dr 1.6:1) (**Scheme 2.4**). In contrast, reduction of **7a** using $NaBH(OAc)_3$ in CH_2Cl_2 at -10 °C afforded mostly a single diastereomer of **8a** (dr 20:1) in high yield. This single diastereomer of **8a** was converted to **9a** (dr 1:1 at the anomeric center) by an acid treatment (**Scheme 2.4**). When **8a** (dr 1.6:1) was treated under the same acidic conditions, it seemed that all four possible diastereomers of **9a** were formed by TLC analysis. Although 18 h reaction time for the reduction was significantly more time than the aldol reaction step, reduction using $NaBH(OAc)_3$ at -10 °C was chosen to combine with an acidic workup to obtain a set of furanose-spirooxindoles.

The major diastereomer of **8a** obtained by the reduction with $NaBH(OAc)_3$ was the same as the major diastereomer of **8a** obtained by the reduction using $NaBH_4$. The relative stereochemistry of the major diastereomer of **8a** was deduced from **9a** (see **Table 6.1** and **Figure 6.1** in **Chapter 6.2.1**).



Scheme 2.4. Reduction of **7a** and transformation of diol **8a** to furanose-spirooxindole **9a**.

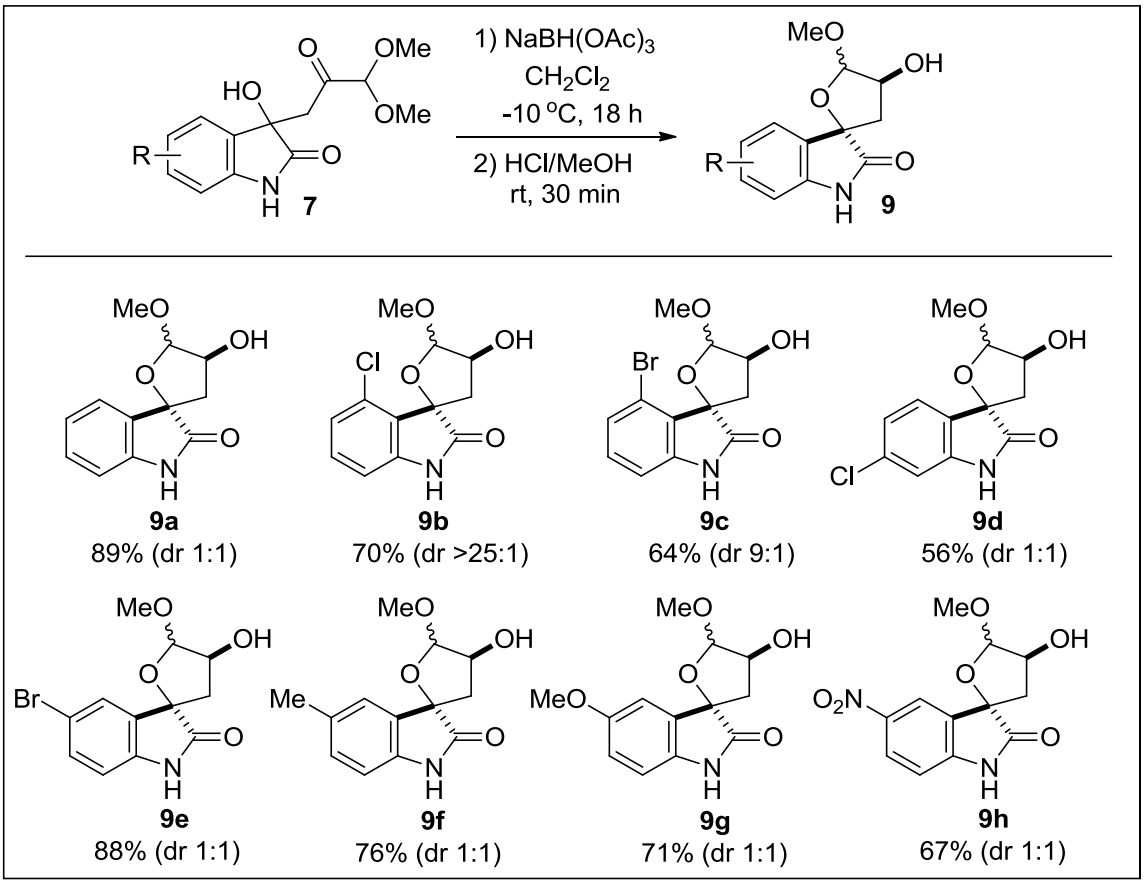
The acid treatment of **7a** did not afford the corresponding five-membered ring product (**Scheme 2.5**). The acetal group of **7a**, located next to the carbonyl group, was also not deprotected under typical acidic conditions used for the deprotection of dimethyl acetals. We attribute this to the formation of a stable dimethoxy-substituted enol/enolate. Once the ketone group was reduced, formation of the five-membered ring proceeded smoothly.



Scheme 2.5. Features of **7a** under acidic conditions.

Results of the formation of **9** by the reduction of **7** using $NaBH(OAc)_3$ followed by an acidic workup are shown in **Scheme 2.6**. Furanose-spirooxindoles **9a-h** were obtained in good to high yields from the corresponding aldol products **7a-h**. The transformation of aldol products **7** with substitudent at the 4-position gave corresponding spirooxindoles **9** with good diastereomer selectivities (**9b** and **9c**).

The relative stereochemistry of **9a** was determined by the coupling constants in ^{1}H NMR and by NOESY experiments (see **Table 6.1** and **Figure 6.1** in **Chapter 6.2.1**).

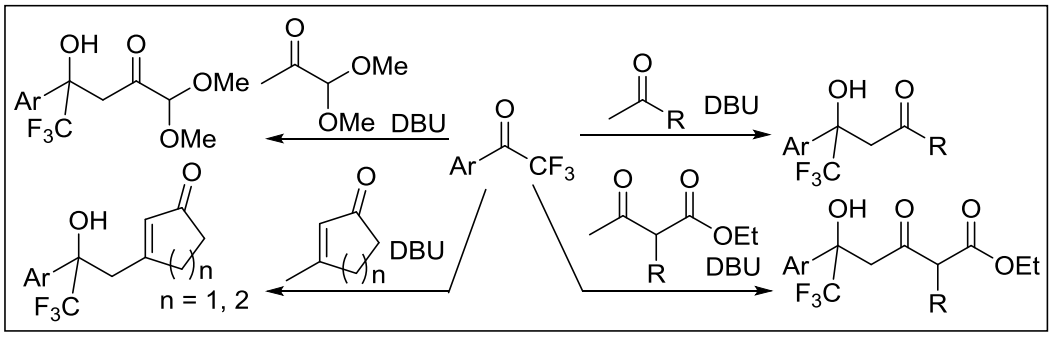


Scheme 2.6. Conversion of aldol products **7** to furanose-spirooxindoles **9**. Diastereomers of **9** were generated at the acetal carbon.

2.3 Development of DBU-Catalyzed Regioselective Aldol Reactions for Concise Access to Aryl- and Trifluoromethyl Substituted Tertiary Alcohols

2.3.1 Development of DBU-Catalyzed Aldol Reactions of Ketone Donors with Aryl Trifluoromethyl Ketone Acceptors

Molecules bearing aryl- and trifluoromethyl-substituted tertiary alcohol moieties are often found in pharmaceuticals, biological probes, enantiomer-discriminating reagents, and synthons and building blocks of these molecules.[85,86,87,88] Accordingly, the development of the methods to efficiently synthesize these molecules is of interest.[74,85,86,87,88,89,90,91,92,93,94,95,96,97] Based on the results of the DBU-catalyzed reactions described in section **2.2.1**, investigation was performed to apply DBU-catalysis to aldol and vinylogous aldol reactions of aryl trifluoromethyl ketones as acceptors that provide molecules bearing tertiary alcohols with aryl and trifluoromethyl groups (**Scheme 2.7**).[69]

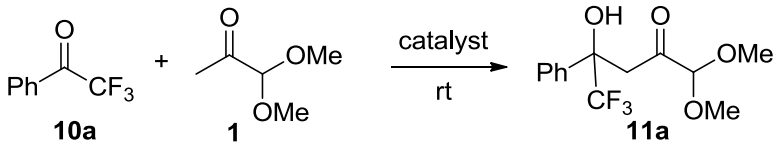


Scheme 2.7. Aldol and vinylogous aldol reactions performed using DBU as catalyst.

First, DBU catalysis conditions were evaluated to obtain the aldol product in the reaction of phenyl trifluoromethyl ketone (**10a**) with pyruvic aldehyde derivative **1**, which was used for previous DBU-catalyzed reactions with isatins. The results are shown in **Table 2.3**. Similar to previous results, the DBU catalysis in toluene afforded aldol product **11a** at room temperature (25°C) (entry 1). But, the reaction rate was not fast; a 6 h-reaction yielded **3** in 52% (entry 1). When reactions were performed in neat conditions, the aldol product was obtained in high yields (83–94%) after 1.5 h (entries 2-5). Use of 0.1 equiv of DBU was sufficient to give **3a** in high yields (entries 4 and 5). The conditions used for entries 4 and 5 (**10a**, 1 equiv; **2**, 5 equiv; DBU 0.1 equiv; 25 °C) were the best of those conditions tested.

Note that other amine bases such as Et_3N, DMAP, and DABCO did not act as catalyst for this aldol reaction (entries 6-8).

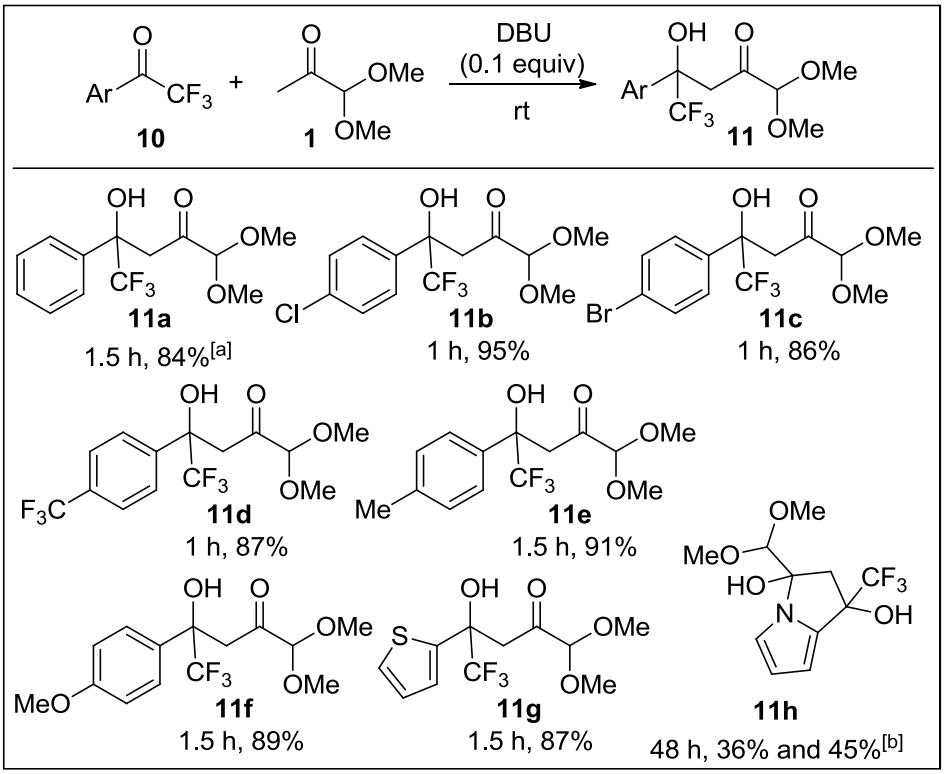
Table 2.3. Reaction of **10a** with **1** to give **11a**.[a]



Entry	Catalyst (equiv)	Time (h)	Conversion[b] (%)	Yield[c] (%)
1[d]	DBU (0.2)	6	ND	52
2	DBU (0.2)	1.5	>95	83
3[e]	DBU (0.2)	1.5	>95	ND
4[e]	DBU (0.1)	1.5	>95	84
5[e,f]	DBU (0.1)	1.5	>95	94
6	Et_3N (**XIII**) (0.2)	6	0	-
7	DABCO (**XV**) (0.2)	6	0	-
8	DMAP (**XVI**) (0.2)	6	0	-

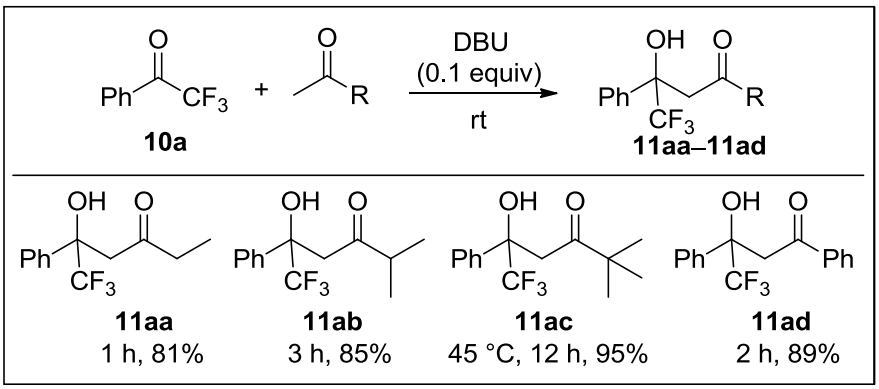
[a] Conditions: Ketone **10a** (0.5 mmol, 1 equiv), **1** (10 equiv), and catalyst (0.2 or 0.1 equiv as indicated) were stirred at 25 °C except where noted. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-(dimethylamino)pyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane. ND = not determined. [b] Conversion of **10a** was determined by ^{1}H NMR. [c] Isolated yield. [d] Toluene (1.0 mL) was used as solvent. [e] Ketone **1** (5.0 equiv). [f] Ketone **10a** (5.0 mmol), ketone **1** (25.0 mmol), DBU (0.5 mmol).

Next, the best conditions identified for the reaction between **10a** and **1** were used for aldol reactions of **1** with various aryl trifluoromethyl ketones (**Scheme 2.8**). A series of trifluoromethyl-substituted aldol products **11a**–**11f** were obtained in high yields within 1.0 h to 1.5 h regardless the electron-withdrawing or electron-donating substituent on the aryl group of the substrate. The thiophene unit in substrate was tolerated under the DBU catalysis, giving corresponding aldol product **11g** in 87% yield within 1.5 h. For the pyrrole-bearing substrate with an acidic proton, protection of the pyrrole NH was not necessary to lead the aldol C-C bond formation, and the reaction gave **11h**, cyclized forms of the product.



Scheme 2.8. Aldol reactions of **1** with various aryl trifluoromethyl ketones. Conditions: Ketone **10** (0.5 mmol, 1.0 equiv), ketone **1** (5.0 equiv), and DBU (0.1 equiv) at 25 °C. [a] Data from **Table 2.3**, entry 4. [b] DBU (0.2 equiv) was used. Two diastereomers of **11h** were separately obtained.

The DBU catalysis was also tested in reactions of various alkyl methyl ketone donors with phenyl trifluoromethyl ketone acceptor (**Scheme 2.9**). The reactions were highly diastereoselective. When using methyl ethyl ketone as the donor, product **11aa** was isolated in 81% yield within 1 h. The C-C bond formation occurred at the methyl group. Reaction of isopropyl methyl ketone with **10a** also successfully afforded product **11ab** with perfect regioselectivities in 85% isolated yield in 3 h (no regioisomer of **11ab** was detected). Whereas, the reaction of the hindered *t*-butyl methyl ketone with **10a** under DBU catalysis failed to give product **11ac** at room temperature for 3 h. By heating the reaction to 45^{o}C for 12 h, product **11ac** was obtained in 95% yield. The reaction of methyl phenyl ketone with **10a** under the DBU catalysis afforded **11ad** in 89% yield in 2 h.

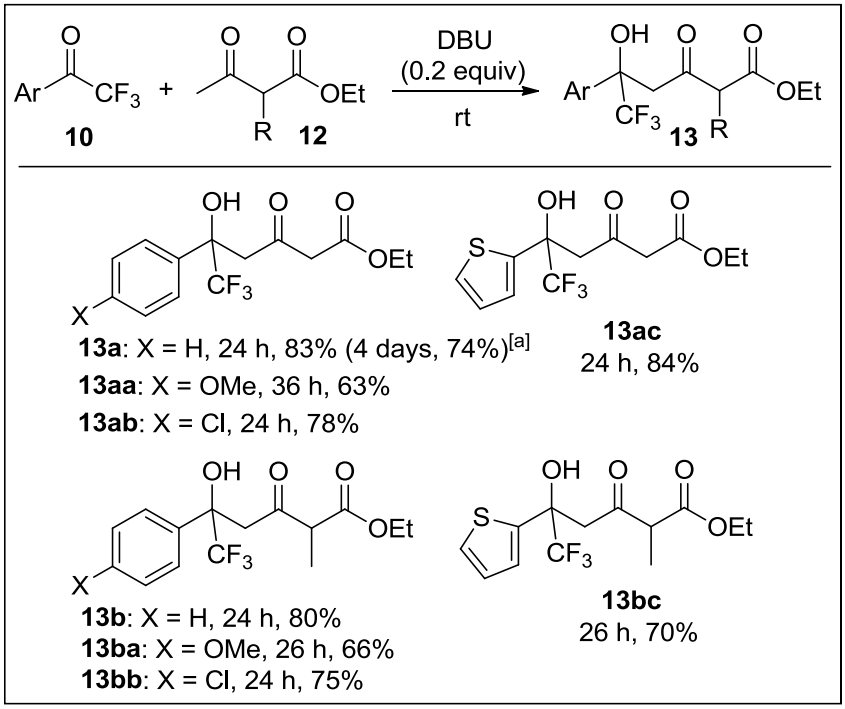


Scheme 2.9. Aldol reactions of **10a** with alkyl methyl ketones and with methyl phenyl ketone. Conditions: Ketone **10a** (0.5 mmol, 1.0 equiv), donor ketone (5.0 equiv), and DBU (0.1 equiv) at 25 °C except as noted.

β-Keto esters also acted as nucleophiles to give corresponding aldol products **13** under the DBU catalysis. For these reactions, the C-C bond formation occurred at the γ-position regioselectively (**Scheme 2.10**). During the reaction to form **13a**, formation of **13a** was observed by ^{1}H NMR analyses even at the initial stages of the reaction (such as at 5 min, 50 min, 130 min, and 220 min); however, no sign of the product with the bond formation at the α-position of the β-keto ester was detected.

In reported reactions of β-keto esters, the bond-formation often occurs at the α-position.[98,99] In previously reported methods for bond-forming reactions at the γ-position of β-keto esters, severe conditions, such as the use of two equivalents of strong bases to form a dianion, are typically required.[100,101,102,103] Alternatively, aldol reactions of β-keto esters at the γ-position have been performed using preformed silyl dienol ethers or alkyl dienol ether derivatives.[104,105,106] In the DBU-catalyzed reactions described above, β-keto esters were directly used as the substrates, and only catalytic amounts of DBU were necessary to give the aldol products of the bond formation at the γ-position of β-keto esters under mild conditions. A series of aldol products were obtained with good to high yields within 24-36 h (**Scheme 2.10**). The reactions of the substrates **10** containing electron-withdrawing groups were faster

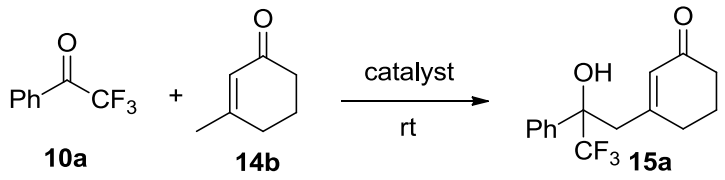
than that with electron-donating groups. The ketone containing a thiophene unit also worked as acceptor for this aldol reaction (formation of **13ac** and **13bc**). Further, the reaction was easily scaled up. A 15-mmol scale reaction of **10a** with ethyl acetoacetate in presence of DBU (10 mol%) gave **13a** in 74% yield after 4 days.



Scheme 2.10. Aldol reactions of β-keto esters with various aryl trifluoromethyl ketones. Conditions: Ketone **10** (0.5 mmol, 1.0 equiv), β-keto ester (10.0 equiv), and DBU (0.2 equiv) at 25 °C except where noted. [a] Data in parentheses from a 15 mmol-scale reaction: ketone **10a** (15 mmol, 1.0 equiv), β-keto ester (5.0 equiv), and DBU (0.1 equiv).

The DBU catalysis was also useful for the vinylogous aldol reactions of β-methyl-substituted cyclic enones **14** with **10** (**Scheme 2.11**). When the reaction of **10a** and **14b** was catalyzed by DBU (0.1 equiv) in toluene, the desired vinylogous aldol reaction product **15a** was obtained in 65% yield in 24 h (**Table 2.4**, entry 1). Similar to above reactions, when the reaction was performed in neat conditions, product **15a** was obtained in high yield (81%) only in 1 h (**Table 2.4**, entry 2). Note that other amine bases such as Et_3N, DMAP, and DABCO did not act as catalyst for this reaction (**Table 2.4**, entries 4-6).

Table 2.4. Reaction of **14b** with **10a** to give **15a**.[a]

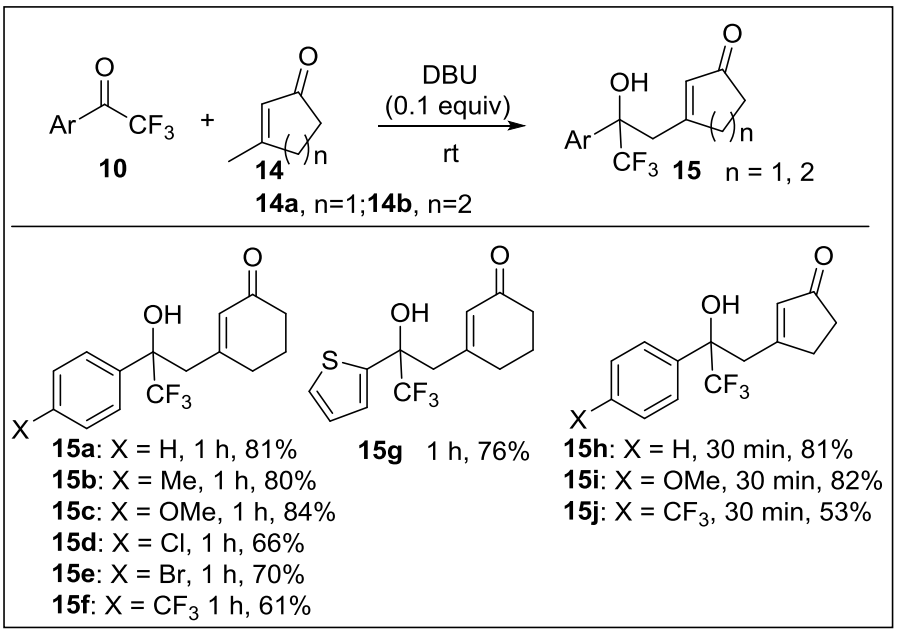


Entry	Catalyst (equiv)	Time (h)	Conversion[b] (%)	Yield[c] (%)
1[d]	DBU (0.1)	24	ND	65
2	DBU (0.1)	1	>95	81
3[e]	DBU (0.1)	1	85	ND
4	Et_3N (**XIII**) (0.2)	3	0	-
5	DABCO (**XV**) (0.2)	3	0	-
6	DMAP (**XVI**) (0.2)	3	0	-

[a] Conditions: Ketone **10a** (0.5 mmol, 1 equiv), **14b** (5 equiv), and catalyst (0.2 or 0.1 equiv as indicated) were stirred at 25 °C except where noted. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-(dimethylamino)pyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane. ND = not determined. [b] Conversion of **10a** was determined by ^{1}H NMR. [c] Isolated yield. [d] Toluene (1.0 mL) was used as solvent. [e] **14b** (2.0 equiv).

With the best reaction conditions (**Table 2.4**, entry 2), a series of trifluoromethyl-substituted aldol products **15** were obtained within 30 min to 1 h in good to high yields under solvent free mild conditions (**Scheme 2.11**). The reactions using trifluoromethyl ketone derivatives **10** with electron donating substituents such as methyl and methoxyl group on the aromatic ring as acceptors were clean and the products were obtained in high yields (80-84%, **15b**, **15c**, and **15i**). For the reactions of electron withdrawing group-substituted phenyl trifluoromethyl ketones, such as chloro-, bromo-, and trifluoromethyl-substituted phenyl ketones **10**, formation of by-products was detected with the desired aldol products by ^{1}H NMR analyses of the reaction mixtures. But, products **15** were reasonably obtained (53-70%, **15d**, **15e**, **15f** and **15j**). The reaction of the substrate with a thiophene unit with **14b** also afforded the desired product **15g** in 76% in 1 h. Both five member ring (**14a**) and six member

ring (**14b**) cyclic enones acted as donors. The reactions of **14a** were faster than the reactions of **14b**.

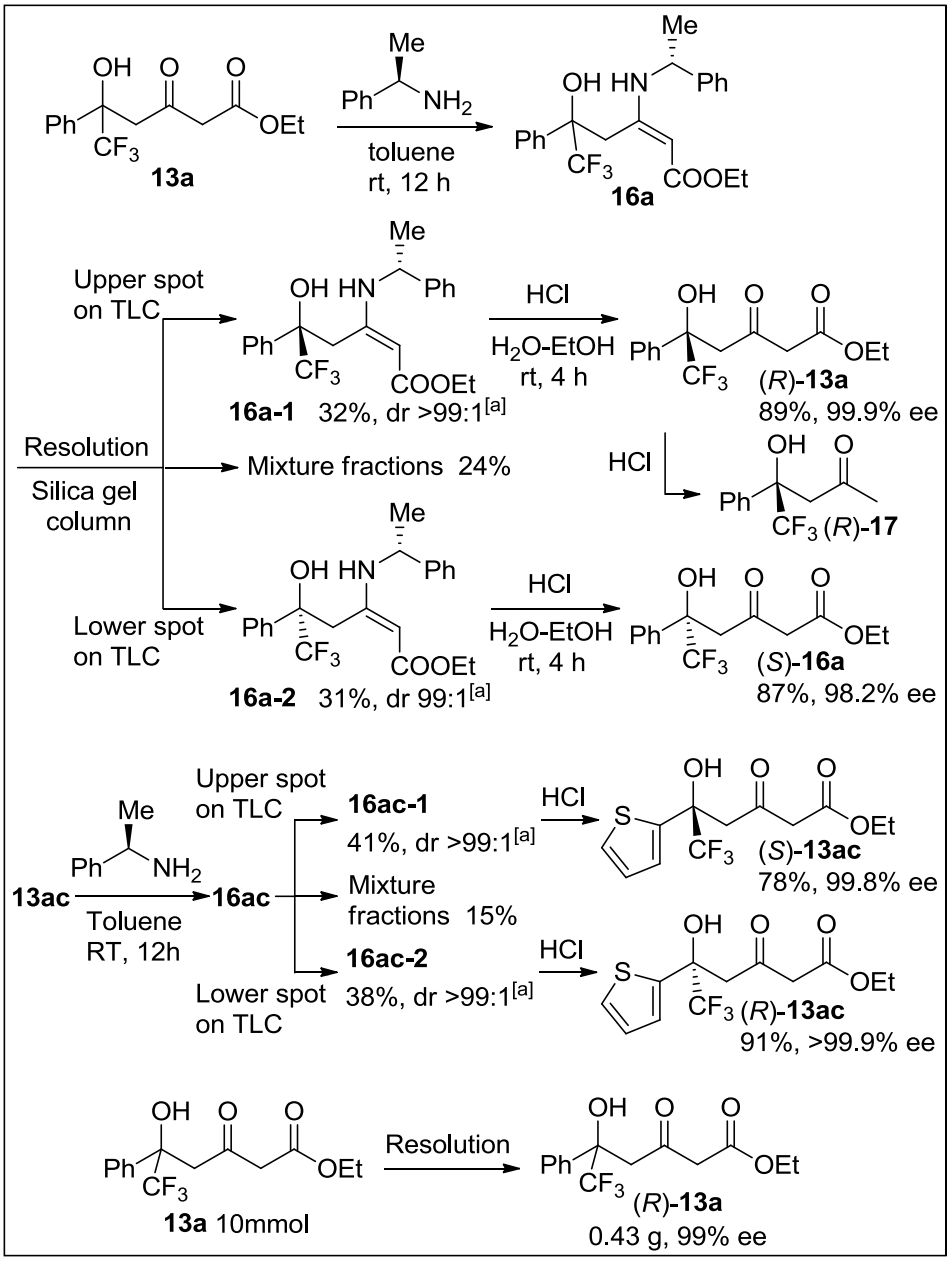


Scheme 2.11. Vinylogous aldol reactions of β-methyl-sustituted cyclic enones. Conditions: Ketone **10** (1.0 equiv), enone (5.0 equiv), and DBU (0.1 equiv) at 25 °C.

Vinylogous aldol reactions of **14b** with α-keto esters were previously reported.[107] In these reactions, a bifunctional primary amine-thiourea catalyst was used and products were obtained in moderate to good yields with good enantioselectivity. However, their reaction method did not work for the reaction of **14a**. Here, the developed DBU catalysis was applicable to reactions of both the six- and five- membered substrates **14** with **10**.

2.3.2 Resolution of the Enantiomers of Aldol Products Derived from β-Keto Esters

The DBU-catalyzed aldol reactions described above give racemic products. For the aldol products generated from β-keto esters, the enantiomerically pure forms were obtained through resolution via the formation of enamines with a homochiral amine (**Scheme 2.12**).



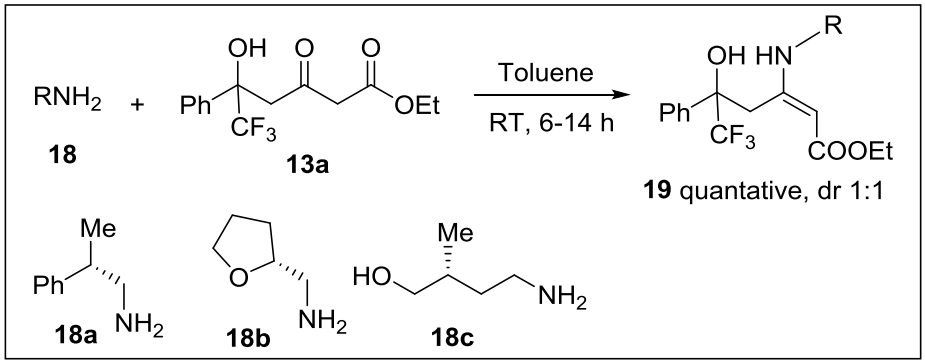
Scheme 2.12. Resolution of **13** to give the enantiomerically pure forms. Separations of **16a-1** and **16a-2**, and of **16ac-1** and **16ac-2**, were performed using single-time, typical silica gel flash column chromatography. The dr values were determined by ^{1}H NMR. The ee values were determined by HPLC. [a] Data after crystallization.

When aldol products **13** were mixed with (*R*)-1-phenylethylamine, stable enamines **16** were obtained. Purification of each of the diastereomers of the enamines by usual silica gel flash column chromotography, followed by hydrolysis of the enamines afforded essentially enantiomerically pure forms (such as >99% ee) of the aldol products (**Scheme 2.12**). A 10

mmol-scale chiral resolution of the aldol product (±)-**13a** was easily performed; with the resolution of enamine **16a**, 0.43 g of the enantiopure form of (*R*)-**13a** (99% ee) was concisely obtained.

The absolute stereochemistry of enantiomer **13a** obtained from enamine **16a-1** (upper spot product on TLC) was determined to be *R* by converting to known ketone **17** and also by X-ray crystal structure analysis of enamine **16a-1**.

Besides 1-phenylethylamine, several other amines **18** were also tested to form enamines **19** with racemic **13a** as shown in **Scheme 2.13**. The enamines **19** were formed smoothly, but the diastereomers were difficult to be separated by silica gel column (see **Experimental Section Chapter 6.2.2** for more information).



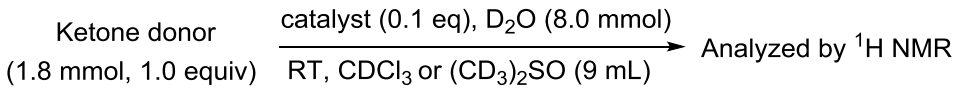
Scheme 2.13. Reactions of amines **18** with **13a** to give enamines **19**.

Chapter 3

Deuteration Studies of Enolizable Ketones under Aldol Reactions Catalysis Conditions

The DBU-catalyzed aldol reactions described in **Chapter 2** were relatively fast and provided the aldol products in good to high yields with perfect regioselectivities under mild conditions. In these aldol reactions, the C-C bonds formed at the methyl group of the pyruvic aldehyde derivative, at the methyl group of alkyl methyl ketones, and at the γ-position of β-keto esters. To elucidate the mechanism of the regioselective formation of the products in the aldol reactions and to understand the relationship between the carbanion formation and the bond-formation, deuteration of the ketone donors in the presence of DBU or other amines was analyzed.

Ketones were treated with amine catalysts in the presence of D_2O in $CDCl_3$ or deuterated DMSO and deuteration was monitored by ^1H NMR (**Scheme 3.1**).



Scheme 3.1. Deuteration of the aldol reaction donors under aldol reaction catalysis conditions.

First, deuteration of ketone **1** was analyzed in the presence of DBU and D_2O in $CDCl_3$. The α-methyl group (position A) was deuterated (**Figure 3.1**, **Table 3.1**); this was consistent with the bond-formation regioselectivity. After 6 h, more than 70% of the protons at position

A were exchanged by deuteriums. No deuteration for the CH at position B was observed after 2 days.

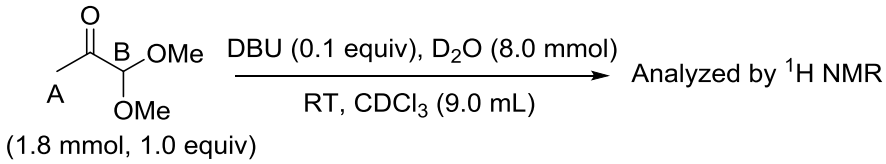
When L-proline was used instead of DBU (in $(CD_3)_2SO$ for the use of L-proline versus in $CDCl_3$ for the use of DBU), the α-methyl group (position A) were also deuterated (**Figure 3.2**, **Table 3.1**). After 7 days, around 40% of the protons at position A were exchanged by deuteriums in the deuteration reaction using L-proline. Similar to the deuteration using DBU, no deuteration for the CH at position B was observed after 7 days.

The initial deuteration rate of α-methyl group in pyruvic aldehyde derivative **1** under DBU-catalysis conditions was approximately 50 times faster than that under L-proline-catalysis conditions. Although the deuteration rates are not necessarily directly related to the aldol reaction rates, it gives the clues for the fast DBU-catalyzed aldol reactions. Reported proline-catalyzed aldol reactions of **1** took 5-10 days;[73] this slow reaction is well explained by the slow deuteration.

Deuteration of **1** was further tested in the presence of β-proline in $(CD_3)_2SO$ (**Figure 3.3**, **Table 3.1**). Deuteration of **1** by β-proline catalysis also occurred only at the methyl group at position A of **1**, and the initial rate of the deuteration by β-proline catalysis was approximately 100-fold faster than that by the proline catalysis and also faster than that by the DBU catalysis in $CDCl_3$ described above.

Deuteration of **1** was also tested in the presence of pyrrolidine-CH_3COOH in $(CD_3)_2SO$ (**Figure 3.4**, **Table 3.1**). In this case, the initial rate of the deuteration at the methyl group was 6.6×10^{-3} min^{-1}, similar to the rate by the DBU catalysis in $CDCl_3$ (5.7×10^{-3} min^{-1}). No deuteration at position B was also detected in the presence of pyrrolidine-CH_3COOH.

When deuteration of **1** was tested in the presence of Et_3N in $CDCl_3$, no deuteration of **1** was observed. This was consistent with that Et_3N did not work as the catalyst for aldol reactions of **1** with phenyl trifluoromethyl ketone.



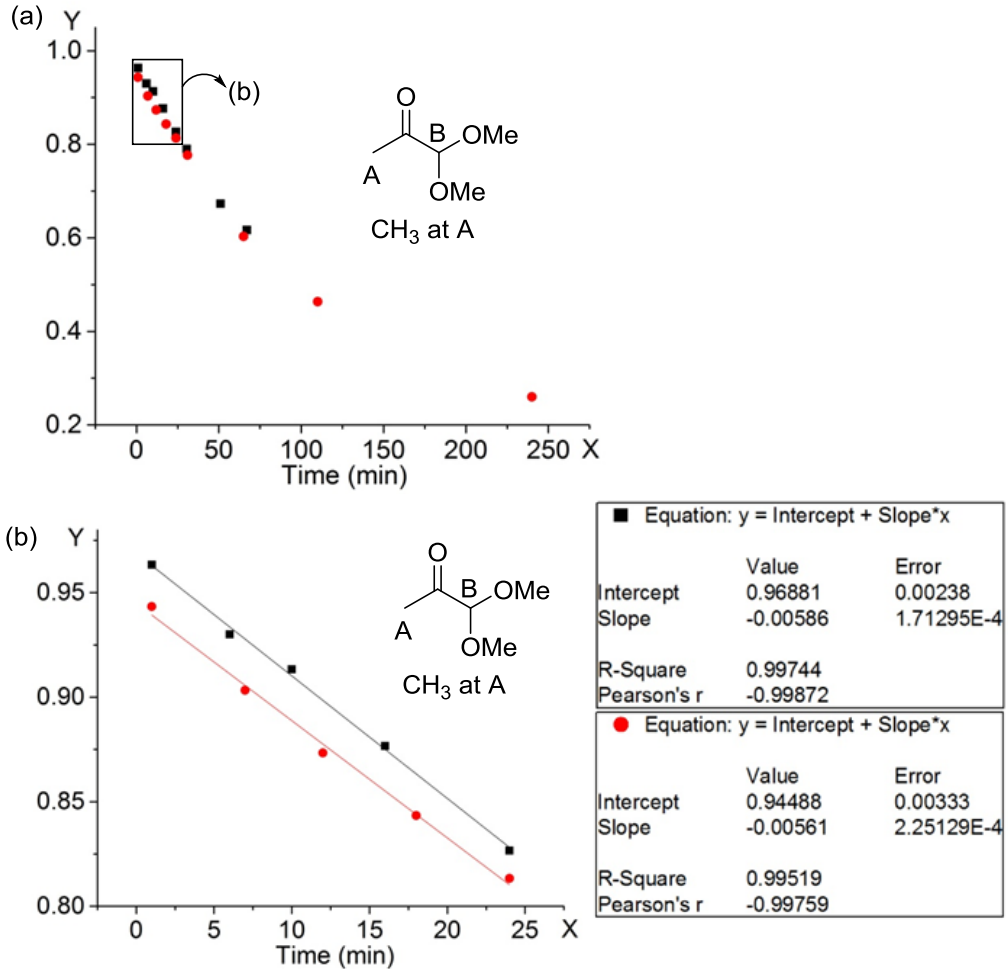


Figure 3.1. Deuteration of CH_3 at position A of pyruvic aldehyde derivative **1** in the presence of DBU. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of DBU, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position A]/{[Integration of $(OCH_3)_2$]×1/2}. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

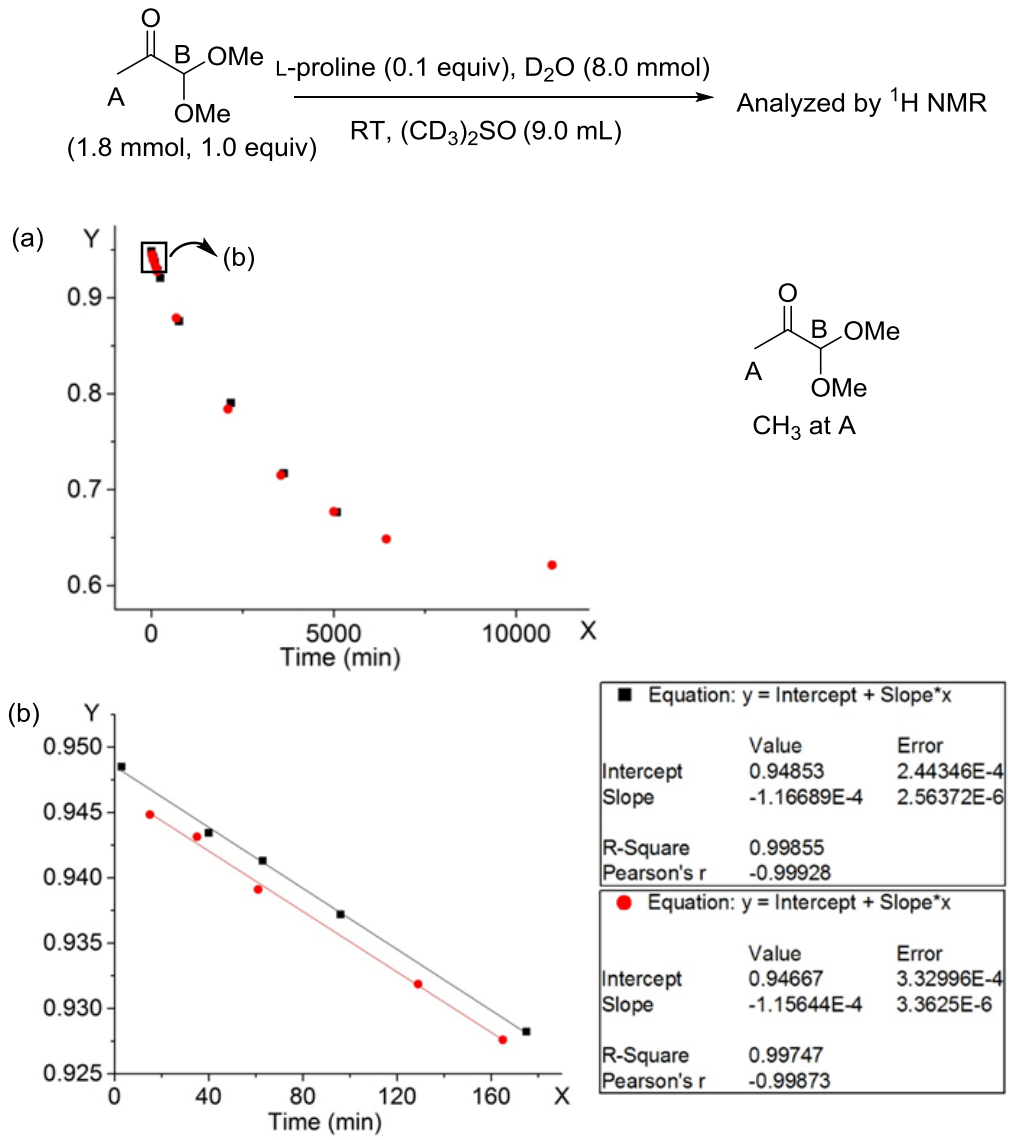


Figure 3.2. Deuteration of CH_3 at position A of pyruvic aldehyde derivative **1** in the presence of L-proline. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of L-proline, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position A]/{[Integration of $(OCH_3)_2$]×1/2}. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

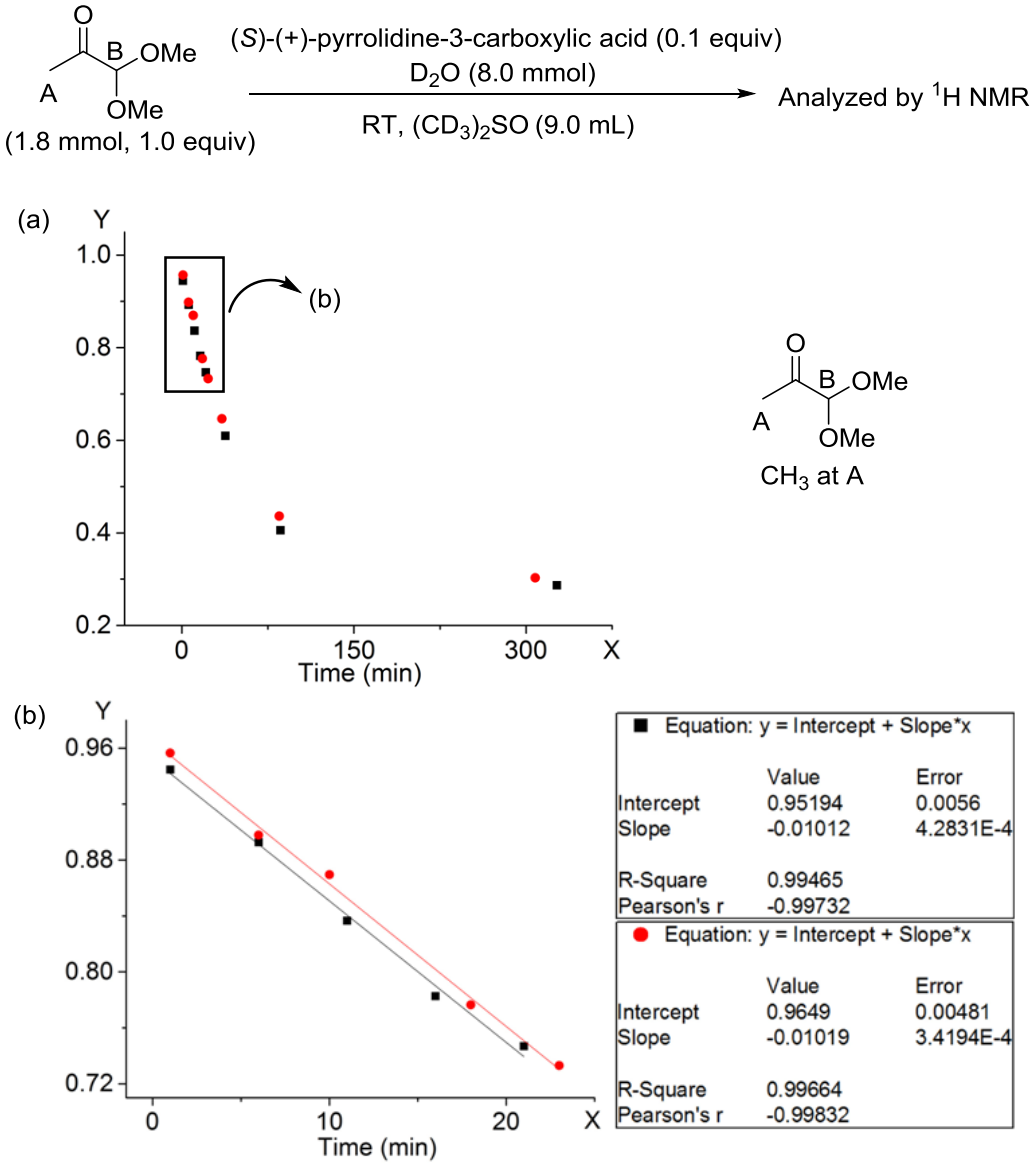


Figure 3.3. Deuteration of CH_3 at position A of pyruvic aldehyde derivative **1** in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position A]/{[Integration of $(OCH_3)_2$]×1/2}. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

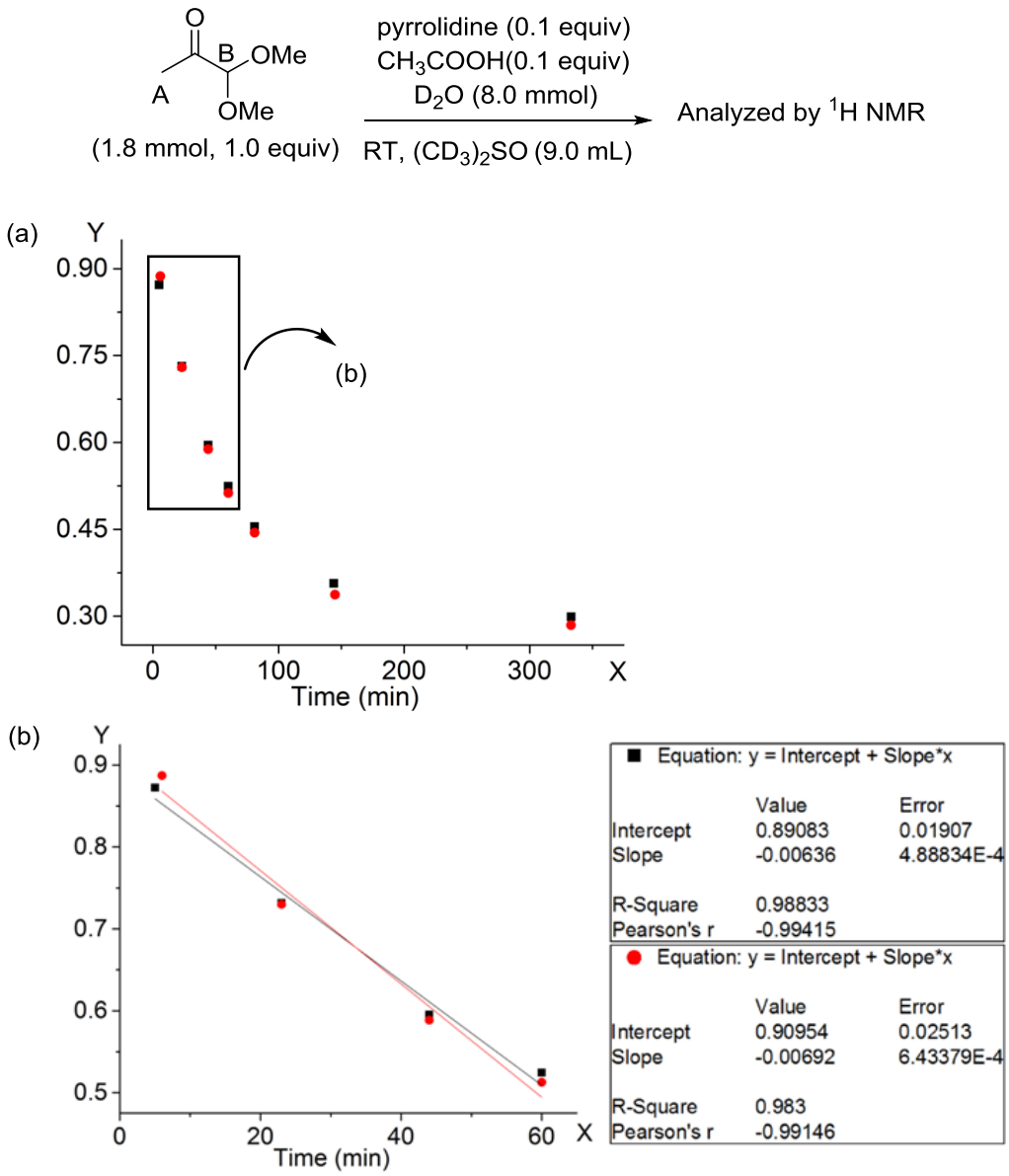


Figure 3.4. Deuteration of CH_3 at position A of pyruvic aldehyde derivative **1** in the presence of pyrrolidine-CH_3COOH. X = Time after addition of pyrrolidine-CH_3COOH, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position A]/{[Integration of $(OCH_3)_2$]×1/2}. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

Similarly, deuteration of methyl ethyl ketone, methoxyacetone, hydroxyacetone, and ethyl acetoacetate with D_2O were also analyzed.

For methyl ethyl ketone, in the presence of DBU, deuteration occurred at both the α-methyl group (position C) and the α-methylene group (position D) as shown in **Figure 3.5**, **Figure 3.6**, and **Table 3.1**. The initial deuteration rates at Position C and position D were similar. In the DBU-catalyzed aldol reaction of methyl ethyl ketone with aryl trifluoromethyl ketone, the bond-formation occurred mostly at the α-methyl group (position C). The regioselectivity of the aldol reaction is likely controlled by steric factors.

In L-proline-catalysis, also both the α-methyl group (position C) and the α-methylene group (position D) were deuterated as shown in **Figure 3.7**, **Figure 3.8**, and **Table 3.1**. The initial deuteration rate at position C was approximately 7-fold faster than that at position D.

In β-proline-catalysis, both position C and position D were deuterated as shown in **Figure 3.9**, **Figure 3.10**, and **Table 3.1**. The initial rate of the deuteration at position C by β-proline catalysis was approximately 40-fold faster than that by proline catalysis and the initial rate of the deuteration at position D by β-proline catalysis was approximately 160-fold faster than that by proline catalysis.

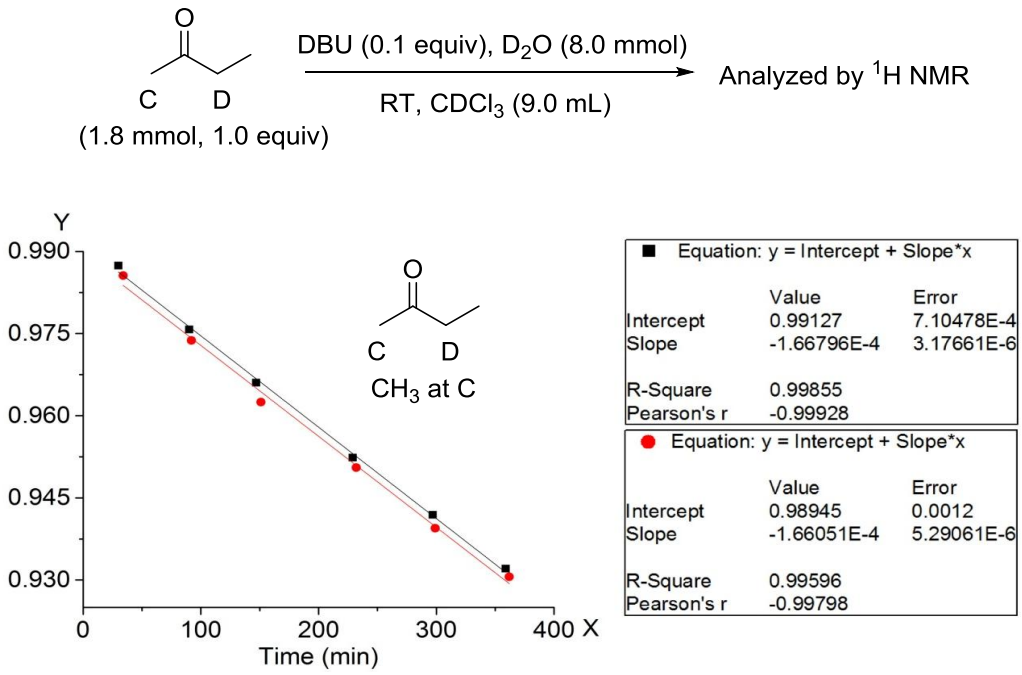


Figure 3.5. Deuteration of CH_3 at position C of methyl ethyl ketone in the presence of DBU. X = Time after addition of DBU, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position C]/(Integration of CH_3 of the ethyl group). As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

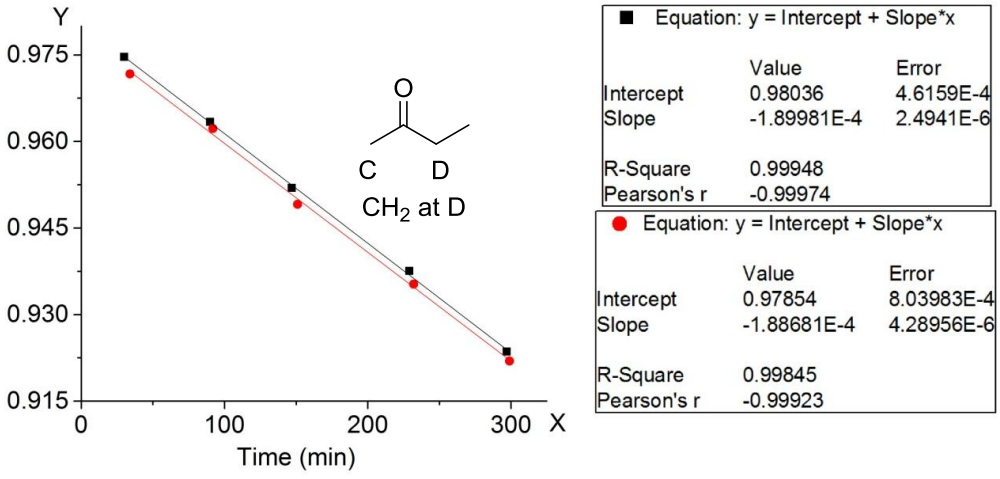


Figure 3.6. Deuteration of CH_2 at position D of methyl ethyl ketone in the presence of DBU. X = Time after addition of DBU, Y = [Integration of the CH_2 (including CHD) at position D]/[(Integration of CH_3 of the ethyl group)×(2/3)]. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice

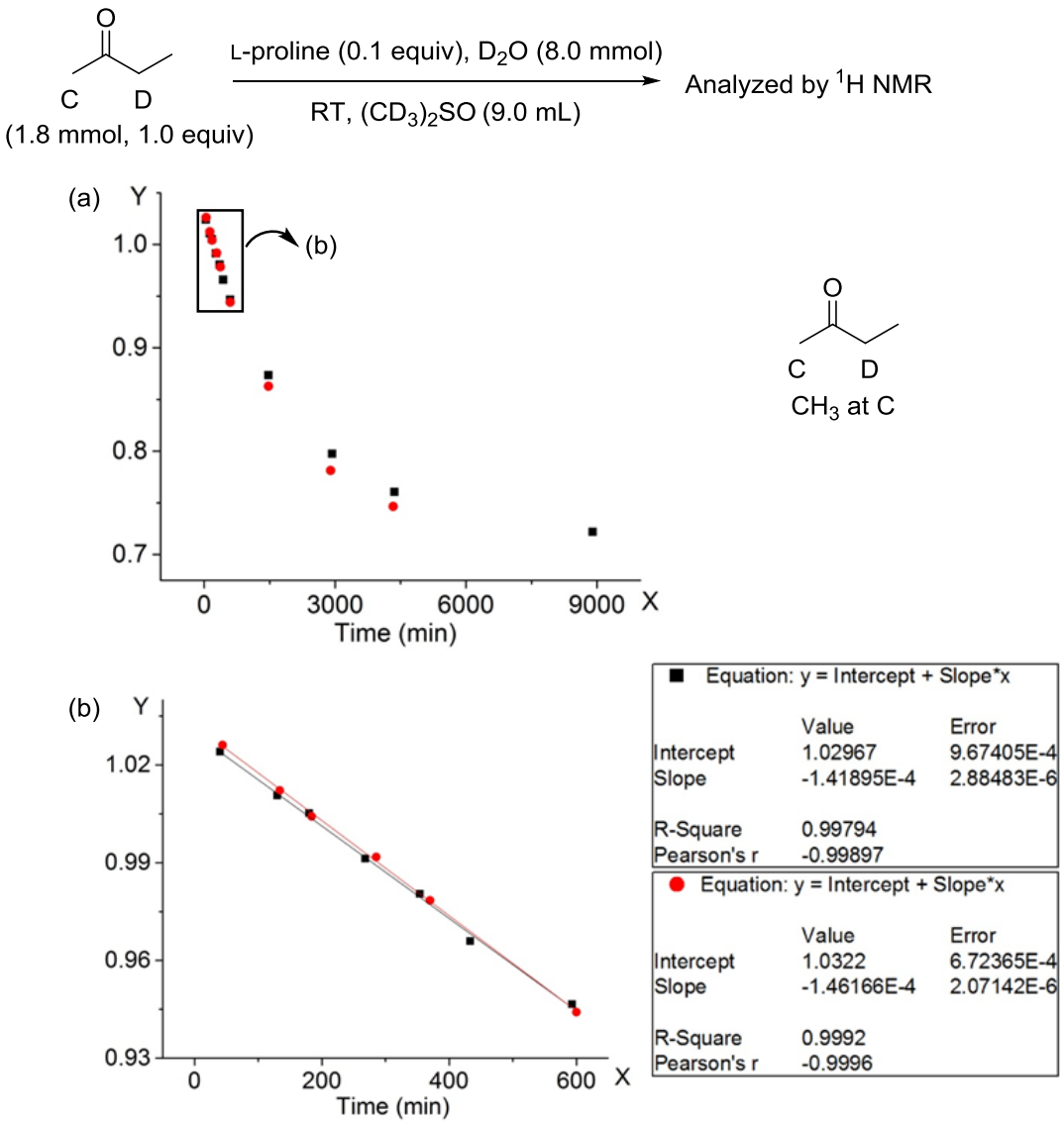


Figure 3.7. Deuteration of CH_3 at position C of methyl ethyl ketone in the presence of L-proline. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of L-proline, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position C]/(Integration of CH_3 of the ethyl group). As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

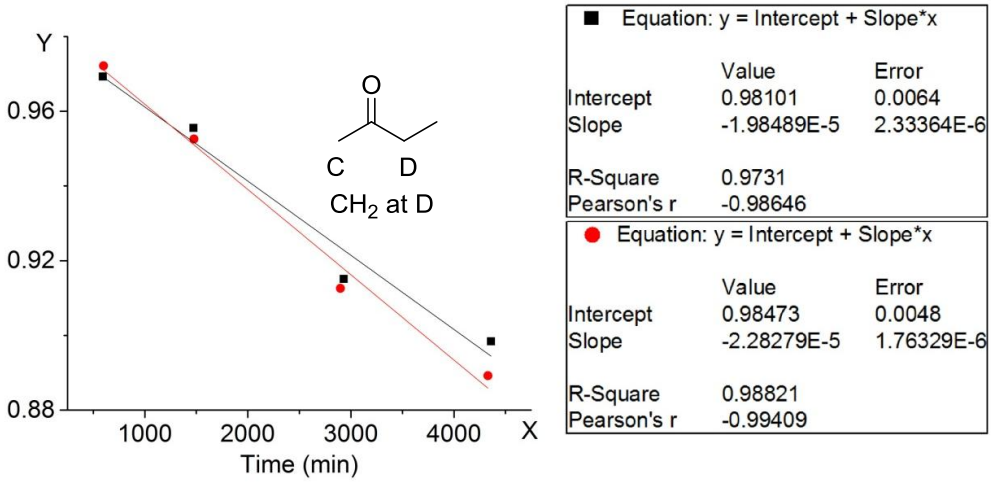


Figure 3.8. Deuteration of CH_2 at position D of methyl ethyl ketone in the presence of L-proline. X = Time after addition of L-proline, Y = [Integration of the CH_2 (including CHD) at position D]/[(Integration of CH_3 of the ethyl group)×(2/3)]. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

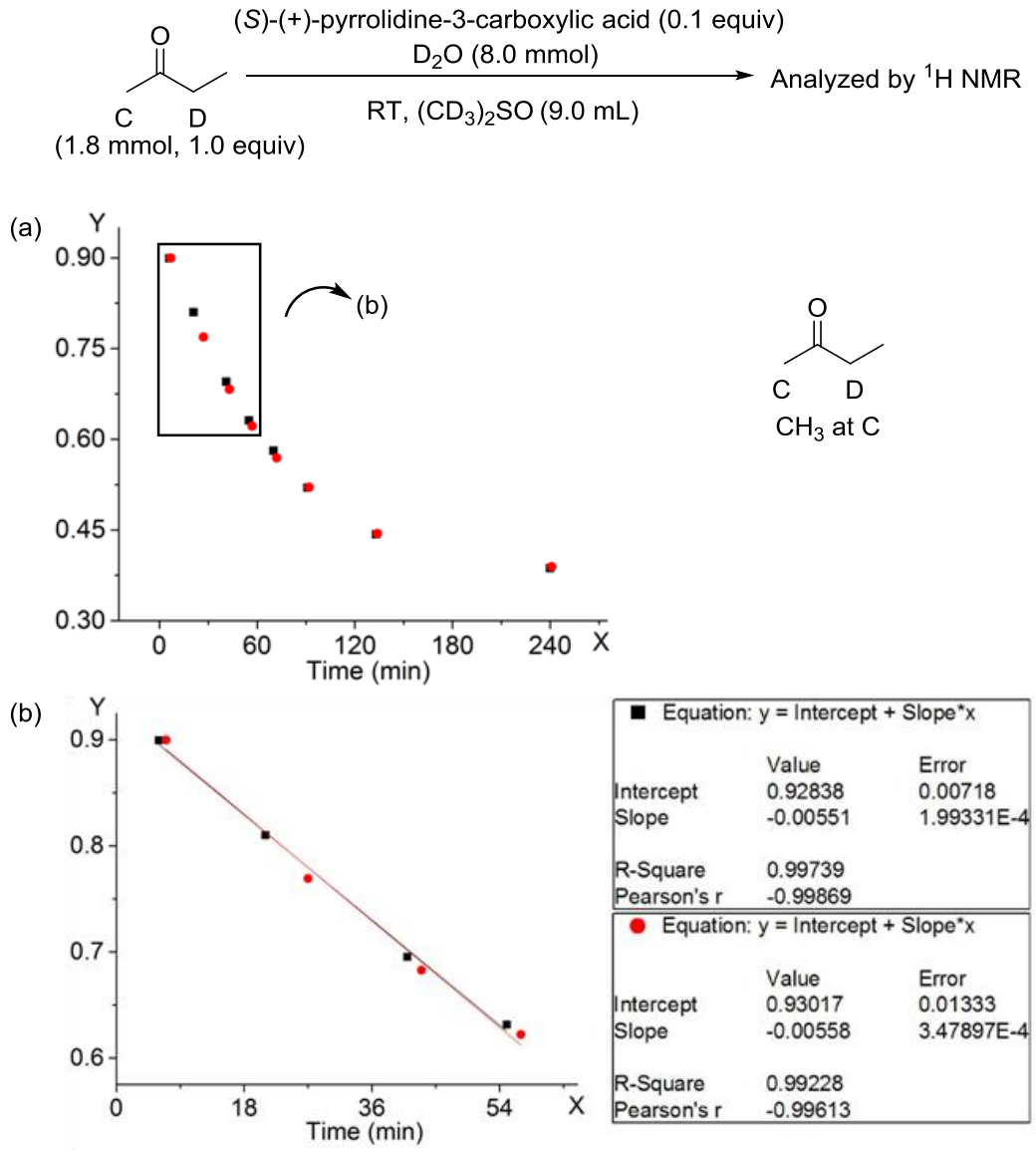


Figure 3.9. Deuteration of CH_3 at position C of methyl ethyl ketone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = [Integration of the CH_3 (including CH_2D and CHD_2) at position C]/(Integration of CH_3 of the ethyl group). As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

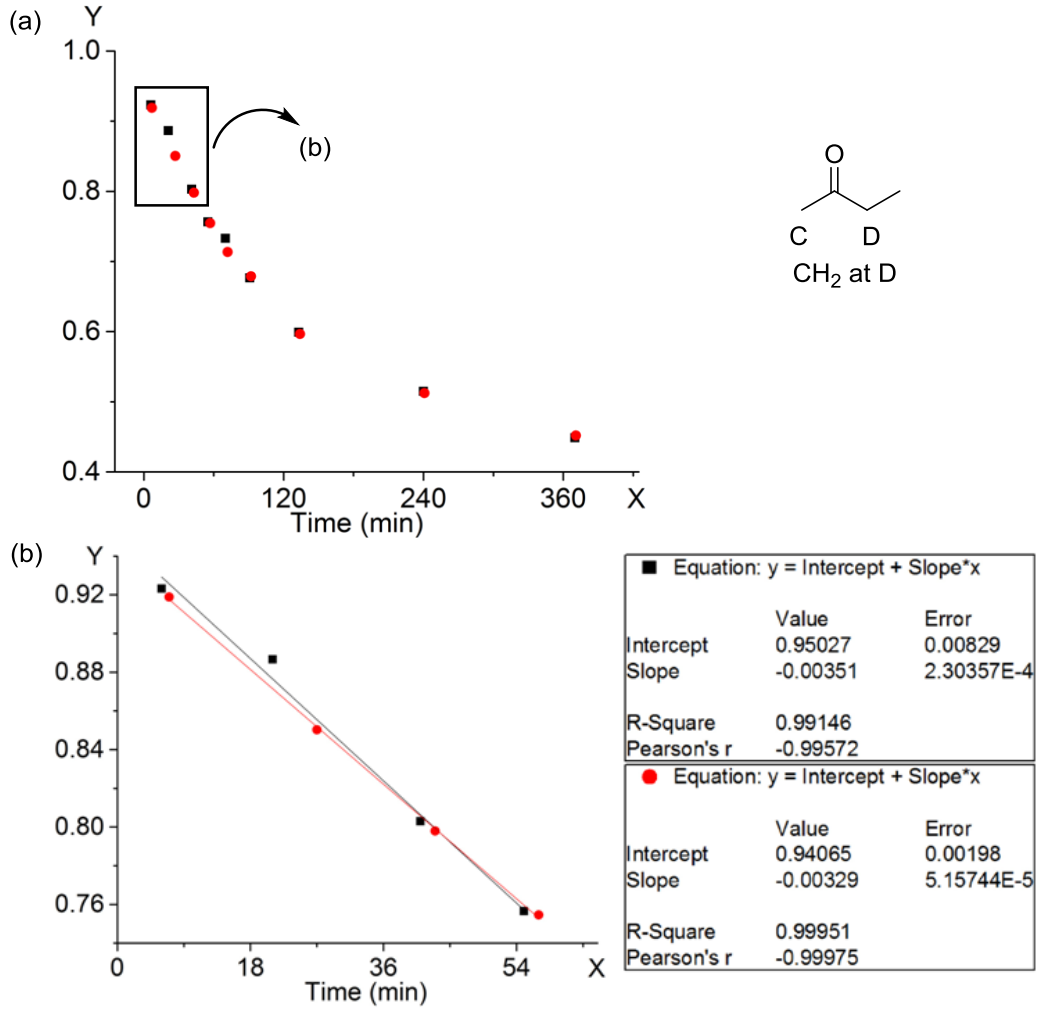


Figure 3.10. Deuteration of CH_2 at position D of methyl ethyl ketone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = [Integration of the CH_2 (including CHD) at position D]/[(Integration of CH_3 of the ethyl group)×(2/3)]. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

For methoxyacetone, the initial rate of the deuteration per proton at the methyl group at position E was 2- to 3-fold faster than that per proton at the methoxy-substituted methylene group at position F in each of all the cases of the DBU-, proline-, and β-proline-catalysis (**Figure 3.11**-**Figure 3.16**, **Table 3.1**).

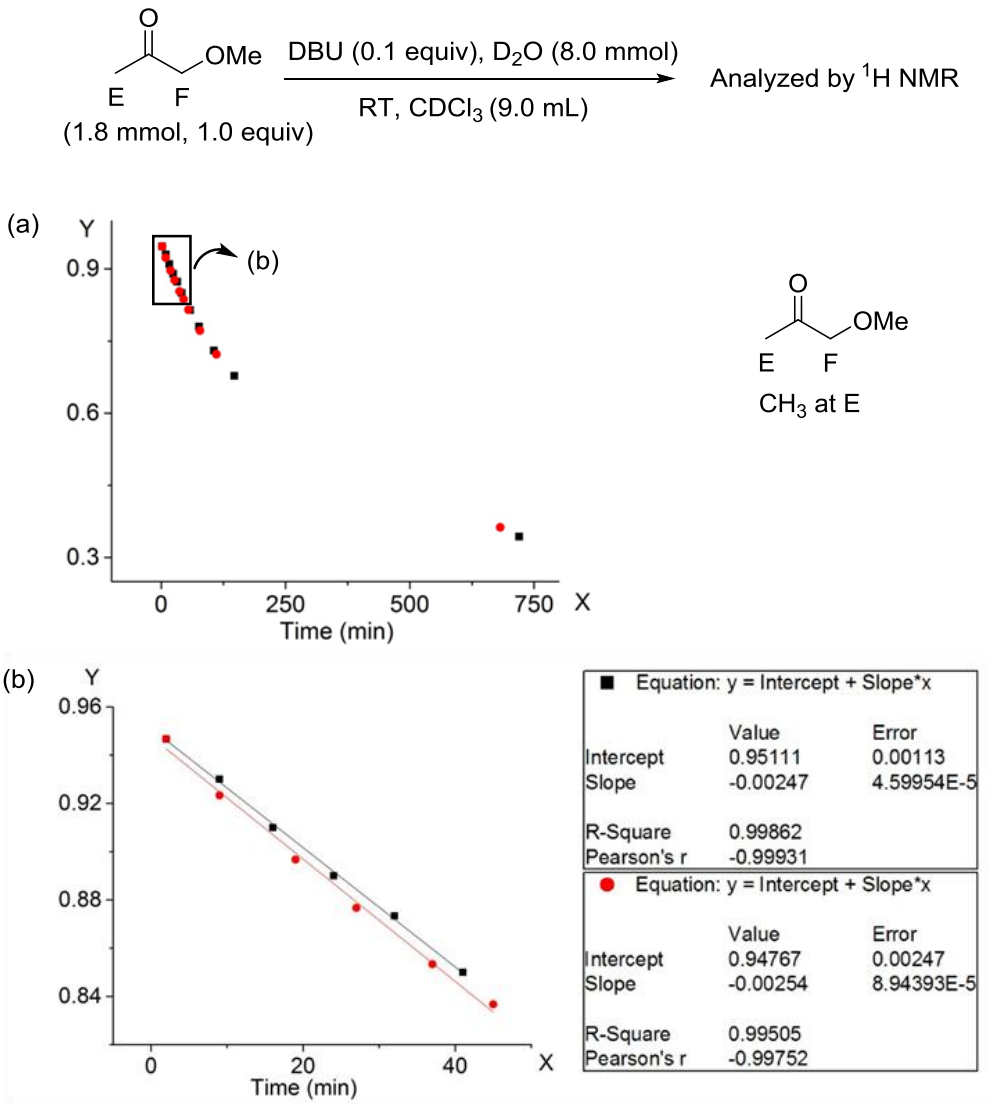


Figure 3.11. Deuteration of CH_3 at position E of methoxyacetone in the presence of DBU. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of DBU, Y = [Integration of the CH_3 (CH_2D and CHD_2) at position E]/(Integration of $OC\underline{H_3}$). As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

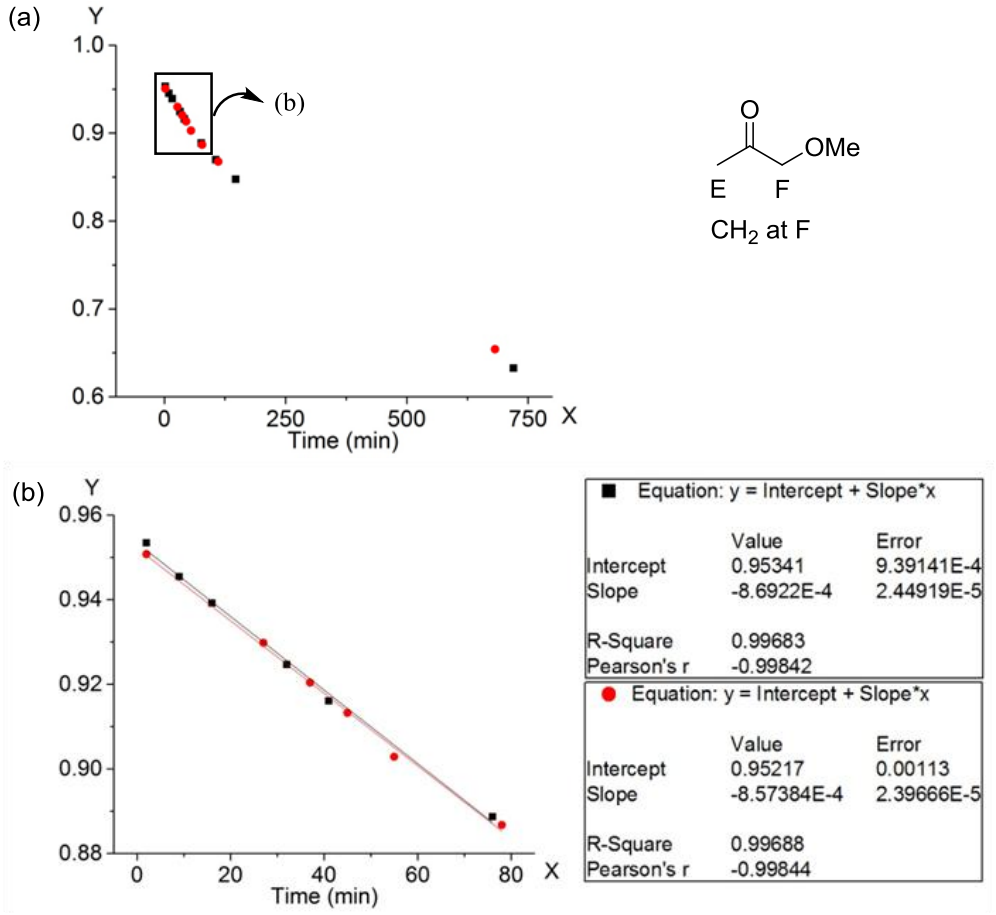


Figure 3.12. Deuteration of CH_2 at position F of methoxyacetone in the presence of DBU. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of DBU, Y = [Integration of the CH_2 (including CHD) at position F]/[(Integration of $OC\underline{H_3}$)×(2/3)]. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

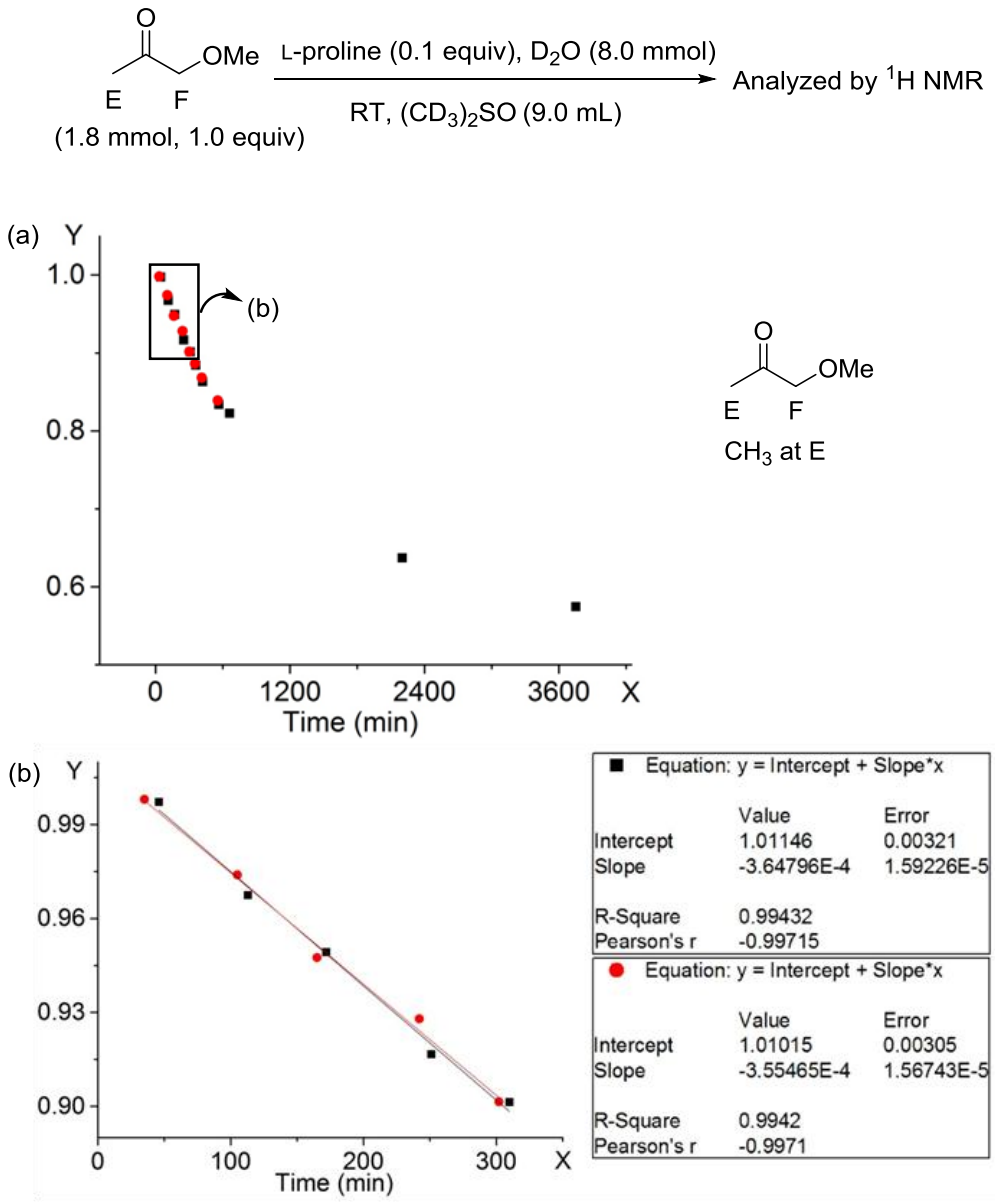


Figure 3.13. Deuteration of CH_3 at position E of methoxyacetone in the presence of L-proline. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of L-proline, Y = Integration of the CH_3 (including CH_2D and CHD_2) per original proton at position E (an internal standard was used). Deuteration experiments were carried out twice.

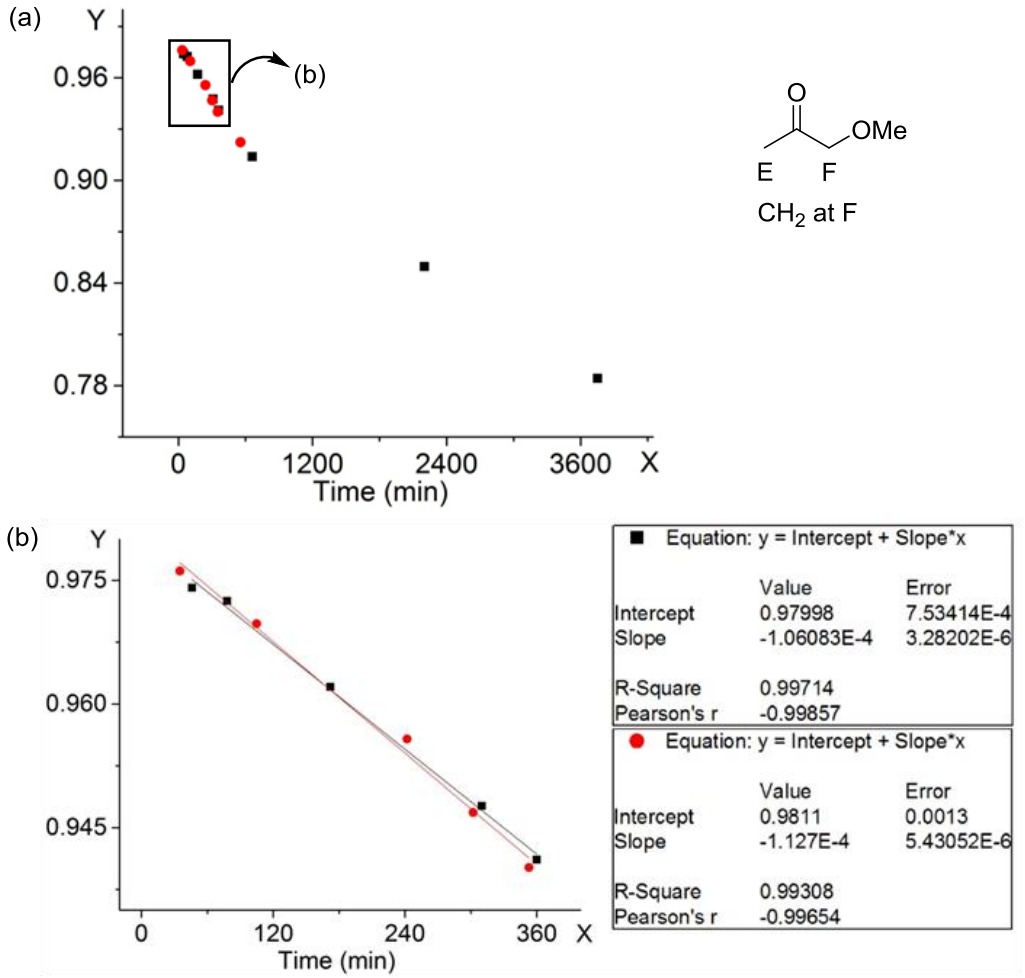


Figure 3.14. Deuteration of CH_2 at position F of methoxyacetone in the presence of L-proline. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of L-proline, Y = Integration of the CH_2 (including CHD) per original proton at position F (an internal standard was used). Deuteration experiments were carried out twice.

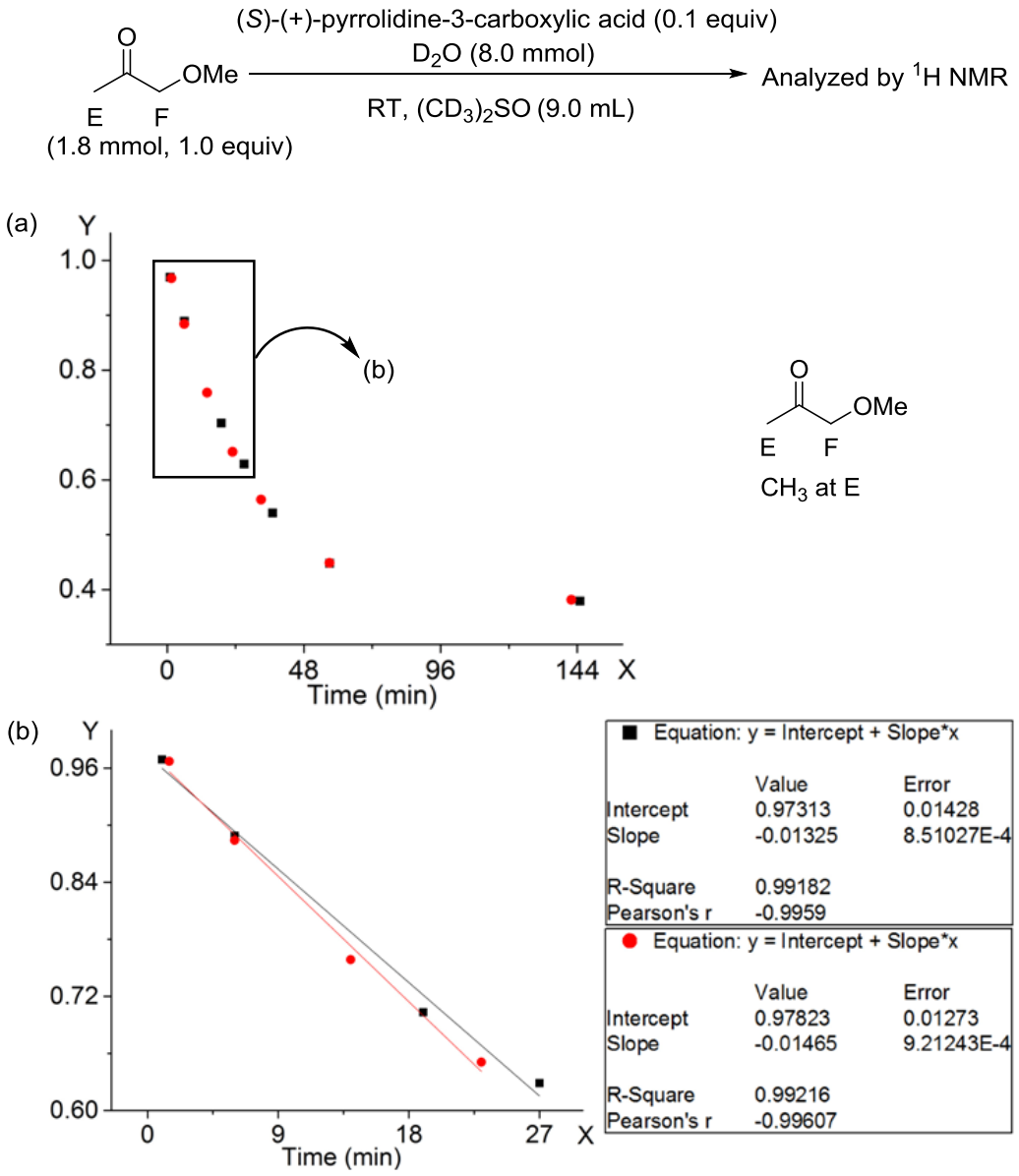


Figure 3.15. Deuteration of CH_3 at position E of methoxyacetone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = [Integration of the CH_3 (CH_2D and CHD_2) at position E]/(Integration of $OC\underline{H_3}$). Deuteration experiments were carried out twice.

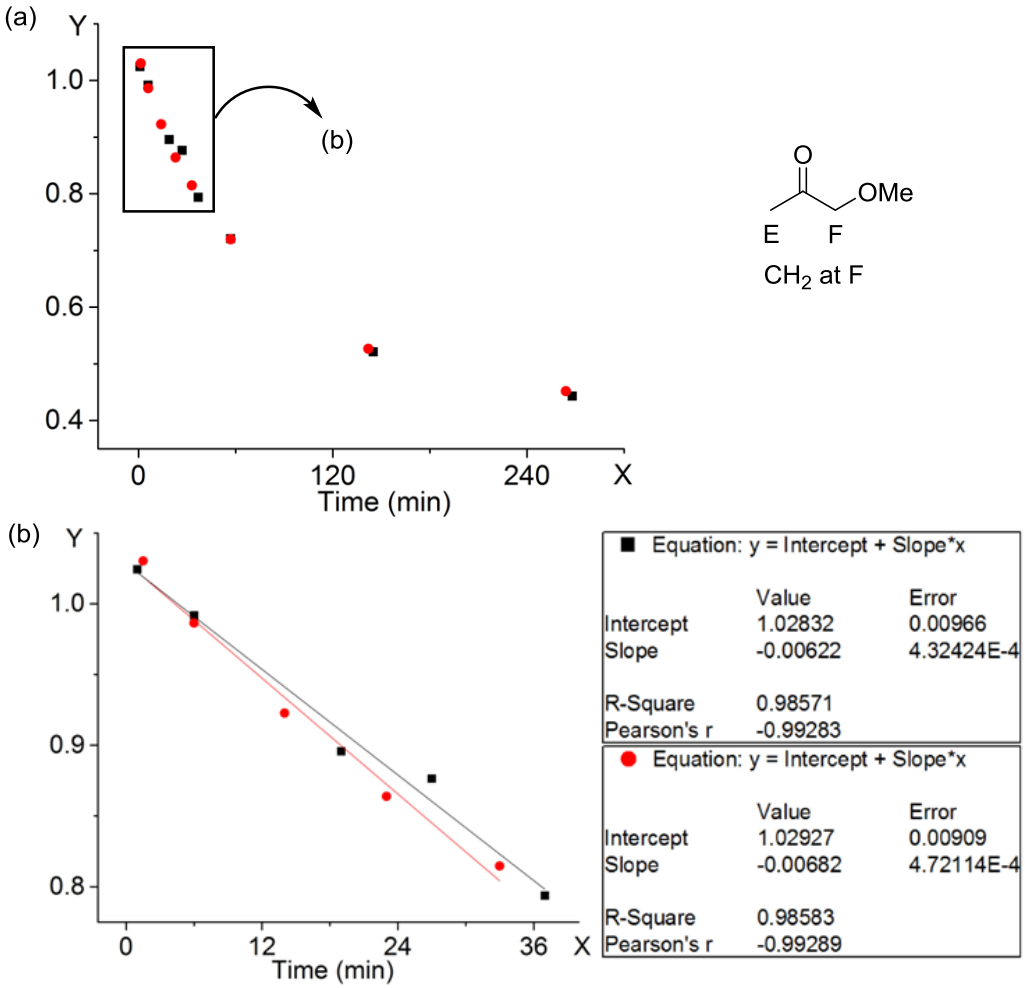


Figure 3.16. Deuteration of CH_2 at position F of methoxyacetone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = [Integration of the CH_2 (including CHD) at position F]/[(Integration of $OC\underline{H}_3$)×(2/3)]. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

For the deuteration of hydroxyacetone, DBU was not used based on the results that the DBU was not a good catalyst for the reaction of hydroxyacetone with aryl trifluoromethyl ketones. Proline and β-proline have been used as the catalysts for reactions of hydroxyacetone; deuteration of hydroxyacetone in the presence of these catalysts was analyzed (**Figure 3.17**-**Figure 3.19**, **Table 3.1**).

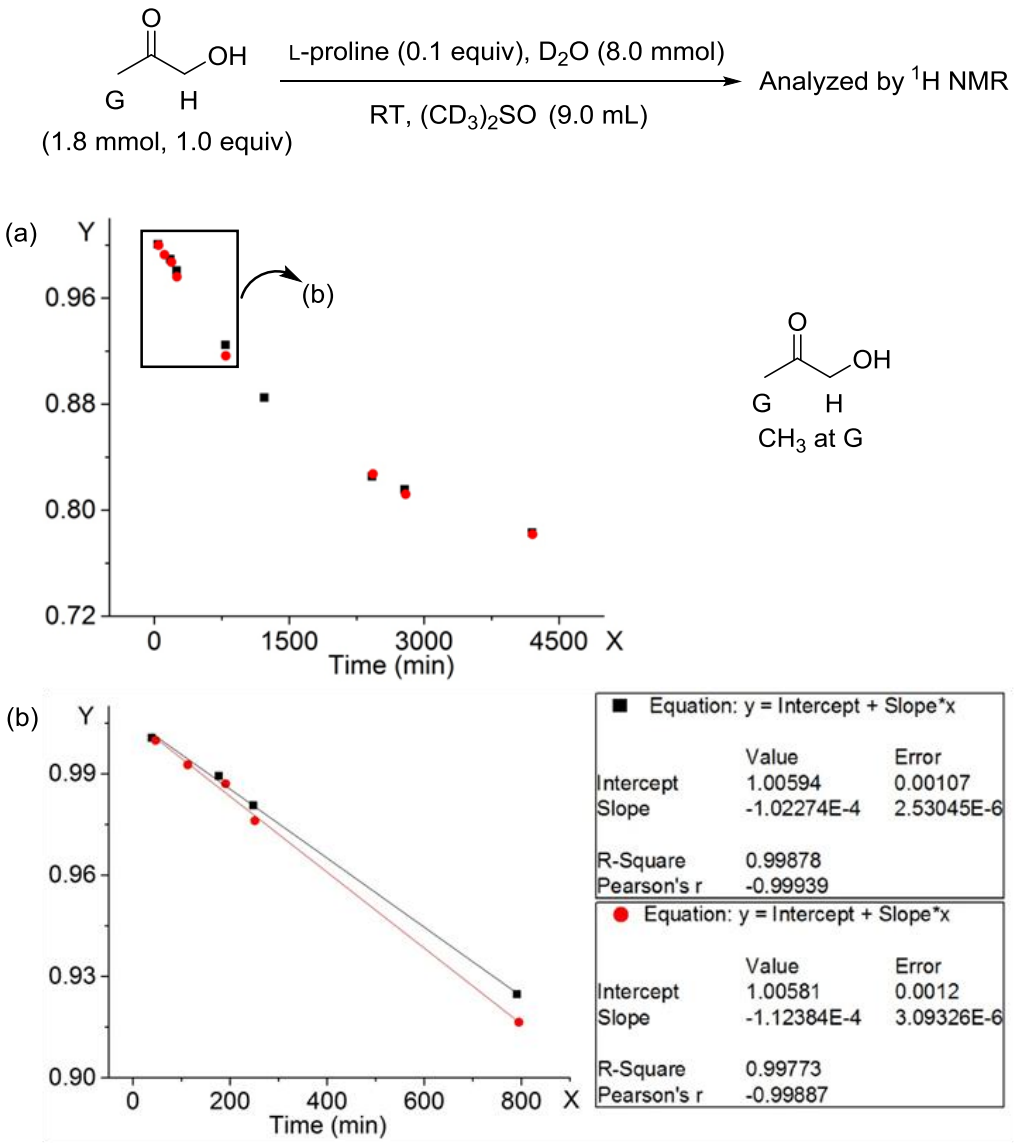


Figure 3.17. Deuteration of CH_3 at position G of hydroxyacetone in the presence of L-proline. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of L-proline, Y = Integration of the CH_3 (including CH_2D and CHD_2) per original proton at position G (an internal standard was used). Deuteration experiments were carried out twice.

The initial deuteration rate at the methyl group at position G of hydroxyacetone was similar to that at the methyl group at position A of ketone **1** under the both proline- and β-proline-catalysis. In proline-catalysis, the deuteration rate of the hydroxyl group-substituted methylene group at position H was significantly slower or at least 10-times slower than that of

the methyl group at position G. In the β-proline-catalysis, initial deuteration rate at the methyl group at position G was approximately 100-fold faster than that at the same methyl group by proline catalysis.

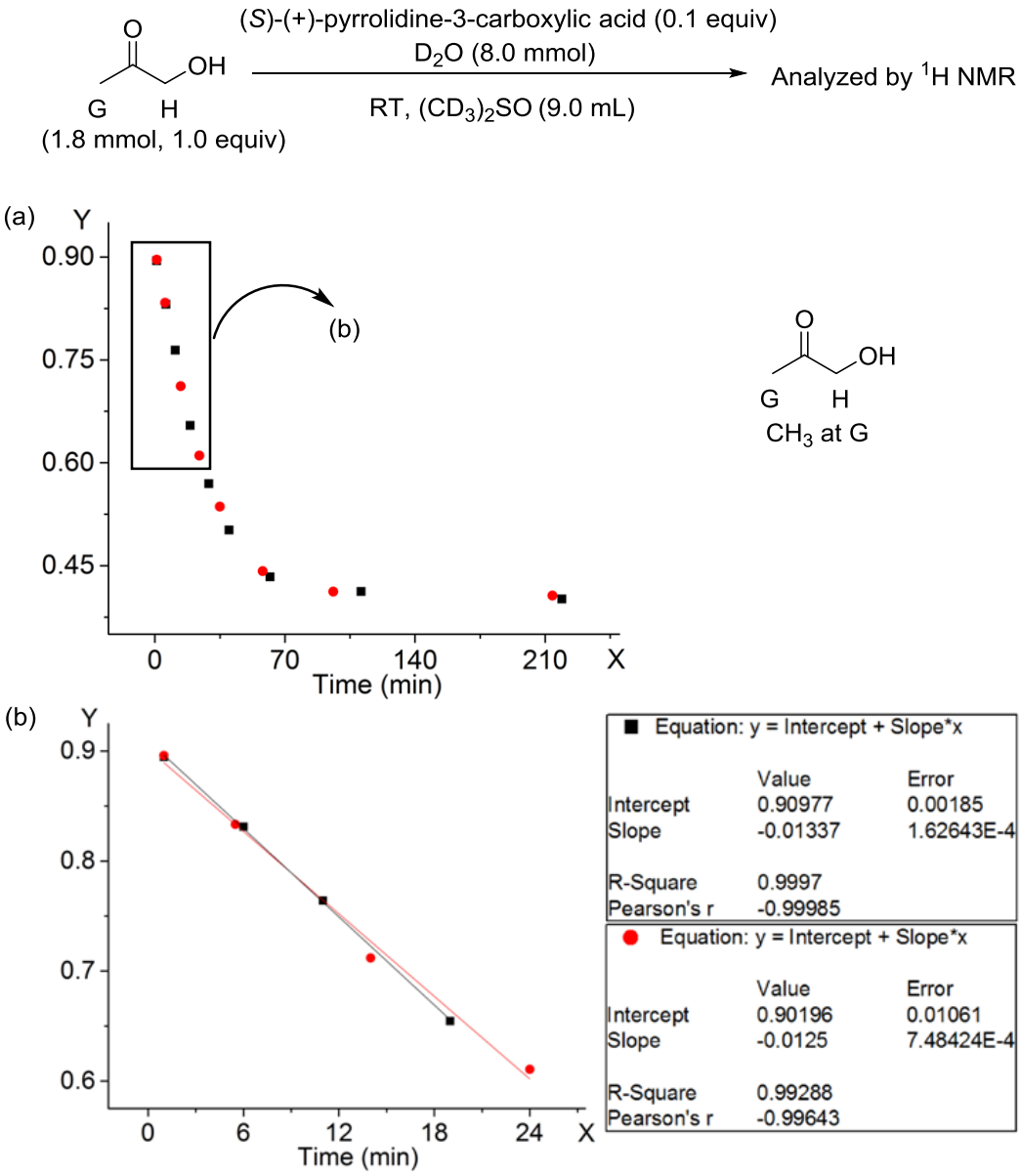


Figure 3.18. Deuteration of CH_3 at position G of hydroxyacetone **4** in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = Integration of the CH_3 (including CH_2D and CHD_2) per original proton at position G (an internal standard was used). Deuteration experiments were carried out twice.

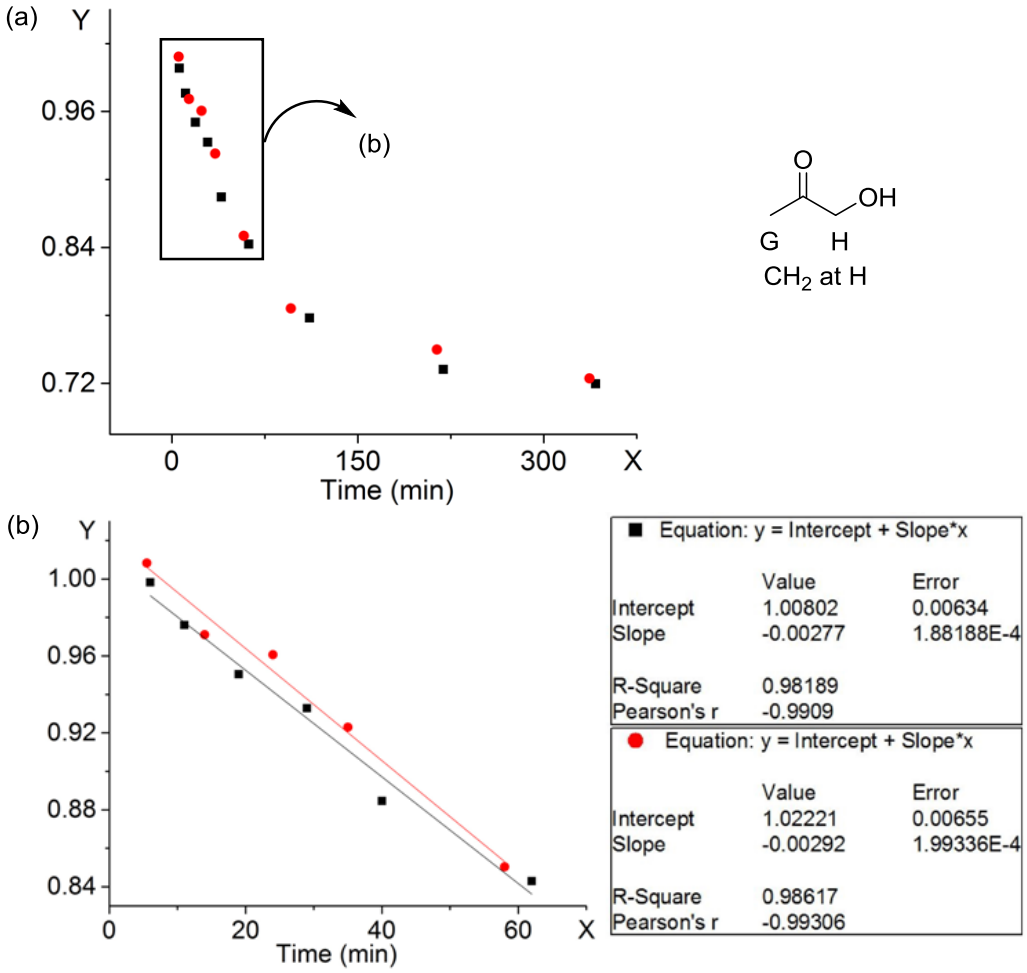


Figure 3.19. Deuteration of CH_2 at position H of hydroxyacetone **4** in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid. (a) Time course, full range of the time analyzed, and (b) the initial range. X = Time after addition of (*S*)-(+)-pyrrolidine-3-carboxylic acid, Y = Integration of the CH_2 (including CHD) per original proton at position H (an internal standard was used). Deuteration experiments were carried out twice.

For ethyl acetoacetate, the deuteration of the methyl group at position I was observed under DBU-catalysis. The methylene group at position J was immediately deuterated in more than 70% in all the cases of the DBU-, proline-, and β-proline-catalysis (**Figure 3.20**, **Table 3.1**). For the reaction of ethyl acetoacetate with aryl trifluoromethyl ketones in the presence of DBU, only afforded the product with C-C bond formation at position I.

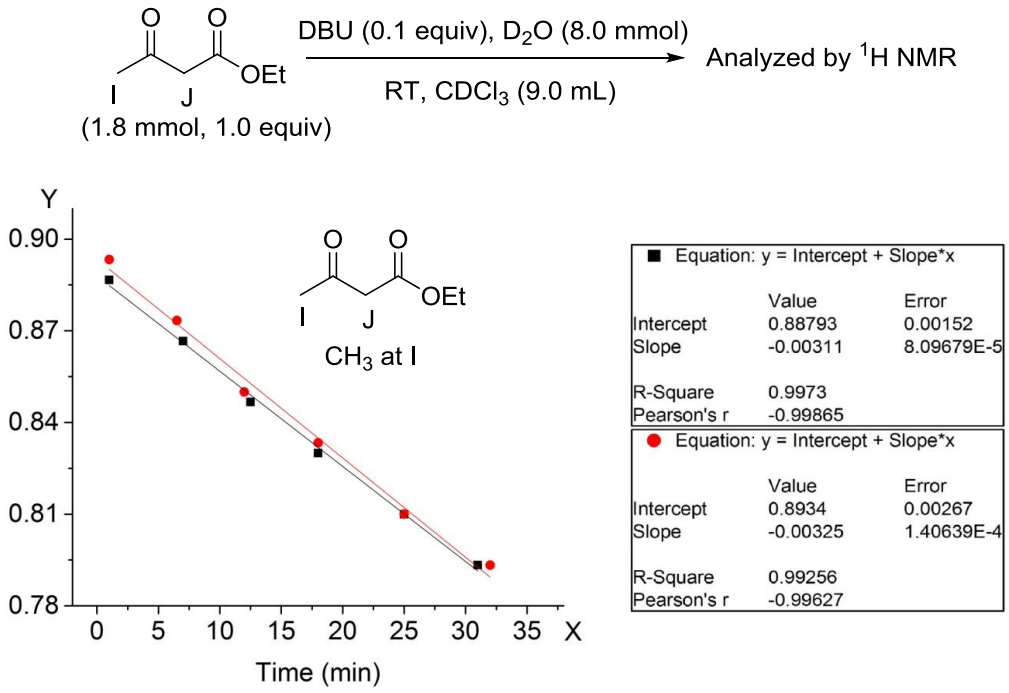
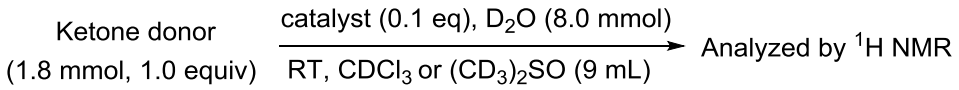
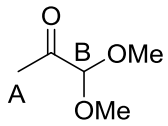
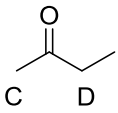
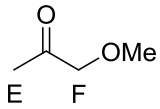
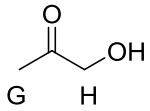
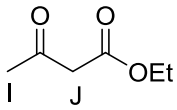


Figure 3.20. Deuteration of CH_3 at position I of ethyl acetoacetate **5** in the presence of DBU. X = Time after addition of DBU, Y = [Integration of the CH_3 (CH_2D and CHD_2) at position I]/[Integration of $OC\underline{H_2}CH_3$)×(3/2)]. As the result, the slope of the equation is the rate of per original proton. Deuteration experiments were carried out twice.

Initial deuteration rates of ketone donors were summarized in **Table 3.1**. To conclude from these deuteration experiments: Carbanion formation is necessary for aldol reactions and DBU can deprotonate ketones to form carbanions. However, the C-C bond formation site is not necessarily to be related to the deprotonation site. The reaction site may be controlled by steric reasons and other factors. For the C-C bond formation in aldol reactions, formation of the products may rely on the transition states to form the bond. Easiness of the formation of carbanions (ie, deuteration) was not directly related to the formation of the aldol products.

Table 3.1. Observed deuteration rates per original proton.[a]



ketone	position	deuteration rate per proton (min^{-1})		
		DBU catalysis	L-proline	β-proline
	CH_3 at A	5.7×10^{-3}	1.2×10^{-4}	1.0×10^{-2}
	CH at B	Not observed	Not observed	Not observed
	CH_3 at C	1.7×10^{-4}	1.4×10^{-4}	5.5×10^{-3}
	CH_2 at D	1.9×10^{-4}	2.1×10^{-5}	3.4×10^{-3}
	CH_3 at E	2.5×10^{-3}	3.6×10^{-4}	1.4×10^{-2}
	CH_2 at F	8.6×10^{-4}	1.1×10^{-4}	6.5×10^{-3}
	CH_3 at G	Not performed	1.1×10^{-4}	1.3×10^{-2}
	CH_2 at H	Not Performed	$<1.3 \times 10^{-5}$	2.8×10^{-3}
	CH_3 at I	3.2×10^{-3}	--[b]	--[b]
	CH_2 at J	--[c]	--[c]	--[c]

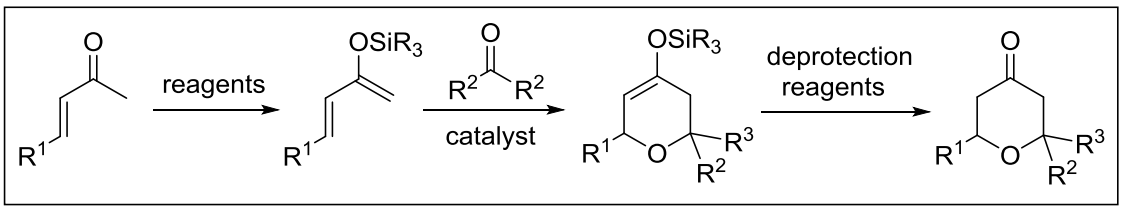
[a] Conditions: Ketone (1.8 mmol). D_2O (8.0 mmol), and catalyst (0.18 mmol) in $CDCl_3$ (9.0 mL) or $(CD_3)_2SO$ (9.0 mL) as indicated. Average data are listed. [b] It was likely that catalyst formed stable enamine with ketone. [c] More than 70% was deuterated within 5 minutes.

Chapter 4

Development of Enantioselective Oxa-Hetero-Diels-Alder Reactions

4.1 Introduction for Chapter 4

Tetrahydropyranones are core structures of great importance, and can be easily transformed to substituted tetrahydropyrans and related derivatives.[53,54,55,108,109,110,111,112,113,114,115,116,117] Compounds featuring a trifluoromethyl carbinol motif are often found in pharmaceuticals, biological probes, enantiomer-discriminating reagents, and synthons and building blocks of these molecules.[69,85,86,87,88] So Trifluoromethyl-substituted tetrahydropyranones will likely be useful to aid the search for biofunctional molecules. Hence, there is a high demand for the development of concise asymmetric methods that providing highly enantiomerically enriched tetrahydropyranones bearing a trifluoromethyl group.



Scheme 4.1. Synthesis of tetrahydropyranones via reactions of preformed dienes with ketones or aldehydes, which has been often used.

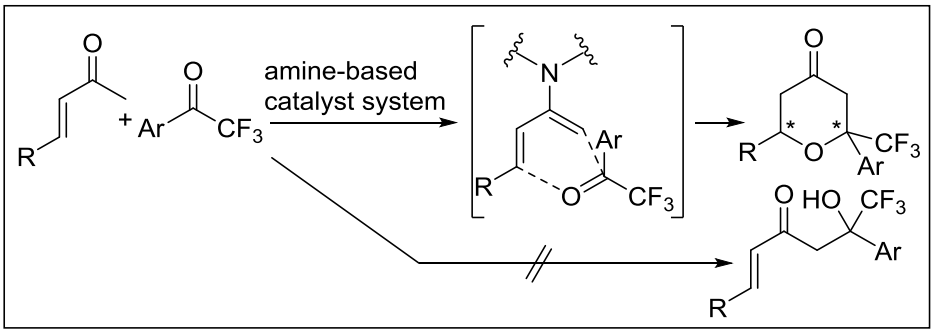
The synthesis of tetrahydropyranones are often based on formal hDA reactions using silyl enol ether derived dienes or siloxybutadiene derivatives as dienes.[108,109,110,111,112,113] In

these reactions, after the reactions, the deprotection step is necessary to give tetrahydropyranones (**Scheme 4.1**).

Both metal catalysis[108,109,110] and organocatalysis using hydrogen bonding donors as catalysts[111,112,113] have been reported by using the preformed dienes. In this chapter, the development of enantioselective direct oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones that afford trifluoromethyl-substituted tetrahydropyranones is described, in which dienes are generated *in situ* from enones.

4.2 Development of Enantioselective Oxa-Hetero-Diels-Alder Reactions of Enones with Aryl Trifluoromethyl Ketones

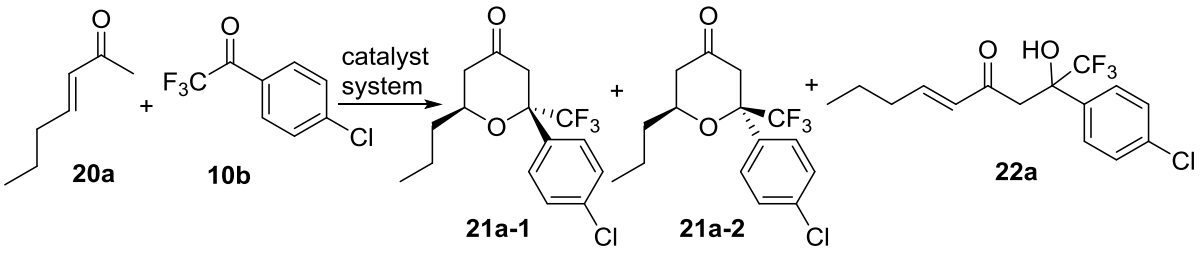
Recently, enantioselective oxa-hetero-Diels-Alder reactions of enones with isatins that are catalyzed by amine-based catalyst systems have been developed to synthesize functionalized tetrahydropyranones.[53,54,55] In the reactions, enamines of enones are formed *in situ*, and the enamines act as dienes of the [4+2] cycloaddition resulting in the formation of the tetrahydropyranones under mild conditions.[53,54,55] Based on these studies, the development of amine-catalyzed enantioselective oxa-hetero-Diels-Alder reactions of enones with trifluomethyl ketones was investigated (**Scheme 4.2**) to provide concise, atom-economical access to trifluoromethyl-substituted tetrahydropyranone derivatives. Inspite of the presence of previous oxa-hetero-Diels-Alder reactions of enones, direct use of enones as diene precursors to form tetrahydropyranones is still a challenge; reported reactions of enones with ketones or aldehydes often give aldol products as the main product or as a significant by-product.[63,118,119,120,121,122,123] That is, formation of oxa-hetero-Diels-Alder reaction product is not promised in the reactions of enones with ketones or aldehydes as dienophiles either in racemic or highly enantioselective versions.[53,54,55,124,125,126]

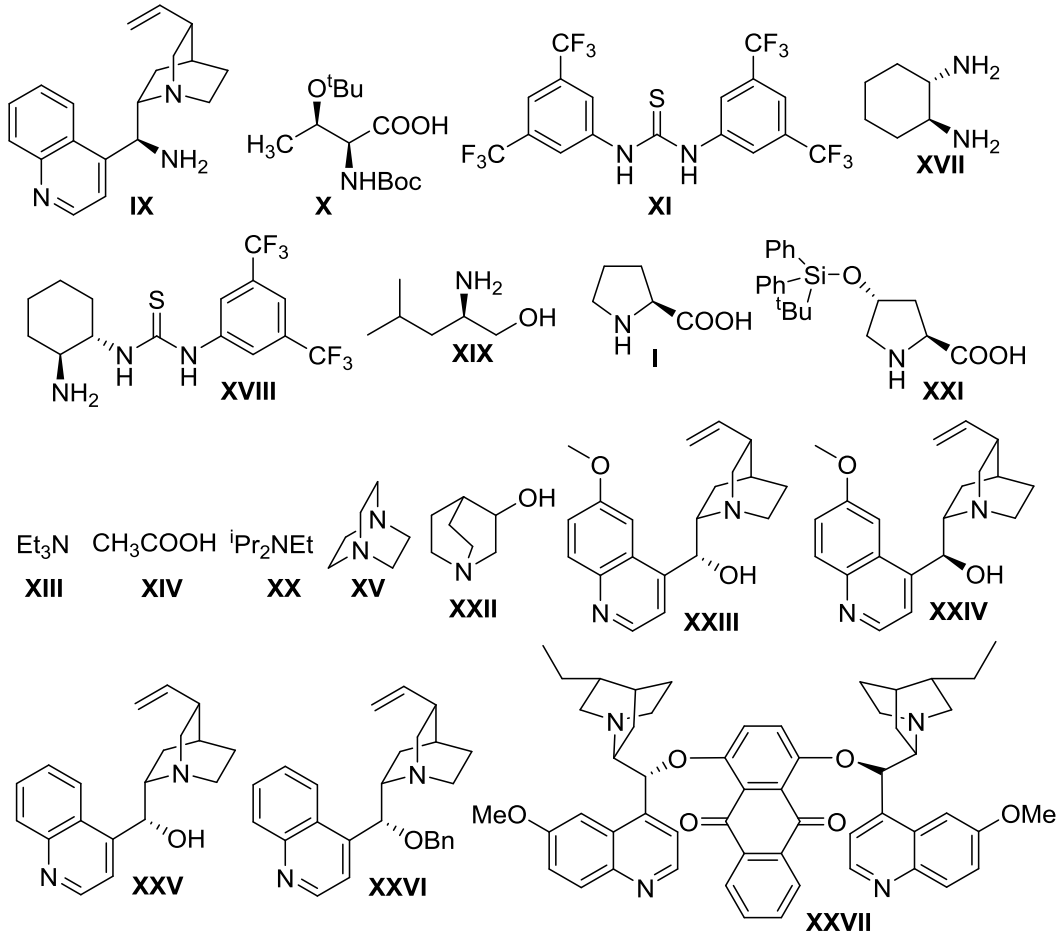


Scheme 4.2. The oxa-hetero-Diels-Alder reactions of enones with aryl trifluoromethyl ketones catalyzed by amine-based catalyst systems to afford trifluoromethyl-substituted tetrahydropyranones.

To synthesize highly enantiomerically enriched trifluoromethyl-substituted tetrahydropyranones, first, catalyst systems for the reaction of enone **20a** with ketone **10b** to form trifluoromethyl-substituted tetrahydropyranone product **21a** (**21a-1** and/or **21a-2**) were screened. Selected results are shown in **Table 4.1**. Previously reported catalyst systems (such as combination of **IX** with **X**, **IX** with **X** and **XI**, and **IX** with **XIV**) for the reactions of enones with isatins to afford tetrahydropyranones in high enantioselectivity did not work efficiently for the reaction with ketone **10b**; the use of these catalysts significantly generated aldol product **22a** with oxa-hetero-Diels-Alder product **21a** (**Table 4.1**, entries 1-4). Use of catalyst systems combining amines **XVIII** and **XIX** with acetic acid (**XIV**) gave desired product **21a** (**Table 4.1**, entries 5 and 6). Although the formation of aldol product **22a** was suppressed in these reactions, the er of the major diastereomer **21a-1** was moderate. When L-proline (**I**) in toluene, the reaction was very slow (**Table 4.1**, entries 7). Switching the solvent of this L-proline (**I**)-catalyzed reaction to DMF, hetero-Diels-Alder product **21a** was obtained and the aldol product **22a** was not detected (**Table 4.1**, entries 8). When the combination of L-proline (**I**) and Et_3N (**XIII**) was used as the catalyst system in toluene, the reaction also afforded only **21a** (**Table 4.1**, entries 9).

Table 4.1. Screening of catalyst systems in the hetero-Diels-Alder reaction of **20a** and **10b**.[a]





entry	catalyst system	time (h)	**21a**:**22a**[b]	dr[b] **21a-1**:**21a-2**	er[c] **21a-1**/**21a-2**
1	**IX** (0.2 equiv)-**X** (0.4 equiv)	24	62:38	5.0:1	85:15/20:80
2	**IX** (0.2 equiv)-**X** (0.4 equiv)-**XI** (0.4 equiv)	36	71:29	2.5:1	ND/ND
3	**XVII** (0.2 equiv)-**X** (0.4 equiv)	12	67:33	3.1:1	ND/ND
4	**IX** (0.2 equiv)-**XIV** (0.4 equiv)	24	70:30	8:1	ND/ND
5	**XVIII** (0.2 equiv)-**XIV** (0.4 equiv)	24	95:5	2.0:1	18:82/1:1
6	**XIX** (0.2 equiv)-**XIV** (0.4 equiv)	24	>95:5	1.7:1	68:32/ND

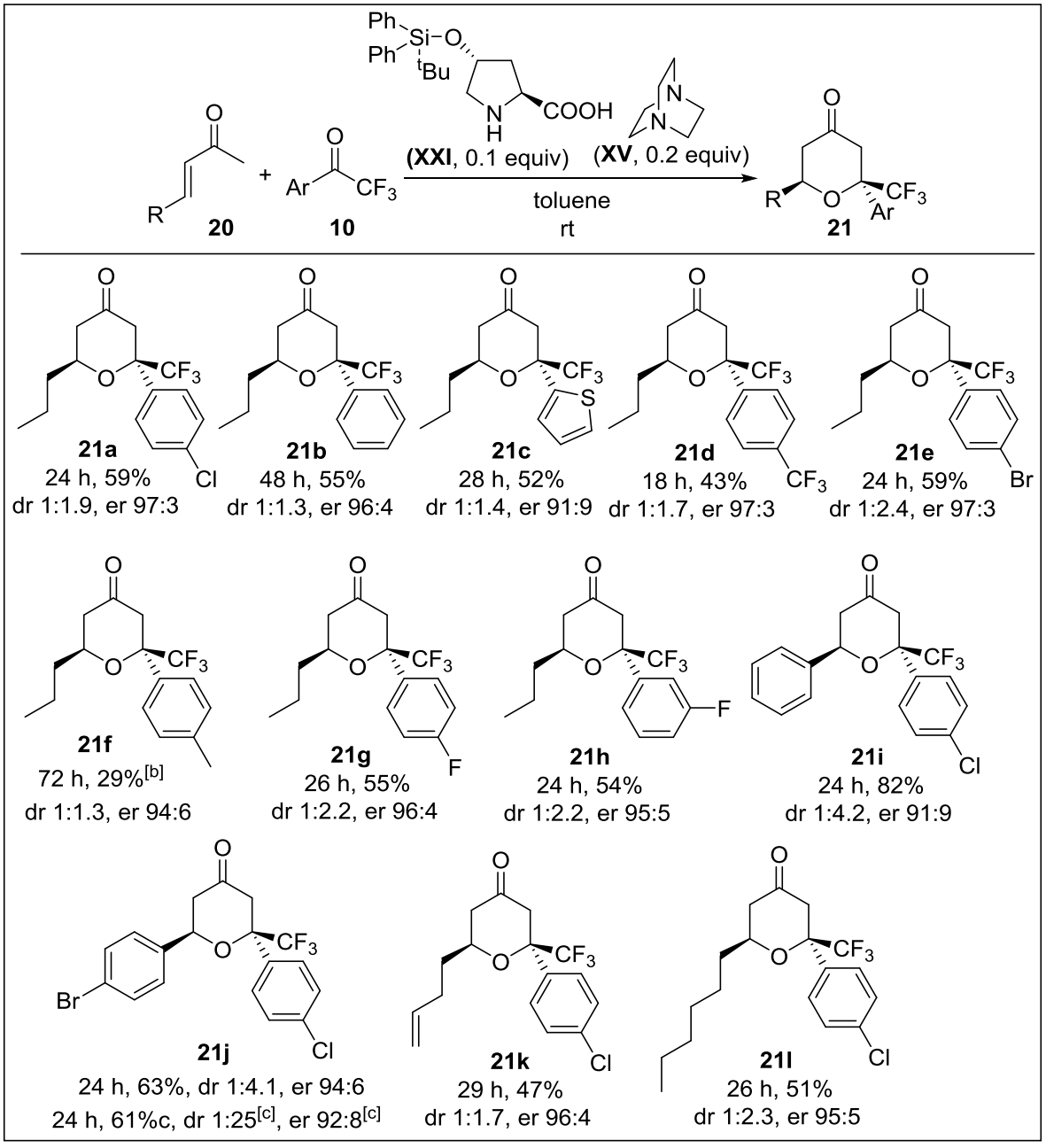
7[d]	**I** (0.2 equiv)	48[d]	-	-	-
8[e]	**I** (0.2 equiv)	24	>95:5	1.6:1	ND/85:15
9	**I** (0.2 equiv)-**XIII** (0.2 equiv)	36	>95:5	1.3:1	ND/91:9
10	**I** (0.2 equiv)-**XX** (0.2 equiv)	30	>95:5	1:2.3	ND/91:9
11	**I** (0.2 equiv)-**XV** (0.2 equiv)	36	>95:5	1:1.2	ND/95:5
12	**XXI** (0.2 equiv)-**XV** (0.2 equiv)	24	>95:5	1:1.9	1:1/97:3
13	**XXI** (0.1 equiv)-**XV** (0.2 equiv)	24	>95:5	1:1.9	1:1/97:3
14	**I** (0.2 equiv)-**XXII** (0.2 equiv)	24	>95:5	1:1	ND/94:6
15	**I** (0.2 equiv)-**XXIII** (0.2 equiv)	24	>95:5	1:1.3	82:18/88:12
16	**I** (0.2 equiv)-**XXIV** (0.2 equiv)	27	95:5	1:2.2	81:19/90:10
17	**I** (0.2 equiv)-**XXV** (0.2 equiv)	36	95:5	1:1.5	85:15/91:9
18	**I** (0.2 equiv)-**XXVI** (0.2 equiv)	48	>95:5	1:1.3	ND/94:6
19	**I** (0.2 equiv)-**XXVII** (0.2 equiv)	36	>95:5	1.3:1	ND/80:20

[a] Reaction was performed by using enone **20a** (0.5 mmol) and aryl trifluoromethyl ketone **10b** (0.1 mmol) in the presence of the indicated catalyst system in toluene (0.2 mL) at 25 °C until **10b** was consumed except where indicated. The relative stereochemistry of **21a-1** and **21a-2** was determined to be as shown; the absolute stereochemistry of **21a-1** and **21a-2** is tentative; see **Experimental Section Chapter 6.4.1**. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis. ND = Not determined. [d] Conversion <20%. [e] Reaction in DMF; DMF: *N*,*N*-dimethylformamide.

Because the use of L-proline (**I**) with a base as the catalyst system in toluene gave the desired hetero-Diels-Alder product without the formation of the aldol product, L-proline (**I**) and proline derivative **XXI** were further screened with a series of organobases as catalyst systems to afford **21a** (**Table 4.1**, entries 9-19). The er of **21a-2** was 91:9 when Et_3N (**XIII**) or *i*Pr_2Et (**XX**) was used (**Table 4.1**, entries 9 and 10). When DABCO (**XV**) was used with L-proline (**I**), hetero-Diels-Alder product **21a** was obtained with dr 1:1.2 and with er 95:5 for the major diastereomer **21a-2** (**Table 4.1**, entry 11). The use of catalyst 4-substituted proline **XXI** with DABCO (**XV**) in the reaction afforded **21a** with dr 1:1.9 and with er 97:3 for **21a-2** (**Table 4.1**, entry 12). The reaction using less loading of **XXI** (0.1 equiv) with **XV** (0.2 equiv) gave essentially the same results as the reaction using **XXI** (0.2 equiv) and **XV** (0.2 equiv)

(**Table 4.1**, entry 13 versus entry 12). The major diastereomer (i.e., **21a-2**) obtained under the catalysis by **XXI-XV** differed from that obtained under the catalysis by **IX-X** (**Table 4.1**, entries 12 and 13 versus entry 1).

Table 4.2. Scope of the hetero-Diels-Alder reaction.[a]



[a] Reaction conditions: Enone **20** (1.0 mmol) and aryl trifluoromethyl ketone **10** (0.2 mmol) in the presence of proline derivative **XXI** (0.02 mmol) and DABCO (**XV**, 0.04 mmol) in toluene (0.4 mL) at 25 °C. The isolated yields of **21** (combined for both the diastereomers) are shown except where noted. The dr was determined by ^{1}H NMR analysis before purification. The er of the major diastereomer was determined by HPLC analysis. The ratio **21**:**22** (**4** = aldol product) was determined by ^{1}H NMR analysis before purification: >95:5 for the formation of

21a-21h and 21j-21l; 95:5 for the formation of **21i**. [b] Ketone **10** was not consumed. [c] Data of 1 mmol-scale reaction; isolated yield of the major isomer, the dr of the major diastereomer after purification.

Next, using the best catalyst system identified [i.e., **XXI** (0.1 equiv)-**XV** (0.2 equiv), **Table 4.1**, entries 13], reactions of various enones and aryl trifluoromethyl ketones were performed (**Table 4.2**). In all cases, trifluoromethyl-substituted tetrahydropyranones were obtained with high enantioselectivities for the major diastereomer products, and tetrasubstituted carbon centers were concisely constructed (**Table 4.2**). The reactions of phenyl trifluoromethyl ketones bearing electron-withdrawing substituents on the phenyl group (such as the formation of **21d**) were faster than the reactions of those bearing electron-donating groups (such as the formation of **21f**). In all cases shown in **Table 4.2**, the formation of the aldol product was negligible (**3**:**4** were >95:5 or 95:5).

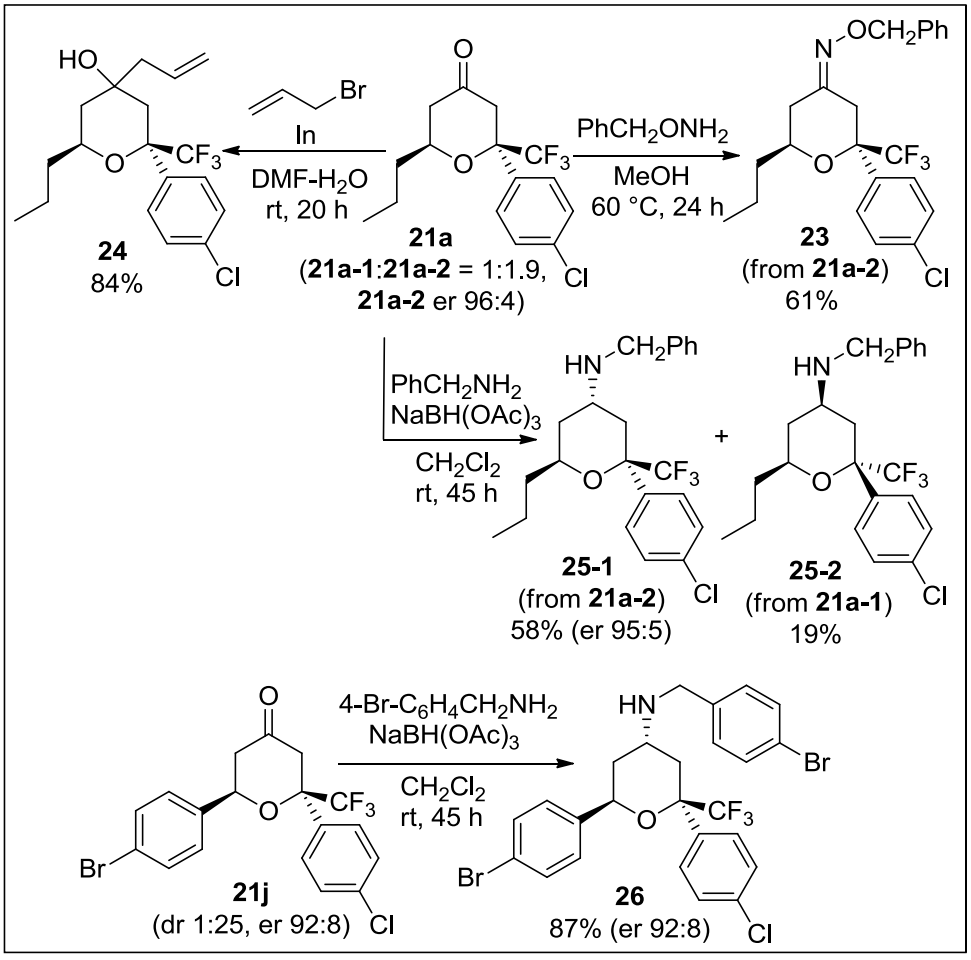
The catalyst system was useful for the reactions of β-alkyl substituted enones and also β-aryl substituted enones to afford the hetero-Diels-Alder reaction products with high enantioselectivities for the major product diastereomers. This is significant because previously reported conditions for the hetero-Diels-Alder reactions of β-alkyl substituted enones often do not work for the β-aryl substituted enones.[53,54,55,124]

Further, the reaction using the **XXI**-**XV** catalyst system was easily scaled up: a 1.0 mmol-reaction to form **21j** gave the major isomer, **21j-2**, as a single diastereomer (purity >95% after flash column chromatography) in 61% yield with er 92:8.

When a mixture of **21a** and **22a** (racemic, **21a**/**22a** = 2.5:1, **21a-1**:**21a-2** = 3:1) was treated under the hetero-Diels-Alder reaction conditions with the **XXI**-**XV** catalyst system, no decomposition of the compounds and no changes in the ratios were detected. This indicates that product **21a** is stable under the **XXI**-**XV** catalyst system and that aldol **22a** is not converted to **21a** in the presence of this catalyst system. Thus, the formation of **21a** under the

XXI-XV catalyst system is likely a kinetically controlled [4+2] cycloaddition reaction of *in situ*-generated enamine of enone **20a** with ketone **10b**.

To demonstrate the use of the hetero-Diels-Alder reactions, the product tetrahydropyranones were transformed into tetrahydropyran derivatives (**Scheme 4.3**). Oxime formation, allylation, and reductive amination gave the corresponding products **23**-**26**. Although for most cases, the hetero-Diels-Alder reactions afforded tetrahydropyranones **21** as diastereomer mixtures which are difficult to be separated by silica gel column, tetrahydropyran derivatives were obtained as a single diastereomer with high enantioselectivity (**25-1** and **26**) via reductive amination of the corresponding tetrahydropyranones.



Scheme 4.3. Transformation of the hetero-Diels-Alder products.

Chapter 5

Summary and Conclusions

In **Chapter 2.2.1**, the development of an efficient method for concise aldol reactions of a pyruvic aldehyde derivative with various isatins catalyzed by DBU is described. The reactions were fast to provide the desired aldol products with tetrasubstituted carbon centers under mild conditions; reactions for only 15 to 30 min gave the aldol products in good to high yields.

In **Chapter 2.2.2**, the development of a concise method to synthesize furanose spirooxindoles via the DBU-catalyzed aldol reaction of a pyruvic aldehyde derivative with isatins is described. The furanose spirooxindoles were obtained in good to high yields from the aldol products through the reaction sequence with reduction followed by the acidic treatment. The furanose spirooxindoles synthesized by this method will likely be useful to aid the search for biofunctional molecules.

In **Chapter 2.3.1**, the developement of DBU-catalyzed aldol and vinylogous aldol reactions of ketone donors with aryl trifluoromethyl ketones is described. The reactions were concise, fast, and practical, to give aldol products bearing tetrasubstituted carbon centers with trifluoromethyl-substituted alcohols under neat, mild conditions. In the reactions, the C-C bond formation occurred regioselectively at the methyl group of alkyl methyl ketones, at the γ-position of β-keto esters, and at the methyl group of β-methyl-substituted cyclic enones to give the products, respectively. The DBU catalysis methods described here efficiently provided products including those that were previously difficult to synthesize, that were

synthesized only in slow reactions, and/or that required preactivation/protection and deprotection steps. The DBU catalysis methods are complementary to other methods including organocatalytic methods, such as amine-based organocatalysis methods involving formation of enamines *in situ*, and Mukaiyama aldol methods.

In **Chapter 2.3.2**, resolution of the aldol products derived from β-keto esters is described. Resolution of the aldol products was concisely achieved via the formation of stable enamines of the β-keto ester groups with a homochiral amine. The enantiomerically pure forms of the aldol products, 5-aryl-5-trifluoromethyl-5-hydroxyl-3-oxo-pentanoate derivatives were concisely obtained. These enantiomerically pure forms of the compounds may be used for chiral resolution of amines that form stable enamines. These homochiral trifluoromethyl-substituted tertiary alcohols may also be useful for the synthesis of functional molecules and as chiral building blocks.

In **Chapter 3**, deuteration studies of enolizable ketone under aldol reaction catalysis conditions are described. The initial deuteration rates of various ketone donors under DBU-, proline-, and β-proline-catalysis were compared. The deuteration results indicate that formation of the carbanion is necessary to be the reaction sites. The results also indicate that the aldol reaction sites and the aldol reaction rates largely depend on the transion states to lead the products, not just on the easiness of the formation of the carbanion.

In **Chapter 4**, the development of an organocatalytic enantioselective oxa-hetero-Diels-Alder reaction of enones with aryl trifluoromethyl ketones that afforded trifluoromethyl-substituted tetrahydropyranones is described. With the novel amine-based catalyst systems, tetrasubstituted carbon centers bearing a trifluoromethyl group were concisely constructed with the formation of the tetrahydropyranone ring. The hetero-Diels-Alder products were further transformed to various trifluoromethyl-substituted tetrahydropyran derivatives. The trifluoromethyl-substituted tetrahydropyranones and

tetrahydropyran derivatives that can be synthesized by the methods described here may be useful in the search for biofunctional molecules.

Chapter 6

Experimental Section

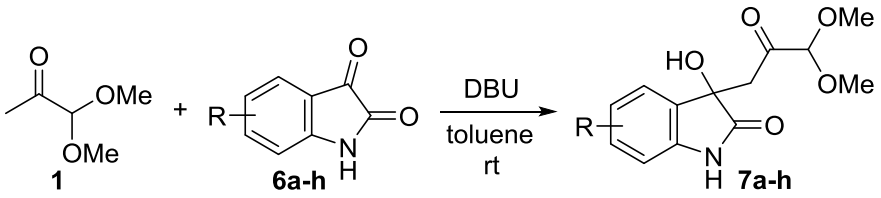
6.1 General Methods

For thin layer chromatography (TLC), Merck silica gel 60 F254 aluminum sheets were used. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) or Yamazen flash column (60 Å, 40 μm). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Advance 400. Proton chemical shifts are reported in ppm downfield from tetramethylsilane or from the residual solvent as internal standard in $CDCl_3$ (δ 7.26 ppm), in CD_3OD (δ 3.31 ppm) and in $(CD_3)_2SO$ (2.50 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.0 ppm), in CD_3OD (δ 49.0 ppm) and in $(CD_3)_2SO$ (39.5 ppm). High-resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap ESI ion trap mass spectrometer. Enantiomeric excesses were determined by chiral-phase HPLC using a Hitachi instrument. Optical rotations were measured on a Jasco P2200 polarimeter.

6.2 Experimental Section for Chapter 2

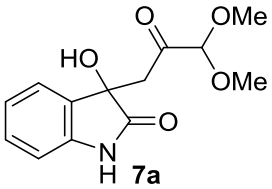
6.2.1Experimental Section for Chapter 2.2

DBU Catalyzed Aldol Reactions of 1 with 6



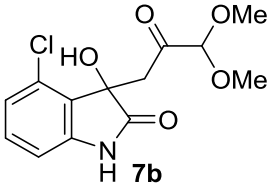
General Procedure for the DBU-Catalyzed Aldol Reactions (Table 2.1 entries 7 and 8, Table 2.2). To a mixture of **1** (5.0 mmol) and **6** (0.5 mmol) in toluene (1.0 mL) was added DBU (0.05 mmol or 0.1 mmol as indicated) and the mixture was stirred at at rt (25 °C) until **6** was consumed (monitored by TLC). EtOAc and saturated NH_4Cl solution were added to the mixture, and the mixture was extracted with EtOAc. Organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel flash column chromatography (hexane/EtOAc = 1:1 or 1:2) to give **7**.

3-(3,3-Dimethoxy-2-oxopropyl)-3-hydroxyindolin-2-one (7a)[75]



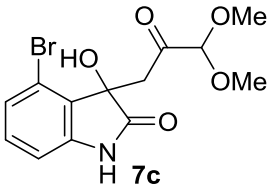
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12 (d, *J* = 17.6 Hz, 1H, C<u>H</u>HC=O), 3.31 (s, 3H, OC<u>H</u>$_3$), 3.35 (s, 3H, OC<u>H</u>$_3$), 3.45 (d, *J* = 17.6 Hz, 1H, C<u>H</u>HC=O), 4.39 (s, 1H, C<u>H</u>(OMe)$_2$), 6.87 (d, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 7.01 (dt, *J* = 0.8 Hz, 7.6 Hz, 1H, Ar<u>H</u>), 7.22 (dt, *J* = 0.8 Hz, 7.6 Hz, 1H, ArH), 7.33 (d, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 8.58 (brs, 1 H, NH) ppm.

4-Chloro-3-(3,3-dimethoxy-2-oxopropyl)-3-hydroxyindolin-2-one (7b)



^{1}H NMR (400 MHz, CD_3OD): δ = 3.28 (s, 3H, $OC\underline{H}_3$), 3.32 (s, 3H, $OC\underline{H}_3$), 3.36 (d, *J* = 18.8 Hz, 1H, $C\underline{H}HC{=}O$), 4.07 (d, *J* = 18.8 Hz, 1H, $C\underline{H}HC{=}O$), 4.41 (s, 1H, $C\underline{H}(OMe)_2$), 6.82 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H, Ar$\underline{H}$), 6.91 (dd, *J* = 0.8 Hz, 8.0 Hz 1H, Ar$\underline{H}$), 7.20 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 42.9, 53.6, 53.6, 73.8, 103.3, 108.6, 110.2, 122.8, 126.8, 130.7, 144.6, 178.7, 202.4 ppm; HRMS (ESI): calcd. for $C_{13}H_{15}NO_5Cl$ ($[M + H]^+$) 300.0633, found 300.0632.

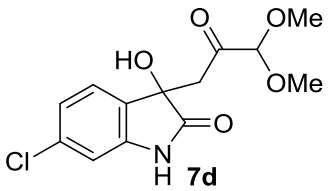
4-Bromo-3-(3,3-dimethoxy-2-oxopropyl)-3-hydroxyindolin-2-one (7c)



7c

^{1}H NMR (400 MHz, CD_3OD): δ = 3.29 (s, 3H, $OC\underline{H}_3$), 3.32 (d, *J* = 18.4 Hz, 1H, $C\underline{H}HC{=}O$), 3.33 (s, 3H, $OC\underline{H}_3$), 4.17 (d, *J* = 18.4 Hz, 1H, $C\underline{H}HC{=}O$), 4.42 (s, 1H, $C\underline{H}(OMe)_2$), 6.87 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H, Ar$\underline{H}$), 7.07-7.15 (m, 2H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 42.8, 53.58, 53.64, 74.5, 103.3, 109.1, 118.7, 126.0, 128.5, 130.9, 144.9, 178.8, 202.4 ppm; HRMS (ESI): calcd. for $C_{13}H_{15}NO_5Br$ ($[M + H]^+$) 344.0128, found 344.0138.

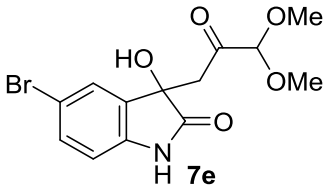
6-Chloro-3-(3,3-dimethoxy-2-oxopropyl)-3-hydroxyindolin-2-one (7d)



7d

^{1}H NMR (400 MHz, CD_3OD): δ = 3.25 (d, *J* = 18.0 Hz, 1H, $C\underline{H}HC{=}O$), 3.27 (s, 3H, $OC\underline{H}_3$), 3.32 (s, 3H, $OC\underline{H}_3$), 3.54 (d, *J* = 18.0 Hz, 1H, $C\underline{H}HC{=}O$), 4.40 (s, 1H, $C\underline{H}(OMe)_2$), 6.90 (d, *J* = 2.0 Hz, 1H, Ar$\underline{H}$), 6.98 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H, Ar$\underline{H}$), 7.24 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 44.3, 53.7, 53.8, 72.6, 103.5, 110.2, 121.7, 124.7, 129.4, 134.8, 143.9, 179.4, 202.1 ppm; HRMS (ESI): calcd. for $C_{13}H_{15}NO_5Cl$ ($[M + H]^+$) 300.0633, found 300.0631.

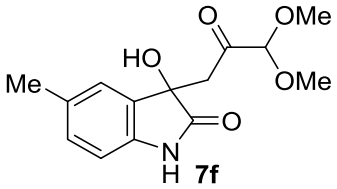
5-Bromo-3-(3,3-dimethoxy-2-oxopropyl)-3-hydroxyindolin-2-one (7e)[75]



7e

^{1}H NMR (400 MHz, CD_3OD): δ = 3.24 (d, *J* = 18.0 Hz, 1H, C<u>H</u>HC=O), 3.28 (s, 3H, OC<u>H</u>$_3$), 3.33 (s, 3H, OC<u>H</u>$_3$), 3.54 (d, *J* = 18.0 Hz, 1H, C<u>H</u>HC=O), 4.40 (s, 1H, C<u>H</u>(OMe)$_2$), 6.81 (d, *J* = 8.4 Hz, 1H, Ar<u>H</u>), 7.38 (dd, *J* = 2.0 Hz, 8.4 Hz, 1H, Ar<u>H</u>), 7.43 (d, *J* = 2.0 Hz, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 44.3, 53.7, 53.8, 73.1, 103.5, 111.5, 114.2, 126.8, 132.1, 133.1, 141.7, 179.0, 202.0 ppm; HRMS (ESI): calcd. for $C_{13}H_{15}NO_5Br$ ([M + H]$^+$) 344.0128, found 344.0125.

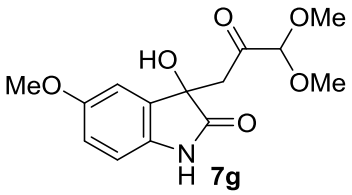
3-(3,3-Dimethoxy-2-oxopropyl)-3-hydroxy-5-methylindolin-2-one (7f)



7f

^{1}H NMR (400 MHz, CD_3OD): δ = 2.27 (s, 3H, ArC<u>H</u>$_3$), 3.20 (d, *J* = 17.6 Hz, 1H, C<u>H</u>HC=O), 3.25 (s, 3H, OC<u>H</u>$_3$), 3.31 (s, 3H, OC<u>H</u>$_3$), 3.53 (d, *J* = 17.6 Hz, 1H, C<u>H</u>HC=O), 4.38 (s, 1H, C<u>H</u>(OMe)$_2$), 6.76 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.02-7.05 (m, 1H, Ar<u>H</u>), 7.12 (d, *J* = 0.8 Hz, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 21.1, 45.8, 55.0, 55.1, 74.6, 104.8, 111.0, 125.6, 131.0, 132.1, 133.0, 141.2, 181.0, 203.4 ppm; HRMS (ESI): calcd. for $C_{14}H_{18}NO_5$ ([M + H]$^+$) 280.1179, found 280.1191.

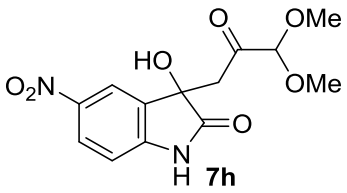
3-(3,3-Dimethoxy-2-oxopropyl)-3-hydroxy-5-methoxyindolin-2-one (7g)



7g

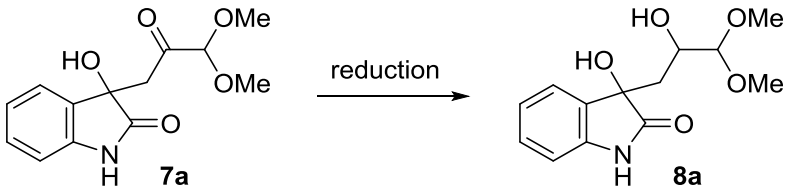
^{1}H NMR (400 MHz, CD_3OD): δ = 3.21 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.28 (s, 3H, CHOC<u>H</u>$_3$), 3.32 (s, 3H, CHOC<u>H</u>$_3$), 3.54 (d, J = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.74 (s, 3H, ArOC<u>H</u>$_3$), 4.40 (s, 1H, C<u>H</u>$(OMe)_2$), 6.79-6.80 (m, 2H, Ar<u>H</u>), 6.94 (t, *J* = 1.6 Hz, H, Ar<u>H</u>) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 44.4, 53.6, 53.7, 54.9, 73.6, 103.5, 110.3, 110.6, 114.0, 131.9, 135.5, 156.0, 179.6, 202.0 ppm; HRMS (ESI): calcd. for $C_{14}H_{18}NO_6$ ($[M + H]^+$) 296.1129, found 296.1142.

3-(3,3-Dimethoxy-2-oxopropyl)-3-hydroxy-5-nitroindolin-2-one (7h)[75]



^{1}H NMR (400 MHz, CD_3OD): δ = 3.28 (s, 3H, OC<u>H</u>$_3$), 3.34 (s, 3H, OC<u>H</u>$_3$), 3.34 (d, *J* = 18.4 Hz, 1H, C<u>H</u>HC=O), 3.65 (d, *J* = 18.4 Hz, 1H, C<u>H</u>HC=O), 4.41 (s, 1H, C<u>H</u>$(OMe)_2$), 7.04 (d, *J* = 8.8 Hz, 1H, Ar<u>H</u>), 8.19-8.24 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 45.8, 55.1, 55.3, 73.9, 104.3, 111.0, 120.8, 127.7, 133.3, 144.5, 150.3, 180.9, 203.6 ppm; HRMS (ESI): calcd. for $C_{13}H_{15}N_2O_7$ ($[M + H]^+$) 311.0874, found 311.0880.

Reduction of Aldol Product 7a



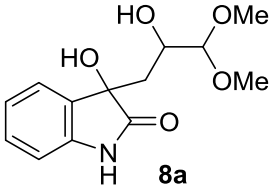
Reduction of 7a Using $NaBH_4$. To a solution of aldol product **7a** (42.8 mg, 0.16 mmol) in MeOH (1.0 mL) was added $NaBH_4$ (12.2 mg, 0.32 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h (consumption of **7a** was analyzed by TLC). Acetic acid (40 μL, 0.70 mmol) was added to the mixture and the solvent was removed in vacuo. The

residue was purified by flash column chromatography (hexane/EtOAc = 1:2 to EtOAc) to give **8a** (28.6 mg, 66%, dr 1.6:1).

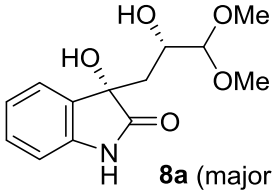
Reduction of 7a Using $NaBH(OAc)_3$. To a solution of aldol product **7a** (52.3 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) was added $NaBH(OAc)_3$ (83.5 mg, 0.39 mmol) at -10 °C. The mixture was stirred at the same temperature for 18 h (consumption of **7a** was analyzed by TLC). Acetic acid (40 μL, 0.70 mmol) was added to the mixture and the solvent was removed in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 1:2 to EtOAc) to give **8a** (72.7 mg, 72 %, dr 20:1).

The major diastereomer of **8a** obtained by the reduction using $NaBH(OAc)_3$ was the same as the major diastereomer of **8a** obtained by the reduction using $NaBH_4$. The relative stereochemistry of the major diastereomer of **8** was deduced from **9a**. The relative stereochemistry of **9a** was determined by the coupling constants in ^1H NMR and by NOESY experiments (see **Table 6.1** and **Figure 6.1**).

3-Hydroxy-3-(2-hydroxy-3,3-dimethoxypropyl)indolin-2-one (8a)



8a



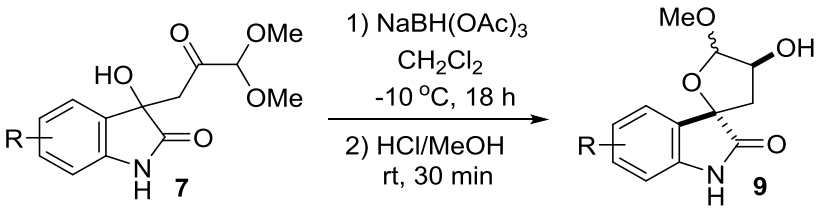
8a (major diastereomer)

Compound 8a (dr 1.6:1). ^1H NMR (400 MHz, CD_3OD): δ =1.88 (dd, *J* = 9.3 Hz, 14.5 Hz, 1H x 1.6/2.6, C<u>H</u>HCH(OH)), 1.98 (dd, *J* = 2.9 Hz, 14.5 Hz, 1H x 1.6/2.6, C<u>H</u>HCH(OH)), 2.01-2.11 (m, 2H x 1.0/2.6, C<u>H</u>$_2$CH(OH)), 3.24 (s, 3H x 1.0/2.6, OC<u>H</u>$_3$), 3.25 (s, 3H x 1.0/2.6, OCH_3), 3.26 (s, 3H x 1.6/2.6, OC<u>H</u>$_3$), 3.30 (s, 3H x 1.6/2.6, OC<u>H</u>$_3$), 3.39 (m, 1H x 1.0/2.6, C<u>H</u>(OH)), 3.87 (m, 1H x 1.6/2.6, C<u>H</u>(OH)), 3.94 (s, *J* = 5.4 Hz, 1H x 1.0/2.6, C<u>H</u>(OMe)$_2$), 4.02 (s, *J* = 5.4 Hz, 1H x 1.6/2.6, C<u>H</u>(OMe)$_2$), 6.77-6.80 (m, 1H, Ar<u>H</u>), 6.92-6.97 (m, 1H, Ar<u>H</u>), 7.12-7.17 (m, 1H, Ar<u>H</u>), 7.21 (d, *J* = 7.4 Hz, 1H x 1.0/2.6, ArH), 7.28 (dd, *J* = 0.6 Hz, 7.4 Hz, 1H x 1.6/2.6, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 38.3, 38.6, 54.0, 54.2,

54.3, 54.4, 67.7, 67.8, 75.3, 75.7, 106.9, 107.2, 109.8, 109.9, 122.0, 122.3, 123.9, 124.1, 129.1, 129.2, 131.0, 132.0, 141.0, 141.8, 180.7, 180.9 ppm.

Compound 8a (major diastereomer). ^{1}H NMR (400 MHz, CD_3OD): δ =1.88 (dd, *J* = 9.3 Hz, 14.5 Hz, 1H, C<u>H</u>HCH(OH)), 1.98 (dd, *J* = 2.9 Hz, 14.5 Hz, 1H, C<u>H</u>HCH(OH)), 3.26 (s, 3H, OC<u>H</u>$_3$), 3.30 (s, 3H, OC<u>H</u>$_3$), 3.87 (m, 1H, C<u>H</u>(OH)), 4.02 (d, *J* = 5.4 Hz, 1H, C<u>H</u>(OMe)$_2$), 6.78 (d, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 6.95 (m, 1H, Ar<u>H</u>), 7.15 (m, 1H, Ar<u>H</u>), 7.28 (dd, *J* = 0.6 Hz, 7.6 Hz, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 38.3, 54.0, 54.4, 67.8, 75.7, 106.9, 109.9, 122.3, 124.1, 129.1, 132.0, 140.9, 180.7 ppm; HRMS (ESI): calcd. for $C_{13}H_{17}NO_5$ ([M + Na]$^+$) 290.0999, found 290.0998.

Synthesis of Furanose Spirooxindoles 9 from Aldol Product 7



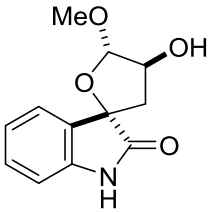
General Procedure for the Synthesis of 9 from 7 (Scheme 2.6). To a solution of aldol product **7** (0.20 mmol) in CH_2Cl_2 (1.0 mL) was added $NaBH(OAc)_3$ (0.40 mmol) at -10 °C. The mixture was stirred at the same temperature for 18 h (consumption of **7** was analyzed by TLC). The mixture was added to 3 M HCl in MeOH (1.5 mL) dropwise at 0 °C, stirred at rt (25 °C) for 30 min, and purified by flash column chromatography (hexane/EtOAc = 1:1 or 1:2) to give **9**. The diastereomers of **9** generated at the acetal carbon were purified separately or purified as a mixture. For **9a**, **9c**, **9d**, and **9f**, the diastereomer with a larger R_f value on TLC is named **9a-1**, **9c-1**, **9d-1**, and **9f-1**, and the diastereomer with a smaller R_f value on the same TLC is named **9a-2**, **9c-2**, **9d-2**, and **9f-2**, respectively.

Isomers **9a-1**, **9d-1**, and **9f-1** were assigned to be OMe/OH *trans* and isomers **9a-2**, **9d-2**, and **9f-2** were assigned to be OMe/OH *cis* based on the coupling constants (*J* values) in

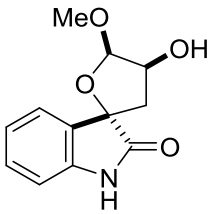
the ^{1}H NMR (see **Table 6.1** on page 81). The relative stereochemistry of **9a** was determined by the coupling constants in ^{1}H NMR and by NOESY experiments (see **Table 6.1** and **Figure 6.1**).

Synthesis of 9a from 8a (Scheme 2.4). To a solution of **8a** (50.4 mg, 0.19 mmol) in MeOH (1.0 mL), 3 M HCl solution in MeOH (1.5 mL) was added at 0 °C. The mixture was stirred at rt (25 °C) for 30 min and purified by flash column chromatography (hexane/EtOAc = 1:1 to 1:2) to give **9a** (44.2 mg, 87%, dr 1:1).

4-Hydroxy-5-methoxy-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9a)



9a-1

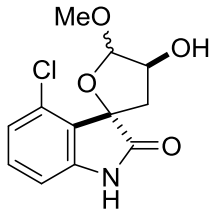


9a-2

Compound 9a-1. R_f = 0.48 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (dd, *J* = 0.4 Hz, 13.6 Hz, 1H, CHHCH(OH)), 2.74 (dd, *J* = 4.8 Hz, 13.6 Hz, 1H, CHHCH(OH)), 3.43 (s, 3 H, OCH_3), 4.59 (dd, *J* = 0.4 Hz, 4.8 Hz, 1H, CH(OH)), 5.19 (s, 1H, CH(OMe)), 6.82 (d, *J* = 7.6 Hz, 1H, ArH), 7.02 (dt, *J* = 1.2 Hz, 7.6 Hz, 1H, ArH), 7.20 (dt, *J* = 1.2 Hz, 7.6 Hz, 1H, ArH), 7.64 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H, ArH), 8.53 (brs, 1H, NH) ppm; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 1:1): δ = 1.77 (dd, *J* = 0.4 Hz, 13.6 Hz, 1H, CHHCH(OH)), 2.33 (dd, *J* = 4.8 Hz, 13.6 Hz, 1H, CHHCH(OH)), 3.09 (s, 3H, OCH_3), 4.13 (dd, *J* = 0.4 Hz, 4.8 Hz, 1H, CH(OH)), 4.81 (s, 1H, CH(OMe)), 6.51 (d, *J* = 7.8 Hz, 1H, ArH), 6.69 (dt, *J* = 0.8 Hz, 7.6 Hz, 1H, ArH), 6.89 (dt, *J* = 1.2 Hz, 7.6 Hz, 1H, ArH), 7.34 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.1, 53.7, 75.4, 84.0, 109.0, 110.2, 122.3, 125.2, 128.7, 129.7, 139.5, 177.7 ppm; HRMS (ESI): calcd. for $C_{12}H_{14}NO_4$ ([M + H]$^{+}$) 236.0917, found 236.0908.

Compound 9a-2. R_f = 0.46 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (dd, *J* = 10.0 Hz, 12.8 Hz, 1H, CHHCH(OH)), 2.55 (d, *J* = 10.0 Hz, 1H, OH), 2.61 (dd, *J* = 7.6 Hz, 12.8 Hz, 1H, CHHCH(OH)), 3.56 (s, 3H, OCH_3), 4.79 (m, 1H, CH(OH)), 5.12 (d, *J* = 4.4 Hz, 1H, CH(OMe)), 6.85 (d, *J* = 7.7 Hz, 1H, ArH), 7.08 (m, 1H, ArH), 7.25 (m, 1H, ArH), 7.33 (d, *J* = 7.4 Hz, 1H, ArH), 8.36 (brs, 1H, NH) ppm; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 1:1): δ = 2.08 (dd, *J* = 10.4 Hz, 12.5 Hz, 1H, CHHCH(OH)), 2.34 (dd, *J* = 7.8 Hz, 12.5 Hz, 1H, CHHCH(OH)), 3.38 (s, 3H, OCH_3), 4.55 (ddd, 1H, *J* = 4.4 Hz, 7.8 Hz, 10.4 Hz, CH(OH)), 4.89 (d, *J* = 4.4 Hz, 1H, CH(OMe)), 6.68 (d, *J* = 7.8 Hz, 1H, ArH), 6.90 (m, 1H, ArH), 7.08 (dt, *J* = 1.2 Hz, 7.8 Hz, 1H, ArH), 7.17 (d, *J* = 7.8 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.7, 54.6, 71.0, 81.3, 102.1, 109.2, 122.5, 123.9, 129.0, 129.2, 139.7, 177.7 ppm; HRMS (ESI): calcd. for $C_{12}H_{14}NO_4$ ($[M + H]^+$) 236.0917, found 236.0909.

4'-Chloro-4-hydroxy-5-methoxy-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9b)

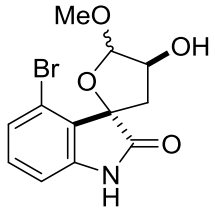


9b

Compound 9b (major diastereomer). R_f = 0.50 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (dd, *J* = 7.4 Hz, 12.4 Hz, 1H, CHHCH(OH)), 2.70 (d, *J* = 10.4 Hz, 1H, OH), 2.76 (dd, *J* = 10.4 Hz, 12.4 Hz, 1H, CHHCH(OH)), 3.55 (s, 3H, OCH_3), 5.06 (m, 1H, CH(OH)), 5.17 (d, *J* = 5.2 Hz, 1H, CH(OMe)), 6.76 (dd, *J* = 0.8 Hz, 7.8 Hz, 1H, ArH), 7.00 (dd, *J* = 0.8 Hz, 8.2 Hz, 1H, ArH), 7.20 (t, *J* = 8.0 Hz, 1H, ArH), 8.45 (brs, 1H, NH) ppm; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 1:1): δ = 2.15 (dd, *J* = 7.2 Hz, 12.0 Hz, 1H, CHHCH(OH)), 2.77 (dd, *J* = 11.2 Hz, 12.0 Hz, 1H, CHHCH(OH)), 3.41 (s, 3H, CH_3), 4.91 (ddd, *J* = 5.2 Hz, 7.2 Hz, 11.2 Hz, 1H, CH(OH)), 4.99 (d, *J* = 5.2 Hz, 1H, CH(OMe)), 6.69 (dd, *J* = 0.8 Hz, 7.8 Hz, 1H, ArH), 6.89 (dd, *J* = 0.8 Hz, 8.2 Hz, 1H, ArH), 7.13 (t, *J* = 8.0 Hz,

1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.8, 54.4, 70.0, 81.6, 101.7, 107.7, 123.2, 123.7, 130.4, 131.3, 141.7, 177.2 ppm; HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Cl$ ($[M + H]^+$) 270.0528, found 270.0534.

4'-Bromo-4-hydroxy-5-methoxy-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9c)

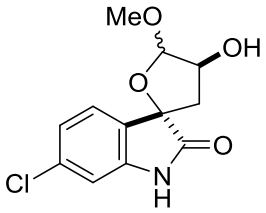


9c

Compound 9c-1 (major diastereomer). R_f = 0.50 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (dd, *J* = 7.2 Hz, 12.5 Hz, 1H, C<u>H</u>HCH(OH)), 2.71 (d, *J* = 10.4 Hz, 1H, O<u>H</u>), 2.81 (dd, *J* = 10.6 Hz, 12.5 Hz, 1H, C<u>H</u>HCH(OH)), 3.59 (s, 3H, OC<u>H</u>$_3$), 5.10 (m, 1H, C<u>H</u>(OH)), 5.20 (d, *J* = 5.2 Hz, 1H, C<u>H</u>(OMe)), 6.79 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H, Ar<u>H</u>), 7.13 (t, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.20 (dd, *J* = 0.8 Hz, 8.0 Hz, 1H, Ar<u>H</u>), 8.15 (brs, 1H, N<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.8, 54.7, 69.8, 82.4, 101.8, 108.3, 119.3, 124.4, 126.9, 130.5, 141.9, 177.3 ppm; HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Br$ ($[M + H]^+$) 314.0022; found 314.0030.

Compound 9c-2 (minor diastereomer). R_f = 0.48 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (m, 1H, O<u>H</u>), 2.44 (dd, *J* = 7.6 Hz, 13.2 Hz, 1H, C<u>H</u>HCH(OH)), 2.76 (dd, *J* = 8.8 Hz, 13.2 Hz, 1H, C<u>H</u>HCH(OH)), 3.46 (s, 3H, OC<u>H</u>$_3$), 4.78 (m, 1H, C<u>H</u>(OH)), 5.27 (d, *J* = 4.4 Hz, 1H, C<u>H</u>(OMe)), 6.72 (m, 1H, Ar<u>H</u>), 7.07 (t, *J* = 7.8 Hz, 1H, Ar<u>H</u>), 7.14 (m, 1H, Ar<u>H</u>), 7.55 (brs, 1H, N<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.3, 55.9, 74.37, 82.86, 108.27, 110.99, 118.87, 125.51, 126.41, 130.54, 141.57, 176.38 ppm; HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Br$ ($[M + H]^+$) 314.0022; found 314.0028.

6'-Chloro-4-hydroxy-5-methoxy-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9d)

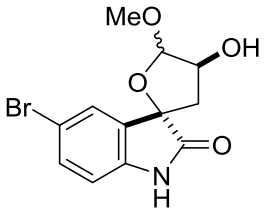


9d

Compound 9d-1. R_f = 0.52 (TLC hexane/ethyl acetate = 1:2); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.91 (d, *J* = 13.2 Hz, 1H, C<u>H</u>HCH(OH)$_2$), 2.48 (dd, *J* = 4.8 Hz, 13.2 Hz, 1H, C<u>H</u>HCH(OH)), 3.26 (s, 3H, OC<u>H</u>$_3$), 4.27 (d, *J* = 4.8 Hz, 1H, C<u>H</u>(OH)), 4.97 (s, 1H, C<u>H</u>(OMe)), 6.75 (d, *J* = 1.9 Hz, 1H, Ar<u>H</u>), 6.89 (dd, *J* = 1.9 Hz, 8.0 Hz, 1H, Ar<u>H</u>), 7.52 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 42.1, 54.9, 76.9, 86.0, 111.2, 112.6, 123.5, 128.9, 131.2, 136.1, 144.1, 180.4 ppm; HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Cl$ ($[M + H]^+$) 270.0528, found 270.0519.

Compound 9d-2. R_f = 0.50 (TLC hexane/ethyl acetate = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (dd, *J* = 9.6 Hz, 12.8 Hz, 1H, C<u>H</u>HCH(OH)), 2.60 (dd, *J* = 7.7 Hz, 12.8 Hz, 1H, C<u>H</u>HCH(OH)), 3.55 (s, 3H, OC<u>H</u>$_3$), 4.76 (m, 1H, C<u>H</u>(OH)), 5.11 (d, *J* = 4.4 Hz, 1H, C<u>H</u>(OMe)), 6.87 (d, *J* = 1.6 Hz, 1H, Ar<u>H</u>), 7.06 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H, Ar<u>H</u>), 7.25 (d, J = 8.0 Hz, 1H, Ar<u>H</u>), 8.12 (brs, 1H, N<u>H</u>) ppm; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 1:1): δ = 2.14 (dd, *J* = 10.4 Hz, 12.6 Hz, 1H, C<u>H</u>HCH(OH)), 2.39 (dd, *J* = 7.8 Hz, 12.6 Hz, 1H, C<u>H</u>HCH(OH)), 3.44 (s, 3H, OC<u>H</u>$_3$), 4.60 (m, 1H, C<u>H</u>(OH)), 4.94 (d, *J* = 4.4 Hz, 1H, C<u>H</u>(OMe)), 6.77 (d, *J* = 1.6 Hz, 1H, Ar<u>H</u>), 6.95 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H, Ar<u>H</u>), 7.18 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6, 54.8, 71.0, 80.8, 102.3, 109.9, 122.5, 125.0, 127.6, 134.6, 140.8, 177.5 ppm; HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Cl$ ($[M + H]^+$) 270.0528; found 270.0518.

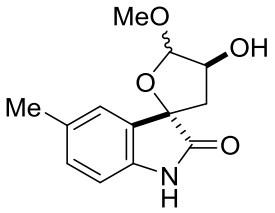
5'-Bromo-4-hydroxy-5-methoxy-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9e)



9e

Compound 9e (dr 1.2:1). R_f = 0.54 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10-2.18 (m, 1H, CHHCH(OH)), 2.58 (dd, *J* = 7.6 Hz, 12.8 Hz, 1H x 1.0/2.2, CHHCH(OH)), 2.69 (dd, *J* = 4.8 Hz, 13.6 Hz, 1H x 1.2/2.2, CHHCH(OH)), 3.40 (s, 3H x 1.2/2.2, OCH_3), 3.55 (s, 3H x 1.0/2.2, OCH_3), 4.54 (d, *J* = 4.4 Hz, 1H x 1.2/2.2, CH(OH)), 4.73 (m, 1H x 1.0/2.2, CH(OH)), 5.10 (d, *J* = 4.4 Hz, 1H x 1.0/2.2, CH(OMe)), 5.16 (s, 1H x 1.2/2.2, CH(OMe)), 6.72-6.76 (m, 1H, ArH), 7.29-7.35 (m, 1H, ArH), 7.41 (d, *J* = 2.0 Hz, 1H x 1.0/2.2, ArH), 7.78 (d, *J* = 2.0 Hz, 1H x 1.2/2.2, ArH), 9.08-9.10 (1H, NH) ppm; ^{1}H NMR (400 MHz, CD_3OD): δ = 2.02 (d, *J* = 13.6 Hz, 1H x 1.2/2.2, CHHCH(OH)), 2.20 (dd, *J* = 10.4 Hz, 12.8 Hz, 1H x 1.0/2.2, CHHCH(OH)), 2.45 (dd, *J* = 8.0 Hz, 12.8 Hz, 1H x 1.0/2.2, CHHCH(OH)), 2.58 (dd, *J* = 4.4 Hz, 13.6 Hz, 1H x 1.2/2.2, CHHCH(OH)), 3.36 (s, 3H x 1.2/2.2, OCH_3), 3.51 (s, 3H x 1.0/2.2, OCH_3), 4.38 (d, *J* = 4.4 Hz, 1H x 1.2/2.2, CH(OH)), 4.62 (m, 1H x 1.0/2.2, CH(OH)), 5.00 (d, *J* = 4.4 Hz, 1H x 1.0/2.2, CH(OMe)), 5.09 (s, 1H x 1.2/2.2, CH(OMe)), 6.75-6.79 (m, 1H, ArH), 7.33-7.40 (m, 1H, ArH), 7.44 (d, *J* = 2.0 Hz, 1H x 1.0/2.2, ArH), 7.80 (d, *J* = 2.0 Hz, 1H x 1.2/2.2, ArH) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 40.6, 42.1, 54.9, 55.9, 72.7, 76.9, 83.3, 86.3, 104.8, 105.1, 112.6, 113.0, 116.1, 116.3, 129.1, 130.8, 133.4, 133.8, 134.3, 134.8, 141.8, 142.2, 179.9, 180.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Br$ ($[M + H]^+$) 314.0022; found 314.0017.

4-Hydroxy-5-methoxy-5'-methyl-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9f)

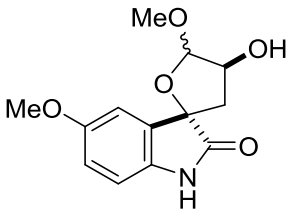


9f

Compound 9f-1. R_f = 0.48 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (d, *J* = 13.6 Hz, 1H, C<u>H</u>HCH(OH)), 2.29 (s, 3H, ArC<u>H</u>$_3$), 2.75 (dd, *J* = 5.2 Hz, 13.6 Hz, 1H, C<u>H</u>HCH(OH)), 3.43 (s, 3H, OC<u>H</u>$_3$), 4.59 (m, 1H, C<u>H</u>(OH)), 5.18 (s, 1H, C<u>H</u>(OMe)), 6.71 (d, *J* = 7.8 Hz, 1H, Ar<u>H</u>), 7.02 (m, 1H, Ar<u>H</u>), 7.45 (m, 1H, Ar<u>H</u>), 8.11 (brs, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 40.1, 53.7, 75.5, 84.0, 108.6, 110.1, 125.8, 129.0, 129.6, 131.9, 1367.0, 177.6 ppm; HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ ($[M + H]^+$) 250.1074; found 250.1078.

Compound 9f-2. R_f = 0.46 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (dd, *J* = 9.9 Hz, 12.7 Hz, 1H, C<u>H</u>HCH(OH)), 2.33 (s, 3H, ArC<u>H</u>$_3$), 2.59 (m, 1H, C<u>H</u>HCH(OH)), 3.57 (s, 3H, OC<u>H</u>$_3$), 4.79 (m, 1H, C<u>H</u>(OH)), 5.12 (d, *J* = 4.5 Hz, 1H, C<u>H</u>(OMe)), 6.74 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.05 (m, 1H, Ar<u>H</u>), 7.13 (m, 1H, Ar<u>H</u>), 8.26 (brs, 1H, N<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 39.7, 54.7, 71.0, 81.5, 102.1, 109.0, 124.6, 129.1, 129.2, 132.0, 137.3, 178.0 ppm; HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ ($[M + H]^+$) 250.1074; found 250.1079.

4-Hydroxy-5,5'-dimethoxy-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9g)

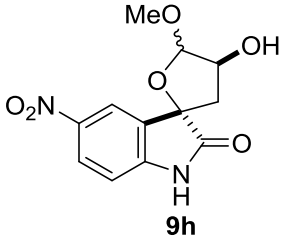


9g

Compound 9g (dr 1:1). R_f = 0.39 (TLC hexane/EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09-218 (m, 1H, CHHCH(OH)), 2.61 (dd, *J* = 7.6 Hz, 12.8 Hz, 1H x 1/2, CHHCH(OH)), 2.75 (dd, *J* = 4.8 Hz, 13.6 Hz, 1H x 1/2, CHHCH(OH)), 3. 44 (s, 3H x 1/2, CHOCH_3), 3.57 (s, 3H x 1/2, CHOCH_3), 3.76 (s, 3H x 1/2, ArOCH_3), 3.80 (s, 3H x 1/2, ArOCH_3), 4.58 (d, *J* = 4.4 Hz, 1H x 1/2, CH(OH)), 4.78 (m, 1H x 1/2, CH(OH)), 5.11 (d, *J* = 4.4 Hz, 1H x 1/2, CH(OMe)), 5.18 (s, 1H x 1/2, CH(OMe)), 6.72-6.78 (m, 2H, ArH), 6.94 (d, *J* = 2.0 Hz, 1H x 1/2, ArH), 7.31 (d, *J* = 2.0 Hz, 1H x 1/2, ArH), 8.15 (brs, 1H x 1/2, NH), 8.17 (brs, 1H x 1/2, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.8, 41.2, 54.7, 55.7, 55.8, 72.1, 76.5, 77.2, 82.7, 85.3, 103.2, 110.4, 110.7, 111.2, 111.9, 113.0, 114.6, 114.8, 131.5, 131.9, 133.7, 133.9, 156.4, 156.6, 178.5, 178.7 ppm; HRMS (ESI): $C_{13}H_{16}NO_5$ ($[M + H]^+$) calcd. for 266.1023, found 266.1028.

When a solution of **9g** (dr 1:1) in $CDCl_3$ was kept at 25 °C for 5 days, the dr was changed to 5:1; the minor diastereomer R_f = 0.4 and the major diastereomer R_f = 0.38 (TLC hexane/EtOAc = 1:2). The major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (dd, *J* = 9.8 Hz, 12.6 Hz, 1H, CHHCH(OH)), 2.61 (dd, *J* = 7.8 Hz, 12.6 Hz, 1H CHHCH(OH)), 2.75 (dd, *J* = 4.8 Hz, 13.6 Hz, 1H x 1/2, CHHCH(OH)), 3.57 (s, 3H, CHOCH_3), 3.79 (s, 3H, ArOCH_3), 4.78 (ddd, *J* = 4.4 Hz, 7.8 Hz, 9.8 Hz, 1H, CH(OH)), 5.11 (d, *J* = 4.4 Hz, 1H, CH(OMe)), 6.72-6.78 (m, 2H, ArH), 6.94 (d, *J* = 2.0 Hz, 1H, ArH), 8.18 (brs, 1H, NH) ppm.

4-Hydroxy-5-methoxy-5'-nitro-4,5-dihydro-3*H*-spiro[furan-2,3'-indolin]-2'-one (9h)



9h

Compound 9h (dr 1:1). R_f = 0.52 (TLC hexane/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16-2.26 (m, 1H, CHHCH(OH)), 2.65 (dd, *J* = 7.6 Hz, 12.8 Hz, 1H x 1/2, CHHCH(OH)),

2.76 (dd, *J* = 4.6 Hz, 13.6 Hz, 1H x 1/2, CHHCH(OH)), 3.43 (s, 3H x 1/2, OCH$_3$), 3.60 (s, 3H x 1/2, OCH$_3$), 4.60 (d, *J* = 4.6 Hz, 1H x 1/2, CH(OH)), 4.76 (m, 1H x 1/2, CH(OH)), 5.15 (d, *J* = 4.4 Hz, 1H x 1/2, CH(OMe)), 5.21 (s, 1H x 1/2, CH(OMe)), 6.97-7.02 (m, 2H, ArH), 8.18-8.25 (m, 1H + 1H x 1/2, ArH), 8.59 (d, *J* = 2.3 Hz, 1H x 1/2, ArH), 8.89 (s, 1H x 1/2, NH), 8.92 (s, 1H x 1/2, NH) ppm.

Compound 9h (dr 1.4:1). R_f = 0.52 (TLC hexane/EtOAc = 2:1); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.08 (d, *J* = 13.6 Hz, 1H x 1.4/2.4, CHHCH(OH)), 2.26 (dd, *J* = 10.0 Hz, 12.8 Hz, 1H x 1.0/2.4, CHHCH(OH)), 2.51 (dd, *J* = 7.6 Hz, 12.8 Hz, 1H x 1.0/2.4, CHHCH(OH)), 2.61 (dd, *J* = 4.4 Hz, 13.6 Hz, 1H x 1.4/2.4, CHHCH(OH)), 3.37 (s, 3H x 1.4/2.4, OCH$_3$), 3.54 (s, 3H x 1.0/2.4, OCH$_3$), 4.40 (d, *J* = 4.4 Hz, 1H x 1.4/2.4, CH(OH)), 4.63 (m, 1H x 1.0/2.4, CH(OH)), 5.04 (d, *J* = 4.4 Hz, 1H x 1.0/2.4, CH(OMe)), 5.13 (s, 1H x 1.4/2.4, CH(OMe)), 6.96-7.01 (m, 1H, ArH), 8.15-8.22 (m, 2H x 1.0/2.4 + 1H x 1.4/2.4, ArH), 8.55 (d, *J* = 2.3 Hz, 1H x 1.4/2.4, ArH) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 40.5, 42.1, 54.9, 56.0, 72.8, 76.8, 82.8, 85.7, 105.3, 110.9, 111.3, 112.7, 121.8, 123.7, 127.4, 127.8, 133.2, 133.5, 144.8, 145.0, 148.9, 149.2, 180.4 ppm; HRMS (ESI): calcd. for $C_{12}H_{13}N_2O_6$ ($[M + H]^+$) 281.0768, found 281.0761.

Table 6.1. Chemical shifts (ppm) and *J* values (Hz) of **9**.

Compound (solvent)	CH(OMe)	CH(OH)	CH$_2$		Compound (solvent)	CH (OMe)	CH (OH)	CH$_2$	
9a-1 ($CDCl_3$)	5.19 (s)	4.59 (dd, 0.4, 4.8)	2.74 (dd, 4.8, 13.6)	2.14 (dd, 0.4, 13.6)	**9a-2** ($CDCl_3$)	5.12 (d, 4.4)	4.79 (m)	2.61 (dd, 7.6, 12.8)	2.18 (dd, 10.0, 12.8)

9a-1 ($CDCl_3$-CD_3OD 1:1)	4.81 (s)	4.13 (dd, 0.4, 4.8)	2.33 (dd, 4.8, 13.6)	1.77 (dd, 0.4, 13.6)	**9a-2** ($CDCl_3$-CD_3OD 1:1)	4.89 (d, 4.4)	4.55 (ddd, 4.4, 7.8, 10.4)	2.34 (dd, 7.8, 12.5)	2.08 (dd, 10.4, 12.5)
9d-1 (CD_3OD)	4.97 (s)	4.27 (d, 4.8)	2.48 (dd, 4.8, 13.2)	1.91 (d, 13.2)	**9d-2** ($CDCl_3$-CD_3OD 1:1)	4.94 (d, 4.4)	4.60 (m)	2.39 (d, 7.8, 12.6)	2.14 (dd, 10.4, 12.6)
9f-1 ($CDCl_3$)	5.18 (s)	4.59 (m)	2.75 (dd, 5.2, 13.6)	2.13 (13.6)	**9f-2** ($CDCl_3$)	5.12 (d, 4.5)	4.79 (m)	2.59 (m)	2.16 (dd, 9.9, 12.7)
9c-1 ($CDCl_3$)	5.20 (d, 5.2)	5.10 (m)	2.81 (dd, 10.6, 12.5)	2.37 (dd, 7.2, 12.5)	**9c-2** ($CDCl_3$)	5.27 (d, 4.4)	4.78 (m)	2.76 (dd, 8.8, 13.2)	2.44 (dd, 7.6, 13.2)
9b ($CDCl_3$)	5.17 (d, 5.2)	5.06 (m)	2.76 (dd, 10.4, 12.4)	2.38 (dd, 7.4, 12.4)	**9b** ($CDCl_3$-CD_3OD 1:1)	4.99 (d, 5.2)	4.91 (ddd, 5.2, 7.2, 11.2)	2.77 (dd, 11.2, 12.0)	2.15 (dd, 7.2, 12.0)

Isomers **9a-1**, **9d-1**, and **9f-1** were assigned to be OMe/OH *trans* and isomers **9a-2**, **9d-2**, and **9f-2** were assigned to be OMe/OH *cis* based on the coupling constants (*J* values) in the ^{1}H NMR.

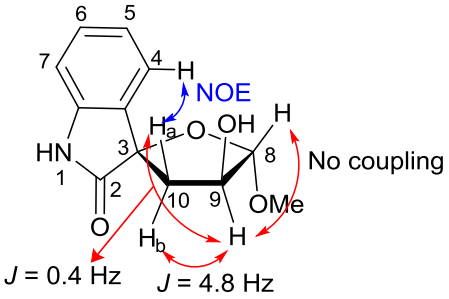


Figure 6.1. NOE in NOESY experimetns and *J* values observed in **9a-1**.

The ratio of the intensities of a pair of NOE signals within that spectrum can be assumed inversely proportional to their ratio of inter-proton distances to the 6th power,[127] i.e.

$$r_{ij} = r_{ref} (a_{ref}/a_{ij})^{1/6}$$

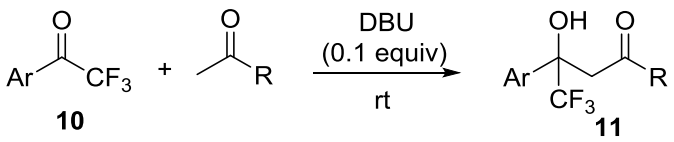
where a_{ij} is the relative NOE intensity (integration of the area of the signal in NOESY specturm) and r_{ij} is the inter-proton distance of the two protons i and j. Given a known distance between two protons (r_{ref}) and its NOE volume (a_{ref}), r_{ij} can be calculated from its relative NOE intensity a_{ij}.

Based on this method, the proton distance between H4 and H10a was estimated as shown below. The proton distance of the geminal protons H10a-H10b was used as the reference to be 1.75 Å.[127] Only F2-slices were usded to determine the NOE intensity.[127]

	Relative NOE Intensity	Proton distance
H10a-H10b	55.89 (a_{ref})	1.75 Å (r_{ref})
H4-H10a	1.72 ($a_{4\text{-}10a}$)	3.13 Å ($r_{4\text{-}10a}$)

6.2.2 Experimental Section for Chapter 2.3

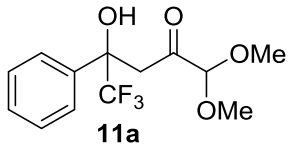
DBU Catalyzed Aldol Reactions of Ketone Donors with 10



General procedure for the DBU-catalyzed aldol reactions of ketone donors with 10 to give 11 (Schemes 2.8 and Scheme 2.9). To a mixture of donor ketone (2.5 mmol) and **10** (0.5 mmol) was added DBU (0.05 mmol), and the mixture was stirred at rt (25 °C) until **10** was consumed (monitored by TLC). The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography (hexane/EtOAc = 8:1 to 4:1) to give **11**.

A gram-scale reaction to give 11a. To a mixture of **1** (2.95 mL, 25.0 mmol) and **10a** (702 μL, 5.0 mmol) was added DBU (74.5 μL, 0.5 mmol), and the mixture was stirred at rt (25 °C) for 1.5 h. The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography (hexane/EtOAc = 8:1 to 4:1) to give **11a (**1.38 g, 94%).

5,5,5-Trifluoro-4-hydroxy-1,1-dimethoxy-4-phenylpentan-2-one (11a)[74]

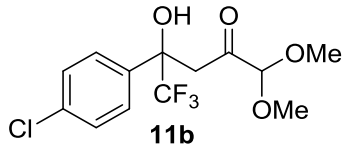


11a

Synthesized by the general procedure, 1.5 h, 122.5 mg (84%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.30 (s, 3H, C<u>H</u>$_3$), 3.40 (s, 3H, OC<u>H</u>$_3$), 3.67 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 4.29 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 5.01 (s, 1H, O<u>H</u>), 7.33-7.40 (m, 3H, Ar<u>H</u>), 7.59 (dd, *J* = 0.4 Hz, 7.5 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.9, 55.21, 55.22, 76.0 (q, $J_{C,F}$ = 29 Hz), 104.4, 124.4 (q, $J_{C,F}$ = 283 Hz), 126.4, 128.3, 128.8, 137.1, 204.7 ppm; HRMS (ESI) calcd for $C_{13}H_{14}O_4F_3$ ([M – H]$^-$) 291.0839, found 291.0843.

4-(4-Chlorophenyl)-5,5,5-trifluoro-4-hydroxy-1,1-dimethoxypentan-2-one (11b)

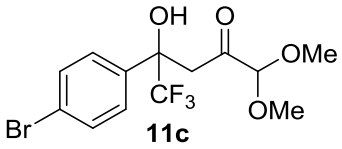


11b

Synthesized by the general procedure, 1.0 h, 155.0 mg (95%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.28 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.33 (s, 3H, OC<u>H</u>$_3$), 3.42 (s, 3H, OC<u>H</u>$_3$), 3.60 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 4.27 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 5.02 (s, 1H, O<u>H</u>), 7.33-7.37 (m, 2H, Ar<u>H</u>), 7.52 (d, *J* = 8.5 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6, 55.4, 55.5, 75.8 (q, $J_{C,F}$ = 30 Hz), 104.5, 124.2 (q, $J_{C,F}$ = 283 Hz), 128.0, 128.5, 135.0, 135.7, 204.5 ppm; HRMS (ESI) calcd for $C_{13}H_{13}O_4F_3Cl$ ([M – H]$^-$) 325.0449, found 329.0458.

4-(4-Bromophenyl)-5,5,5-trifluoro-4-hydroxy-1,1-dimethoxypentan-2-one (11c)

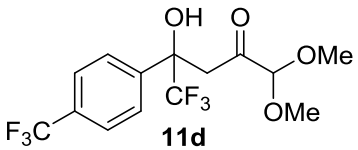


11c

Synthesized by the general procedure, 1.0 h, 159.4 mg (86%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.32 (s, 3H, OC<u>H</u>$_3$), 3.41 (s, 3H, OC<u>H</u>$_3$), 3.60 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 4.27 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 5.03 (s, 1H, O<u>H</u>), 7.46 (d, *J* = 8.5 Hz, 2H, Ar<u>H</u>), 7.49-7.52 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.5, 55.37, 55.42, 75.8 (q, $J_{C,F}$ = 29 Hz), 104.4, 123.2, 124.1 (q, $J_{C,F}$ = 283 Hz), 128.3, 131.4, 136.3, 204.4 ppm; HRMS (ESI) calcd for $C_{13}H_{13}O_4F_3Br$ ([M – H]$^-$) 368.9944, found 368.9975.

5,5,5-Trifluoro-4-hydroxy-1,1-dimethoxy-4-(4-(trifluoromethyl)phenyl)pentan-2-one (11d)



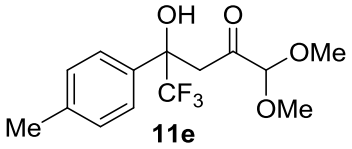
11d

Synthesized by the general procedure, 1.0 h, 156.4 mg (87%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 3H, OC<u>H</u>$_3$), 3.34 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.42 (s, 3H, OC<u>H</u>$_3$), 3.64 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 4.28 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 5.12 (s, 1H, O<u>H</u>), 7.64 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 7.73 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>)

ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6, 55.4, 55.5, 75.9 (q, $J_{C,F}$ = 29 Hz), 104.5, 123.9 (q, $J_{C,F}$ = 271 Hz), 124.1 (q, $J_{C,F}$ = 283 Hz), 125.2 (q, $J_{C,F}$ = 4.0 Hz), 127.1, 131.0 (q, $J_{C,F}$ = 32 Hz), 141.2, 204.4 ppm; HRMS (ESI) calcd for $C_{14}H_{13}O_4F_6$ ($[M - H]^-$) 359.0713, found 359.0716.

5,5,5-Trifluoro-4-hydroxy-1,1-dimethoxy-4-(p-tolyl)pentan-2-one (11e)

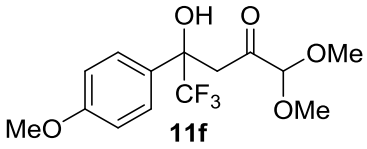


11e

Synthesized by the general procedure, 1.5 h, 139.3 mg (91%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3H, ArC<u>H</u>$_3$) 3.27 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.32 (s, 3H, OC<u>H</u>$_3$), 3.40 (s, 3H, OC<u>H</u>$_3$) 3.66 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 4.29 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 4.95 (s, 1H, O<u>H</u>), 7.19 (d, *J* = 8.0 Hz, 2H, Ar<u>H</u>), 7.47 (d, *J* = 8.0 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 39.8, 55.15, 55.20, 75.9 (q, $J_{C,F}$ = 29 Hz), 104.3, 124.4 (q, $J_{C,F}$ = 283 Hz), 126.3, 129.0, 134.1, 138.6, 204.8 ppm; HRMS (ESI) calcd for $C_{14}H_{16}O_4F_3$ ($[M - H]^-$) 305.0995, found 305.0994.

5,5,5-Trifluoro-4-hydroxy-1,1-dimethoxy-4-(4-methoxyphenyl)pentan-2-one (11f)

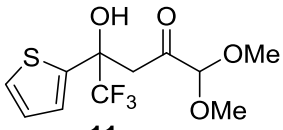


11f

Synthesized by the general procedure, 1.5 h, 143.3 mg (89%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.32 (s, 3H, OC<u>H</u>$_3$), 3.40 (s, 3H, OC<u>H</u>$_3$), 3.64 (d, *J* = 17.8 Hz, 1H, C<u>H</u>HC=O), 3.80 (s, 3H, OC<u>H</u>$_3$), 4.28 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 4.95 (s, 1H, O<u>H</u>), 6.87-6.91 (m, 2H, Ar<u>H</u>), 7.50 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.8, 55.13, 55.18, 55.23, 75.8 (q, $J_{C,F}$ = 29 Hz), 104.4, 113.6, 124.4 (q, $J_{C,F}$ = 283 Hz), 127.7, 129.0, 159.9, 204.7 ppm; HRMS (ESI) calcd for $C_{14}H_{16}O_5F_3$ ($[M - H]^-$) 321.0944, found 321.0946.

5,5,5-Trifluoro-4-hydroxy-1,1-dimethoxy-4-(thiophen-2-yl)pentan-2-one (11g)

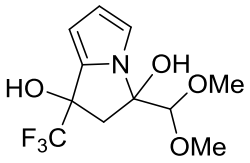


11g

Synthesized by the general procedure, 1.5 h, 129.7 mg (87%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (d, *J* = 17.7 Hz, 1H, C<u>H</u>HC=O), 3.34 (s, 3H, OC<u>H</u>$_3$), 3.41 (s, 3H, OC<u>H</u>$_3$), 3.58 (d, *J* = 17.7 Hz, 1H, C<u>H</u>HC=O), 4.32 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 5.45 (s, 1H, O<u>H</u>), 6.99 (dd, *J* = 3.6 Hz, 5.1 Hz, 1H, Ar<u>H</u>), 7.10 (d, *J* = 3.6 Hz, 1H, Ar<u>H</u>), 7.32 (dd, *J* = 1.2 Hz, 5.1 Hz, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.6, 55.2, 55.3, 75.4 (q, $J_{C,F}$ = 31 Hz), 104.3, 123.7 (q, $J_{C,F}$ = 283 Hz), 126.0, 126.6, 127.0, 141.4, 204.5 ppm; HRMS (ESI) calcd for $C_{11}H_{12}O_4F_3S$ ([M – H]$^-$) 297.0403, found 297.0417.

3-(Dimethoxymethyl)-1-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine-1,3-diol (11h)



11h

Synthesized by the general procedure using DBU (0.1 mmol, 0.2 equiv), 48 h.

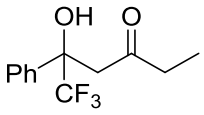
Upper spot on TLC, R_f = 0.34 (hexane/EtOAc = 2:1): **11h-1** (50.5 mg, 36%)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.87 (d, *J* = 14.8 Hz, 1H, C<u>H</u>HC=O), 2.94 (d, *J* = 14.8 Hz, 1H, C<u>H</u>HC=O), 3.32 (s, 3H, OC<u>H</u>$_3$), 3.52 (s, 3H, OC<u>H</u>$_3$), 3.50-3.70 (br, 2H, O<u>H</u>), 4.41 (s, 1H, C<u>H</u>(OCH$_3$)$_2$), 6.16 (d, *J* = 3.2 Hz, 1H, Ar<u>H</u>), 6.33 (t, *J* = 3.2 Hz, 1H, Ar<u>H</u>), 6.80 (m, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.4, 57.2, 58.3, 74.6 (q, $J_{C,F}$ = 32 Hz), 89.7, 102.4, 106.9, 113.7, 114.9, 124.5 (q, $J_{C,F}$ = 289 Hz), 132.9 ppm; HRMS (ESI) calcd for $C_{11}H_{15}NO_4F_3$ ([M + H]$^+$) 282.0948, found 282.0949.

Lower spot on TLC, R_f = 0.23 (hexane/EtOAc = 2:1): **11h-2** (63.1 mg, 45%)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (d, *J* = 14.8 Hz, 1H, C<u>H</u>HC=O), 3.20 (d, *J* = 14.8 Hz, 1H, C<u>H</u>HC=O), 3.49 (s, 3H, OC<u>H</u>$_3$), 3.52 (s, 3H, OC<u>H</u>$_3$), 4.09 (br, 1H, O<u>H</u>), 4.44 (s, 1H, C<u>H</u>$(OCH_3)_2$), 6.12 (d, *J* = 3.2 Hz, 1H, Ar<u>H</u>),6.29 (t, *J* = 3.2 Hz, 1H, Ar<u>H</u>), 6.81-6.82 (m, 1H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.5, 56.85, 56.99, 74.8 (q, $J_{C,F}$ = 32 Hz), 89.4, 102.3, 105.3, 114.70, 114.72, 124.5 (q, $J_{C,F}$ = 280 Hz), 133.1 ppm; HRMS (ESI) calcd for $C_{11}H_{15}NO_4F_3$ ($[M + H]^+$) 282.0948, found 282.0947.

6,6,6-Trifluoro-5-hydroxy-5-phenylhexan-3-one (11aa)[91]

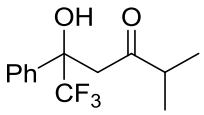


11aa

Synthesized by the general procedure, 1.0 h, 99.7 mg (81%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 3H, C<u>H</u>$_3$), 2.35-2.45 (m, 1H, C<u>H</u>HCH$_3$), 2.50-2.60 (m, 1H, C<u>H</u>HCH$_3$), 3.18 (d, *J* = 17.2 Hz, 1H, C(OH)C<u>H</u>HC=O), 3.31 (d, *J* = 17.2 Hz,1H, C(OH)C<u>H</u>HC=O), 5.65 (s, 1 H, O<u>H</u>), 7.34-7.44 (m, 3 H, Ar<u>H</u>), 7.57-7.59 (m, 2 H, Ar<u>H</u>) ppm.

6,6,6-Trifluoro-5-hydroxy-2-methyl-5-phenylhexan-3-one (11ab)[94]



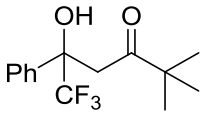
11ab

Synthesized by the general procedure, 3.0 h, 110.3 mg (85%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.0 Hz, 3H, C<u>H</u>$_3$), 1.11 (d, *J* = 7.0 Hz, 3H, C<u>H</u>$_3$), 2.59 (septet, *J* = 7.0 Hz, 1H, C<u>H</u>$(CH_3)_2$), 3.23 (d, *J* = 17.2 Hz, 1H, C<u>H</u>HC=O), 3.35 (d, *J* = 17.2 Hz, 1H, C<u>H</u>HC=O), 5.79 (s, 1H, O<u>H</u>), 7.33-7.41 (m, 3H, Ar<u>H</u>), 7.57-7.59 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 17.5, 42.3, 42.5, 76.1 (q, $J_{C,F}$ = 30 Hz),

124.6 (q, $J_{C,F}$ = 283 Hz), 126.1, 128.3, 128.7, 137.6, 215.1 ppm; HRMS (ESI) calcd for $C_{13}H_{16}O_2F_3$ ($[M + H]^+$) 261.1097, found 261.1078.

6,6,6-Trifluoro-5-hydroxy-2,2-dimethyl-5-phenylhexan-3-one (11ac)[94]

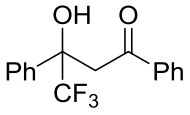


11ac

Synthesized by the general procedure at 45 °C, 12 h, 130.0 mg (95%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 9H, ($C\underline{H}_3$)$_3$), 3.24 (d, *J* = 17.6 Hz, 1H, C<u>H</u>HC=O), 3.41 (d, *J* = 17.6 Hz, 1H, C<u>H</u>HC=O), 5.97 (s, 1H, O<u>H</u>), 7.33-7.41 (m, 3H, Ar<u>H</u>), 7.58 (d, *J* = 7.2 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 38.9, 45.1, 76.2 (q, $J_{C,F}$ = 29 Hz), 124.7 (q, $J_{C,F}$ = 283 Hz), 126.1, 128.3, 128.6, 137.8, 216.6 ppm; HRMS (ESI) calcd for $C_{14}H_{18}O_2F_3$ ($[M + H]^+$) 275.1253, found 275.1239.

4,4,4-Trifluoro-3-hydroxy-1,3-diphenylbutan-1-one (11ad)[94]

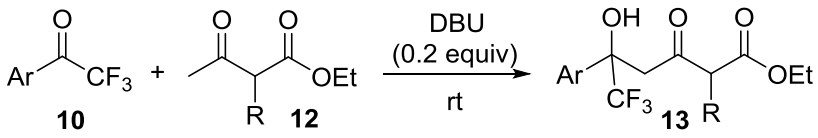


11ad

Synthesized by the general procedure, 2.0 h, 130.4 mg (89%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (d, *J* = 17.2 Hz, 1H, C<u>H</u>HC=O), 4.06 (d, *J* = 17.2 Hz, 1H, C<u>H</u>HC=O), 5.74 (s, 1H, O<u>H</u>), 7.34-7.40 (m, 3H, Ar<u>H</u>), 7.48-7.52 (m, 2H, Ar<u>H</u>), 7.94-7.96 (m, 2 H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.2, 76.5 (q, $J_{C,F}$ = 29 Hz), 124.6 (q, $J_{C,F}$ = 283 Hz), 126.3, 128.2, 128.4, 128.7, 128.9, 134.4, 136.2, 137.6, 199.7 ppm.

DBU Catalyzed Aldol Reactions of β-Keto Esters 12 with 10

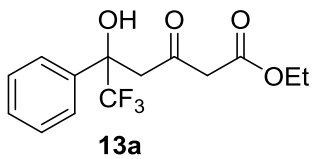


General procedure for the DBU-catalyzed aldol reactions of β-keto esters 12 with 10 to give 13 (Scheme 2.10). To a mixture of β-keto ester **12** (5.0 mmol) and **10** (0.5 mmol) was added DBU (0.1 mmol), and the mixture was stirred at rt (25 °C) until **10** was consumed (monitored by TLC). The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography (hexane/EtOAc = 8:1 to 4:1) to give **13**.

A 15 mmol-scale reaction to give 13a. To a mixture of ethyl acetoacetate (9.48 mL, 75.0 mmol, 5.0 equiv) and **10a** (2.11 mL, 15.0 mmol, 1.0 equiv) was added DBU (224 μL, 1.50 mmol, 0.1 equiv), and the mixture was stirred at rt (25 °C) for 4 days. The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography (hexane/EtOAc = 15:1 to 8:1) to give **13a (**3.29 g, 72%).

^{1}H NMR analyses during the progress of the reaction to form 13a. A reaction mixture to form **13a** was prepared. At 5 min, 50 min, 130 min, and 220 min, an aliquot was taken from the mixture, diluted with $CDCl_3$, and analyzed by ^{1}H NMR. Formation of product **13a** was observed at each time point. But, no sign of the presence of the product with the bond formation at the α-position of the β-keto ester was detected.

Ethyl 6,6,6-trifluoro-5-hydroxy-3-oxo-5-phenylhexanoate (13a)

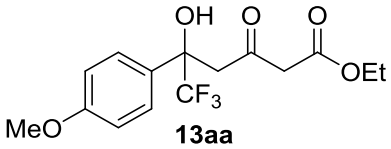


13a

Synthesized by the general procedure, 24 h, 126.0 mg (83%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 3.36 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 3.41 (d, *J* = 15.6 Hz, 1H, C(=O)C<u>H</u>HCOOEt), 3.45 (d, *J* = 15.6 Hz, 1H, C(=O)C<u>H</u>HCOOEt), 3.59 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 4.19 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.98 (s, 1H, O<u>H</u>), 7.34-7.42 (m, 3H, Ar<u>H</u>), 7.56-7.58 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 45.2, 50.6, 61.9, 76.0 (q, $J_{C,F}$ = 29 Hz), 124.4 (q, $J_{C,F}$ = 283 Hz), 126.2, 128.5, 128.9, 136.9, 166.1, 202.5 ppm; HRMS (ESI) calcd for $C_{14}H_{16}O_4F_3$ ($[M + H]^+$) 305.0995, found 305.0981.

Ethyl 6,6,6-trifluoro-5-hydroxy-5-(4-methoxyphenyl)-3-oxohexanoate (13aa)

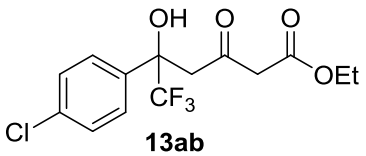


13aa

Synthesized by the general procedure, 36 h, 105.3 mg (63%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 3.31 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 3.40 (d, *J* = 15.6 Hz, 1H, C(=O)C<u>H</u>HCOOEt), 3.44 (d, *J* = 15.6 Hz, 1H, C(=O)C<u>H</u>HCOOEt), 3.56 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 3.80 (s, 3H, $OC\underline{H}_3$) 4.19 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.92 (brs, 1H, O<u>H</u>), 6.90 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 7.48 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 45.2, 50.5, 55.2, 61.8, 75.7 (q, $J_{C,F}$ = 29 Hz), 113.8 124.4 (q, $J_{C,F}$ = 283 Hz), 127.5, 128.7, 159.9, 166.2, 202.5 ppm; HRMS (ESI) calcd for $C_{15}H_{16}O_5F_3$ ($[M + H]^+$) 335.1101, found 335.1088.

Ethyl 5-(4-chlorophenyl)-6,6,6-trifluoro-5-hydroxy-3-oxohexanoate (13ab)



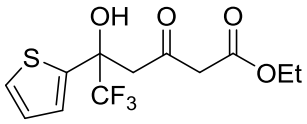
13ab

Synthesized by the general procedure, 24 h, 131.5 mg (78%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 3.35 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 3.41 (d, *J* = 15.6 Hz, 1H, C(=O)C<u>H</u>HCOOEt), 3.46 (d, *J* =

15.6 Hz, 1H, C(=O)C<u>H</u>HCOOEt), 3.56 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 4.19 (q, *J* = 7.2 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 5.04 (s, 1H, O<u>H</u>), 7.36 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 7.51 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 45.0, 50.4, 62.0, 75.7 (q, $J_{C,F}$ = 29 Hz), 124.1 (q, $J_{C,F}$ = 283 Hz), 127.7, 128.7, 135.1, 135.5, 166.2, 202.3 ppm; HRMS (ESI) calcd for $C_{14}H_{15}O_4F_3Cl$ ([M + H]$^+$) 339.0605, found 339.0591.

Ethyl 6,6,6-trifluoro-5-hydroxy-3-oxo-5-(thiophen-2-yl)hexanoate (13ac)

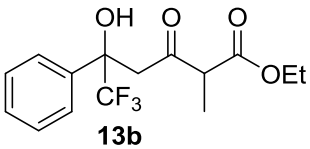


13ac

Synthesized by the general procedure, 24 h, 130.4 mg (84%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 3.32 (d, *J* = 17.2 Hz, 1H, C(OH)C<u>H</u>HC=O), 3.46 (s, 2H, C(=O)C<u>H</u>$_2$COOEt), 3.52 (d, *J* = 17.6 Hz, 1H, C(OH)C<u>H</u>HC=O), 4.19 (q, *J* = 7.2 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 5.42 (s, 1H, O<u>H</u>), 6.99-7.01 (m, 2H, Ar<u>H</u>), 7.32-7.34 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 45.8, 50.5, 61.9, 75.3 (q, $J_{C,F}$ = 31 Hz), 123.7 (q, $J_{C,F}$ = 283 Hz), 126.0, 126.7, 127.2, 141.0, 166.1, 202.4 ppm; HRMS (ESI) calcd for $C_{12}H_{14}O_4F_3S$ ([M + H]$^+$) 311.0559, found 311.0549.

Ethyl 6,6,6-trifluoro-5-hydroxy-2-methyl-3-oxo-5-phenylhexanoate (13b)



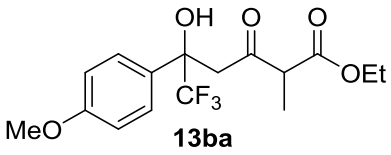
13b

Synthesized by the general procedure, 24 h, 127.5 mg (80%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22-1.29 (m, 6H, OCH$_2$C<u>H</u>$_3$, C<u>H</u>$_3$CHC=O), 3.31-3.61 (m, 3H, CH$_3$C<u>H</u>C=O, C(OH)C<u>H</u>$_2$C=O), 4.11-4.24 (m, 2H, OC<u>H</u>$_2$CH$_3$), 5.20 (brs, 1H×1/2, O<u>H</u>), 5.24 (brs, 1H×1/2, O<u>H</u>) 7.33-7.41 (m, 3H, Ar<u>H</u>), 7.56-7.57 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 12.2, 13.9, 43.8, 44.0, 53.9, 54.4, 61.8, 61.9, 75.69 (q, $J_{C,F}$ = 29 Hz), 76.01 (q, $J_{C,F}$ = 29 Hz), 124.37 (q, $J_{C,F}$ = 283 Hz), 124.44 (q, $J_{C,F}$ = 283 Hz),

126.05, 126.09, 128.3, 128.4, 128.79, 128.83, 137.05, 137.16, 169.21, 169.23, 205.7, 206.0 ppm; HRMS (ESI) calcd for $C_{15}H_{18}O_4F_3$ ($[M + H]^+$) 319.1152, found 319.1135.

Ethyl 6,6,6-trifluoro-5-hydroxy-5-(4-methoxyphenyl)-2-methyl-3-oxohexanoate (13ba)

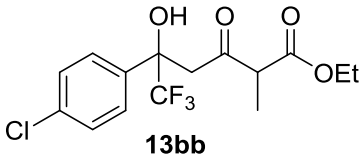


13ba

Synthesized by the general procedure, 26 h, 115.3 mg (66%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23-1.29 (m, 6H, $OCH_2C\underline{H}_3$, $C\underline{H}_3CHC{=}O$), 3.27-3.59 (m, 3H, $CH_3C\underline{H}C{=}O$, $C(OH)C\underline{H}_2C{=}O$), 3.79 (s, 3H×1/2, $OC\underline{H}_3$), 3.80 (s, 3H×1/2, $OC\underline{H}_3$), 4.13-4.23 (m, 2 H, $OC\underline{H}_2CH_3$), 5.08 (brs, 1H×1/2, O<u>H</u>), 5.16 (brs, 1H×1/2, O<u>H</u>), 6.87-6.92 (m, 2H, Ar<u>H</u>), 7.45-7.47 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 12.2, 13.9, 43.7, 44.0, 53.9, 54.4, 55.2, 61.8, 61.9, 75.7 (q, $J_{C,F}$ = 29 Hz), 75.8 (q, $J_{C,F}$ = 29 Hz), 113.7, 113.8, 124.4 (q, $J_{C,F}$ = 283 Hz), 124.5 (q, $J_{C,F}$ = 283 Hz), 127.39, 127.44, 129.0, 129.1, 159.87, 159.88, 169.29, 169.30, 205.7, 206.1 ppm; HRMS (ESI) calcd for $C_{16}H_{20}O_5F_3$ ($[M + H]^+$) 349.1257, found 349.1250.

Ethyl 5-(4-chlorophenyl)-6,6,6-trifluoro-5-hydroxy-2-methyl-3-oxohexanoate (13bb)



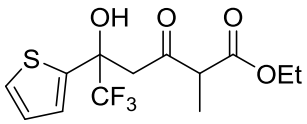
13bb

Synthesized by the general procedure, 24 h, 132.3 mg (75%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22-1.29 (m, 6H, $OCH_2C\underline{H}_3$, $C\underline{H}_3CHC{=}O$), 3.28-3.59 (m, 3H, $CH_3C\underline{H}C{=}O$, $C(OH)C\underline{H}_2C{=}O$), 4.12-4.23 (m, 2 H, $OC\underline{H}_2CH_3$), 5.17 (brs, 1H×1/2, O<u>H</u>), 5.28 (brs, 1H×1/2, O<u>H</u>), 7.33-7.37 (m, 2H, Ar<u>H</u>), 7.48-7.50(m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 12.2, 13.88, 13.89, 43.5, 43.9, 53.8, 54.3, 61.9, 62.0, 75.73 (q, $J_{C,F}$ = 29 Hz), 75.74 (q, $J_{C,F}$ = 29 Hz), 124.17 (q, $J_{C,F}$ = 283 Hz), 124.20 (q, $J_{C,F}$ =

283 Hz), 127.6, 127.7, 128.5, 128.6, 135.00, 135.03 135.7, 135.8, 169.21, 169.22, 205.6, 205.8 ppm; HRMS (ESI) calcd for $C_{15}H_{17}O_4F_3Cl$ ($[M + H]^+$) 353.0762, found 353.0747.

Ethyl 6,6,6-trifluoro-5-hydroxy-2-methyl-3-oxo-5-(thiophen-2-yl)hexanoate (13bc)

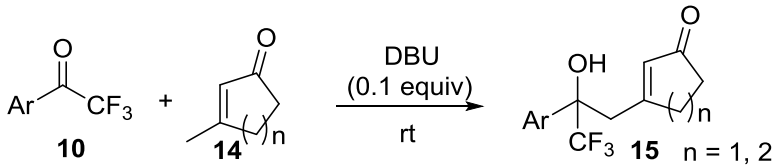


13bc

Synthesized by the general procedure, 26 h, 113.5 mg (70%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23-1.31 (m, 6H, $OCH_2C\underline{H}_3$, $C\underline{H}_3CHC{=}O$), 3.27-3.60 (m, 3H, $CH_3C\underline{H}C{=}O$, $C(OH)C\underline{H}_2C{=}O$), 4.13-4.23 (m, 2H, $OC\underline{H}_2CH_3$), 5.59 (brs, 1H×1/2, O<u>H</u>), 5.62 (brs, 1H×1/2, O<u>H</u>), 6.98-7.01 (m, 1 H, Ar<u>H</u>), 7.07-7.10 (m, 1 H, Ar<u>H</u>), 7.32-7.33 (m, 1 H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 12.2, 13.9, 44.5, 44.6, 54.0, 54.4, 61.8, 61.9, 75.41 (q, $J_{C,F}$ = 30 Hz), 75.44 (q, $J_{C,F}$ = 31 Hz), 123.7 (q, $J_{C,F}$ = 283 Hz), 123.8 (q, $J_{C,F}$ = 283 Hz), 125.7, 125.8, 126.5, 126.6, 127.1, 127.2, 141.2, 141.3, 169.12, 169.15, 205.6, 206.0 ppm; HRMS (ESI) calcd for $C_{13}H_{16}O_4F_3S$ ($[M + H]^+$) 325.0716, found 325.0703.

DBU Catalyzed Vinylogous Aldol Reactions of Cyclic Enones 14 with 10



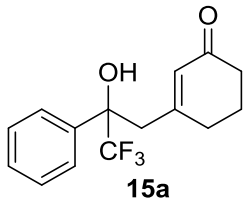
10 **14** **15** n = 1, 2

14a, n=1;**14b**, n=2

General procedure for the DBU-catalyzed vinylogous aldol reactions of cyclic enones 14 with 10 to give 15 (Scheme 2.11). To a mixture of cyclic enones **14** (2.5 mmol) and **10** (0.5 mmol) was added DBU (0.05 mmol), and the mixture was stirred at rt (25 °C) until **10** was consumed (monitored by TLC). The reaction mixture was diluted with hexane-

EtOAc and purified by silica gel flash column chromatography (hexane/EtOAc = 8:1 to 4:1) to give **15**.

3-(3,3,3-Trifluoro-2-hydroxy-2-phenylpropyl)cyclohex-2-enone (15a)

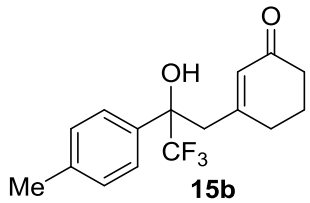


15a

Synthesized by the general procedure, 1.0 h, 115.1 mg (81%).

Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72-1.79 (m, 2H, $CH_2C\underline{H}_2CH_2$), 1.88 (dt, *J* = 18.3 Hz, 5.7 Hz, 1H, C=CC$\underline{H}$HCH$_2$), 2.12 (dt, *J* = 18.3 Hz, 5.7 Hz, 1H, C=CC$\underline{H}$HCH$_2$), 2.19-2.23 (m, 2H, C(=O)C$\underline{H}_2$CH$_2$), 2.99 (d, *J* = 14.1 Hz, 1H, C(OH)C$\underline{H}$H), 3.05 (d, *J* = 14.1 Hz, 1H, C(OH)C$\underline{H}$H), 3.42 (s, 1H, O$\underline{H}$), 5.82 (s, 1H, C=C$\underline{H}$C=O), 7.36-7.42 (m, 3H, Ar$\underline{H}$), 7.54-7.56 (m, 2H, Ar$\underline{H}$), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 30.9, 37.0, 43.8, 76.8 (q, $J_{C,F}$ = 28 Hz), 125.3 (q, $J_{C,F}$ = 285 Hz), 126.1, 128.5, 128.9, 129.6, 130.7, 136.0, 159.0, 199.6 ppm; HRMS (ESI) calcd for $C_{15}H_{16}O_2F_3$ ([M + H]$^+$) 285.1097, found 285.1110.

3-(3,3,3-Trifluoro-2-hydroxy-2-(p-tolyl)propyl)cyclohex-2-enone (15b)



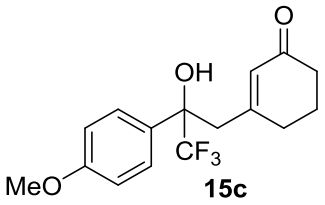
15b

Synthesized by the general procedure, 1.0 h, 119.3 mg (80%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.70-1.77 (m, 2H, $CH_2C\underline{H}_2CH_2$), 1.99-2.06 (m, 1H, C=CC$\underline{H}$HCH$_2$), 2.14-2.18 (m, 2H, C(=O)C$\underline{H}_2$CH$_2$), 2.21-2.29 (m, 1H, C=CC$\underline{H}$HCH$_2$), 2.33 (s, 3H, ArC$\underline{H}_3$), 2.98 (d, *J* = 14.5 Hz, 1H, C(OH)C$\underline{H}$H), 3.13 (d, *J* = 14.5 Hz, 1H, C(OH)C$\underline{H}$H), 5.78 (s, 1H, C=C$\underline{H}$C=O), 7.18 (d, *J* = 8.0 Hz, 2H, Ar$\underline{H}$) 7.46 (d, *J* = 8.0 Hz, 2H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 21.0, 23.6, 32.0, 37.8, 43.9, 77.7 (q, $J_{C,F}$ = 28

Hz), 127.1 (q, $J_{C,F}$ = 285 Hz), 127.8, 129.7, 130.7, 135.1, 139.4, 163.4, 202.3 ppm; HRMS (ESI) calcd for $C_{16}H_{18}O_2F_3$ ($[M + H]^+$) 299.1253, found 299.1233.

3-(3,3,3-Trifluoro-2-hydroxy-2-(4-methoxyphenyl)propyl)cyclohex-2-enone (15c)

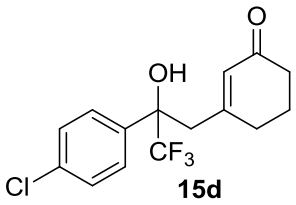


15c

Synthesized by the general procedure, 1.0 h, 131.8 mg (84%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.70-1.77 (m, 2H, $CH_2C\underline{H}_2CH_2$), 1.99-2.06 (m, 1H, C=CC$\underline{H}$HCH$_2$), 2.14-2.18 (m, 2H, C(=O)C$\underline{H}_2$CH$_2$), 2.21-2.28 (m, 1H, C=CC$\underline{H}$HCH$_2$), 2.97 (d, *J* = 14.4 Hz, 1H, C(OH)C$\underline{H}$H), 3.12 (d, *J* = 14.4 Hz, 1H, C(OH)C$\underline{H}$H), 3.78 (s, 3H, OC$\underline{H}_3$), 5.79 (s, 1H, C=C$\underline{H}$C=O), 6.91 (d, *J* = 8.7 Hz, 2H, Ar$\underline{H}$), 7.50 (d, *J* = 8.7 Hz, 2H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 23.6, 32.0, 37.8, 43.9, 55.7, 77.5 (q, $J_{C,F}$ = 28 Hz), 114.4, 127.1 (q, $J_{C,F}$ = 285 Hz), 129.1, 129.9, 130.7, 161.1, 163.4, 202.2 ppm; HRMS (ESI) calcd for $C_{16}H_{18}O_3F_3$ ($[M + H]^+$) 315.1203, found 315.1191.

3-(2-(4-Chlorophenyl)-3,3,3-trifluoro-2-hydroxypropyl)cyclohex-2-enone (15d)



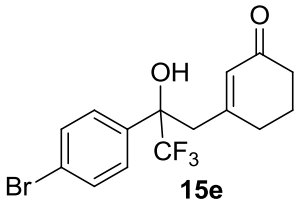
15d

Synthesized by the general procedure, 1.0 h, 105.2 mg (66%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.73-1.80 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.01-2.09 (m, 1H, C=CC$\underline{H}$HCH$_2$), 2.15-2.19 (m, 2H, C(=O)C$\underline{H}_2$CH$_2$), 2.23-2.30 (m, 1H, C=CC$\underline{H}$HCH$_2$), 3.01 (d, *J* = 14.1 Hz, 1H, C(OH)C$\underline{H}$H), 3.16 (d, *J* = 14.1 Hz, 1H, C(OH)C$\underline{H}$H), 5.78 (s, 1H, C=C$\underline{H}$C=O), 7.38 (d, *J* = 8.5 Hz, 2H, Ar$\underline{H}$), 7.59 (d, *J* = 8.5 Hz, 2H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 23.6, 32.0, 37.8, 43.6, 77.6 (q, $J_{C,F}$ = 28 Hz), 126.9 (q, $J_{C,F}$ = 285

Hz), 129.2, 129.7, 130.8, 135.5, 137.0, 162.8, 202.1 ppm; HRMS (ESI) calcd for $C_{15}H_{15}O_2F_3Cl$ ($[M + H]^+$) 319.0707, found 319.0693.

3-(2-(4-Bromophenyl)-3,3,3-trifluoro-2-hydroxypropyl)cyclohex-2-enone (15e)

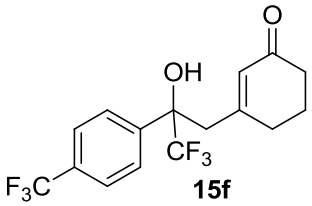


15e

Synthesized by the general procedure, 1.0 h, 127.1 mg (70%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.72-1.79 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.01-2.09 (m, 1H, $C{=}CC\underline{H}HCH_2$), 2.15-2.19 (m, 2H, $C(=O)C\underline{H}_2CH_2$), 2.22-2.30 (m, 1H, $C{=}CC\underline{H}HCH_2$), 3.00 (d, *J* = 14.6 Hz, 1H, $C(OH)C\underline{H}H$), 3.15 (d, *J* = 14.6 Hz, 1H, $C(OH)C\underline{H}H$), 5.78 (s, 1H, $C{=}C\underline{H}C{=}O$), 7.53 (s, 4H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 23.6, 32.0, 37.8, 43.6, 77.6 (q, $J_{C,F}$ = 278 Hz), 123.6, 126.8 (q, $J_{C,F}$ = 285 Hz), 129.9, 130.8, 132.3, 137.5, 162.7, 202.1 ppm; HRMS (ESI) calcd. for $C_{15}H_{15}O_2F_3Br$ ($[M + H]^+$) 363.0202; found 363.0174.

3-(3,3,3-Trifluoro-2-hydroxy-2-(4-(trifluoromethyl)phenyl)propyl)cyclohex-2-enone (15f)



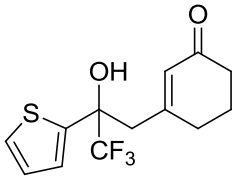
15f

Synthesized by the general procedure, 1.0 h, 107.4 mg (61%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.72-1.79 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.02-2.10 (m, 1H, $C{=}CC\underline{H}HCH_2$), 2.13-2.18 (m, 2H, $C(=O)C\underline{H}_2CH_2$), 2.24-2.31 (m, 1H, $C{=}CC\underline{H}HCH_2$), 3.06 (d, *J* = 14.8 Hz, 1H, $C(OH)C\underline{H}H$), 3.16 (d, *J* = 14.8 Hz, 1H, $C(OH)C\underline{H}H$), 5.79 (s, 1H, $C{=}C\underline{H}C{=}O$), 7.69 (d, *J* = 8.4 Hz, 2H, Ar$\underline{H}$), 7.82 (d, *J* = 8.4 Hz, 2H, Ar$\underline{H}$) ppm; ^{13}C NMR

(100 MHz, CD_3OD): δ = 23.6, 32.0, 37.8, 43.6, 77.6 (q, $J_{C,F}$ = 28 Hz), 125.5 (q, $J_{C,F}$ = 270 Hz), 126.0 (q, $J_{C,F}$ = 4 Hz), 126.8 (q, $J_{C,F}$ = 285 Hz), 128.8, 130.8, 131.6 (q, $J_{C,F}$ = 32 Hz 142.6, 162.7, 202.1 ppm; HRMS (ESI) calcd for $C_{16}H_{15}O_2F_6$ ($[M + H]^+$) 353.0971, found 353.0940.

3-(3,3,3-Trifluoro-2-hydroxy-2-(thiophen-2-yl)propyl)cyclohex-2-enone (15g)

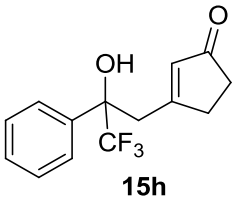


15g

Synthesized by the general procedure, 1.0 h, 110.3 mg (76%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.77-1.83 (m, 2H, $CH_2C\underline{H}_2CH_2$), 2.01-2.09 (m, 1H, C=CC$\underline{H}$HCH$_2$), 2.19-2.22 (m, 2H, C(=O)C$\underline{H}_2$CH$_2$), 2.33-2.40 (m, 1H, C=CC$\underline{H}$HCH$_2$), 3.00 (s, 2H, C(OH)C$\underline{H}_2$), 5.81 (s, 1H, C=C$\underline{H}$C=O), 7.02 (dd, *J* = 3.6 Hz, 5.1 Hz, 1H, Ar$\underline{H}$), 7.14 (d, *J* = 3.6 Hz, 1H, Ar$\underline{H}$), 7.39 (dd, *J* = 1.2 Hz, 5.1 Hz, 1H, Ar$\underline{H}$) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 23.7, 32.0, 37.8, 45.3, 77.7 (q, $J_{C,F}$ = 29 Hz), 126.5 (q, $J_{C,F}$ = 284 Hz), 126.9 (q, $J_{C,F}$ = 1 Hz), 127.0, 127.9, 130.8, 142.3, 162.7, 202.2 ppm; HRMS (ESI) calcd for $C_{13}H_{14}O_2F_3S$ ($[M + H]^+$) 291.0661, found 291.0650.

3-(3,3,3-Trifluoro-2-hydroxy-2-phenylpropyl)cyclopent-2-enone (15h)



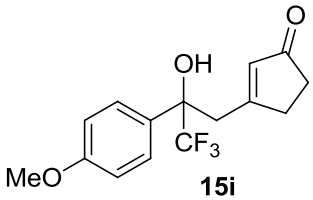
15h

Synthesized by the general procedure, 30 min, 109.4 mg (81%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.18 (t, *J* = 4.6 Hz, 2H, C$\underline{H}_2$C=O), 2.34-2.42 (m, 1H, C$\underline{H}$HCH$_2$C=O), 2.49-2.57 (m, 1H, C$\underline{H}$HCH$_2$C=O), 3.21 (d, *J* = 15.7 Hz, 1H, C(OH)C$\underline{H}$H), 3.51 (d, *J* = 15.7 Hz, 1H, C(OH)C$\underline{H}$H), 5.81 (m, 1H, C=C$\underline{H}$C=O), 7.31-7.40 (m,

3H, ArH), 7.62 (d, J = 7.5 Hz, 2H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 34.0, 35.9, 39.2, 77.3 (q, $J_{C,F}$ = 28 Hz), 127.0 (q, $J_{C,F}$ = 285 Hz), 127.9, 129.2, 129.5, 133.9, 138.0, 179.3, 212.9 ppm; HRMS (ESI) calcd for $C_{14}H_{14}O_2F_3$ ($[M + H]^+$) 271.0940, found 271.0921.

3-(3,3,3-Trifluoro-2-hydroxy-2-(4-methoxyphenyl)propyl)cyclopent-2-enone (15i)

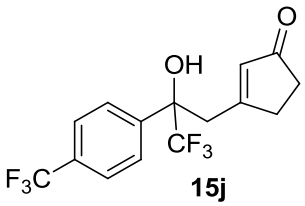


15i

Synthesized by the general procedure, 30 min, 123.2 mg (82%).

Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.19 (t, J = 4.4 Hz, 2H, CH$_2$C=O), 2.36-2.42 (m, 1H, CHHCH$_2$C=O), 2.49-2.57 (m, 1H, CHHCH$_2$C=O), 3.18 (d, J = 15.6 Hz, 1H, C(OH)CHH), 3.46 (d, J = 15.6 Hz, 1H, C(OH)CHH), 3.77 (s, 3H, OCH$_3$), 5.82 (s, 1H, C=CHC=O), 6.91(d, J = 8.8 Hz, 2H, ArH), 7.52 (d, J = 8.8 Hz, 2H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 34.0, 35.9, 39.1, 55.7, 77.1 (q, $J_{C,F}$ = 28 Hz), 114.5, 127.0 (q, $J_{C,F}$ = 285 Hz), 129.2, 129.7, 133.9, 161.2, 179.6, 213.0 ppm; HRMS (ESI) calcd for $C_{15}H_{16}O_3F_3$ ($[M + H]^+$) 301.1046, found 301.1030.

3-(3,3,3-trifluoro-2-hydroxy-2-(4-(trifluoromethyl)phenyl)propyl)cyclopent-2-enone (15j)



15j

Synthesized by the general procedure, 30 min, 89.5 mg (53%).

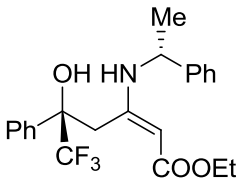
Colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.21 (t, J = 4.7 Hz, 2H, CH$_2$C=O), 2.40-2.46 (m, 1H, CHHCH$_2$C=O), 2.53-2.60 (m, 1H, CHHCH$_2$C=O), 3.25 (d, J = 16.0 Hz, 1H, C(OH)CHH), 3.58 (d, J = 16.0 Hz, 1H, C(OH)CHH), 5.82 (s, 1H, C=CHC=O), 7.70 (d, J =

8.4 Hz, 2H, ArH), 7.85 (d, J = 8.4 Hz, 2H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ =34.0, 35.9, 38.9, 77.3 (q, $J_{C,F}$ = 28 Hz), 125.5 (q, $J_{C,F}$ = 270 Hz) 126.1 (q, $J_{C,F}$ = 4 Hz), 126.7 (q, $J_{C,F}$ = 285 Hz), 128.9, 131.8 (q, J = 32 Hz), 134.0, 142.5, 178.6, 212.7 ppm; HRMS (ESI) calcd for $C_{15}H_{13}O_2F_6$ ($[M + H]^+$) 339.0814, found 339.0797.

Resolution of the Aldol products 13

Synthesis of enamine 16a and the resolution to 16a-1 and 16a-2 (Scheme 2.12). To a solution of **13a** (243.4 mg, 0.8 mmol) in toluene (1.5 mL), (*R*)-1-phenylethylamine (112 μL, 0.88 mmol) was added, and the mixture was stirred at rt (25 °C) for 12 h. The mixture was purified by silica gel flash column chromatography (hexane/EtOAc = 30:1 to 15:1) to give **16a-1** (upper spot on TLC) (108.5 mg, 32%, dr 20:1), mixtures of **16a-1** and **16a-2** (81.7 mg, 24%, dr 1:1), and **16a-2** (lower spot on TLC) (105.5 mg, 31%, dr 20:1); the dr values of **16a-1** and **16a-2** were determined by ^{1}H NMR analyses. Compound **16a-1** (dr 20:1) was crystallized from hexane-CH_2Cl_2 to give the essentially pure form (50.5 mg, dr >99:1). Compound **16a-2** (dr 20:1) was also crystallized from hexane-CH_2Cl_2 to increase the purity (60.0 mg, dr 99:1). The absolute stereochemistry of **16a-1** was determined to be (*R*,*R*) by the X-ray structural analysis. Note that the fractions containing **16a-1** and **16a-2** were able to be purified further to give pure **16a-1** and also pure **16a-2**.

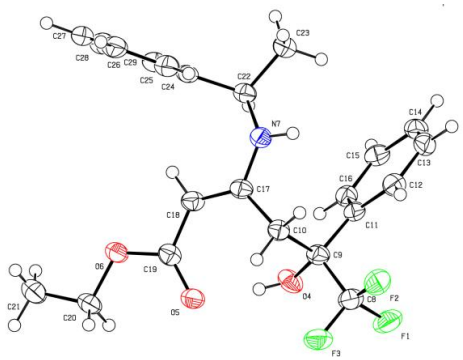
Compound 16a-1



16a-1

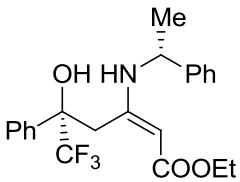
Colorless crystals, mp 126 °C, R_f = 0.38 (hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (d, J = 6.4 Hz, 3H, NCH(CH$_3$)Ph, 1.13 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.58

(d, *J* = 13.6 Hz, 1H, C(OH)C<u>H</u>H), 3.52 (d, *J* = 5.6 Hz, 1H, C=C<u>H</u>COOEt), 3.87-4.10 (m, 3H, NC<u>H</u>(CH_3)Ph, OC<u>H</u>$_2$$CH_3$), 4.16 (d, *J* = 13.6 Hz, 1H, C(OH)C<u>H</u>H), 4.49 (s, 1H, O<u>H</u>), 6.89-6.91 (m, 3H, Ar<u>H</u>, N<u>H</u>), 7.12-7.21 (m, 3H, Ar<u>H</u>), 7.32-7.41 (m, 3H, Ar<u>H</u>), 7.65-7.67 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 22.2, 38.7, 53.1, 59.9, 76.8 (q, $J_{C,F}$ = 25 Hz), 87.6, 125.4, 125.8 (q, $J_{C,F}$ = 285 Hz), 126.1, 127.5, 128.6, 128.77, 128.80, 137.8, 142.4, 155.2, 172.2 ppm; HRMS (ESI) calcd for $C_{22}H_{25}NO_3F_3$ ($[M + H]^+$) 408.1781, found 408.1762.



X-ray crystal structure of **16a-1** (CCDC 1401982). The analysis of the X-ray crystal structure of **16a-1** was performed using a custom anaysis service.

Compound 16a-2



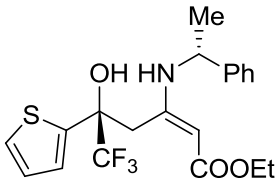
16a-2

Colorless solid, R_f = 0.28 (hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20-1.24 (m, 6H, NCH($C\underline{H}_3$)Ph, OCH$_2$$C\underline{H}_3$), 2.80 (d, *J* = 13.6 Hz, 1H, C(OH)C<u>H</u>H), 3.85 (d, *J* = 5.6 Hz, 1H, C=C<u>H</u>COOEt), 4.04-4.23 (m, 4H, NC<u>H</u>(CH_3)Ph, OC<u>H</u>$_2$$CH_3$, C(OH)C<u>H</u>H), 4.55 (s, 1H, O<u>H</u>), 6.49-6.51 (m, 2H, Ar<u>H</u>), 6.94 (s, 1H, N<u>H</u>), 7.15-7.17 (m, 3H, Ar<u>H</u>), 7.36-7.46 (m, 4H, Ar<u>H</u>), 7.70-7.72 (m, 2H, Ar<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 23.4, 38.5, 52.9, 60.0, 76.8 (q, $J_{C,F}$ = 28 Hz), 87.8, 125.4, 125.7 (q, $J_{C,F}$ = 286 Hz) 126.4, 127.2, 128.5,

128.5, 128.6, 128.7, 137.4, 141.9, 154.5, 172.1 ppm; HRMS (ESI) calcd for $C_{22}H_{25}NO_3F_3$ ([M + H]$^+$) 408.1781, found 408.1762.

Synthesis of enamine 16ac and the resolution to 16ac-1 and 16ac-2 (Scheme 2.11). To a solution of **13ac** (248.2 mg, 0.8 mmol) in toluene (1.5 mL), (*R*)-1-phenylethylamine (112 μL, 0.88 mmol) was added, and the mixture was stirred at rt (25 °C) for 12 h. The mixture was purified by silica gel flash column chromatography (hexane/EtOAc = 30:1 to 15:1) to give **16ac-1** (upper spot on TLC) (169.0 mg, 41%), mixtures of **16ac-1** and **16ac-2** (62.9 mg, 15%), and **16ac-2** (lower spot on TLC) (156.4 mg, 38%). Compound **16ac-1** was crystallized from hexane-CH_2Cl_2 to give the essentially pure form (72.4 mg, dr >99:1). Compound **16ac-2** was also crystallized from hexane-CH_2Cl_2 to give the pure form (65.6 mg, dr >99:1).

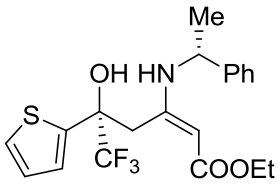
Compound 16ac-1



16ac-1

Colorless crystals, mp 133 °C, R_f = 0.33 (hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.8 Hz, 3H, NCH(C<u>H</u>$_3$)Ph), 1.13 (t, *J* = 7.2 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 2.45 (d, *J* = 13.2 Hz, 1H, C(OH)C<u>H</u>H), 3.75 (d, *J* = 5.2 Hz, 1H, C=C<u>H</u>COOEt), 3.93-4.09 (m, 3H, NC<u>H</u>(CH$_3$)Ph, OC<u>H</u>$_2$CH$_3$), 4.16 (d, *J* = 13.2 Hz, 1H, C(OH)C<u>H</u>H), 4.53 (s, 1H, O<u>H</u>), 6.96-7.05 (m, 3H, Ar<u>H</u>), 7.13-7.18 (m, 2H, Ar<u>H</u>), 7.23-7.26 (m, 2H, Ar<u>H</u>), 7.30-7.31 (m, 1H, Ar<u>H</u>), 7.38 (s, 1H, N<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.6, 40.1, 53.4, 60.1, 76.8 (q, $J_{C,F}$ = 30 Hz), 87.8, 123.8, 125.1 (q, $J_{C,F}$ = 285Hz), 125.5, 126.1, 127.5, 127.6, 128.9, 142.4, 143.2, 155.0, 172.4 ppm; HRMS (ESI) calcd for $C_{20}H_{23}NO_3F_3S$ ([M + H]$^+$) 414.1345, found 414.1327.

Compound 16ac-2



16ac-2

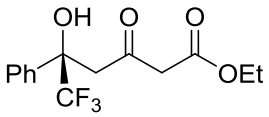
Colorless crystals, R_f = 0.24 (hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.31 (d, *J* = 6.8 Hz, 3H, $NCH(C\underline{H}_3)Ph$), 2.68 (d, *J* = 13.6 Hz, 1H, $C(OH)C\underline{H}H$), 4.03-4.27 (m, 5H, $NC\underline{H}(CH_3)Ph$, $OC\underline{H}_2CH_3$, $C(OH)C\underline{H}H$, $C{=}C\underline{H}COOEt$), 4.64 (s, 1H, O<u>H</u>), 6.69-6.72 (m, 2H, Ar<u>H</u>), 7.00-7.02 (m, 1H, Ar<u>H</u>), 7.17-7.26 (m, 4H, Ar<u>H</u>), 7.29-7.31 (m, 1H, Ar<u>H</u>), 7.41 (s, 1H, N<u>H</u>) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 23.1, 40.0, 53.2, 60.1, 76.7 (q, $J_{C,F}$ = 29 Hz), 87.6, 124.5, 125.0 (q, $J_{C,F}$ = 285 Hz), 125.6, 126.2, 127.3, 128.6, 141.9, 142.3, 154.2, 172.3 ppm; HRMS (ESI) calcd for $C_{20}H_{23}NO_3F_3S$ ($[M + H]^+$) 414.1345, found 414.1327.

Hydrolysis of enamine 16a-1 to give (*R*)-13a (Scheme 2.12). A mixture of **16a-1** (0.12 mmol, 50.0 mg, dr >99:1) and 10% HCl/(H_2O/EtOH = 1:1) (1.0 mL) was stirred at rt (25 °C) for 4 h (note: when the mixture was stirred for 2 days, the decarboxylation product **17** was obtained, see below). The reaction mixture was extracted with CH_2Cl_2 (3 mL × 3). Organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (hexane/EtOAc = 5:1) to give (*R*)-**13a (**31.5 mg, 89%, >99%). The ee value was determined by HPLC analysis.

Resolution of (±)-13a (10 mmol-scale) to give (*R*)-13a. To a solution of (±)-**13a** (3.05g, 10.0 mmol) in toluene (15.0 mL), (*R*)-1-phenylethylamine (1.53 mL, 12.0 mmol) was added, and the mixture was stirred at rt (25 °C) for 16 h. The reaction mixture was directly purified by silica gel flash column chromatography (hexane/EtOAc = 40:1 to 20:1) to give **16a-1** (1.40 g, 33%, the theoretical maximum yield 50%). This was crystallized from hexane-

CH_2Cl_2 to give **16a-1** as the pure diastereomer (dr > 99:1 determined by ^1H NMR). To the **16a-1** crystals, 10% HCl/(H_2O/EtOH = 1:1) (5.0 mL) was added at rt (25 °C), and the mixture was stirred at the same temperature for 4 h. The mixture was extracted with CH_2Cl_2 (15 mL × 3). Organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (hexane/EtOAc = 5:1) to give (*R*)-**13a** (0.43 g, 14% from (±)-**13a,** 99% ee). Note that the fractions containing **16a-1** and **16a-2** were able to be purified further to give pure **16a-1** and also pure **16a-2**.

Compound (*R*)-13a

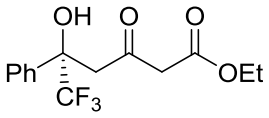


(*R*)-**13a**

Colorless oil. $[\alpha]_D^{26}$ -34.2 (c = 0.67, CH_2Cl_2), >99% ee. HPLC (Daicel Chiralpak IA, hexane/2-PrOH = 98:2, 0.6 mL/min, λ = 254 nm): t_R (major, (*R*)-**13a**) = 27.9 min, t_R (miner, (*S*)-**13a**) = 31.8 min.

The absolute stereochemistry of **13a** obtained from enamine **16a-1** (upper spot product on TLC) was determined to be *R* by converting to known ketone **17** and also by X-ray crystal structure analysis of enamine **16a-1** (see above).

Compound (*S*)-13a

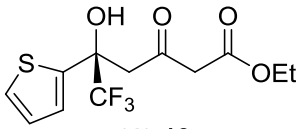


(*S*)-**13a**

Compound (*S*)-**13a** (39.0 mg, 87%) was obtained from the hydrolysis of **16a-2** (60.0 mg, 0.15 mmol) by the same method used for the hydrolysis of **16a-1**.

Colorless oil. $[\alpha]_D^{26}$ +30.5 (c = 0.37, CH_2Cl_2), 98 % ee. HPLC (Daicel Chiralpak IA, hexane/2-PrOH = 98:2, 0.6 mL/min, λ = 254 nm): t_R (miner, (*R*)-**13a**) = 27.8 min, t_R (major, (*S*)-**13a**) = 31.6 min.

Compound (*S*)-13ac

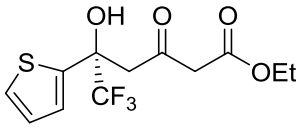


(*S*)-**13ac**

Compound (*S*)-**13ac** (40.6 mg, 78%) was obtained from the hydrolysis of **16ac-1** (69.5 mg, 0.17 mmol). Absolute stereochemistry was determined by analogy.

Colorless oil. $[\alpha]_D^{25}$ –40.9 (c = 0.53, CH_2Cl_2), >99% ee. HPLC (Daicel Chiralpak AS, hexane/2-PrOH = 98:2, 0.6 mL/min, λ = 254 nm): t_R (major, (*S*)-**13ac**) = 39.7 min, t_R (miner, (*R*)-**13ac**) = 53.0 min.

Compound (*R*)-13ac



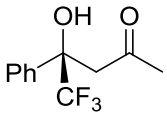
(*R*)-**13ac**

Compound (*R*)-**13ac** (41.8 mg, 91%) was obtained from the hydrolysis of **16ac-2** (61.0 mg, 0.15 mmol).

Colorless oil. $[\alpha]_D^{25}$ +40.5 (c = 0.74, CH_2Cl_2), >99% ee. HPLC (Daicel Chiralpak AS, hexane/2-PrOH = 98:2, 0.6 mL/min, λ = 254 nm): t_R (miner, (*S*)-**13ac**) =40.8 min, t_R (major, (*R*)-**13ac**) = 50.5 min.

Formation of (*R*)-17 (Scheme 2.11). A mixture of (*R*)-**13a** (30.0 mg, 0.10 mmol, 99% ee) and 10% HCl/(H_2O/EtOH = 1:1) (1.0 mL) was stirred at rt (25 °C) for 2 days. The mixture was extracted with CH_2Cl_2 (3 mL × 3). Organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated and purified by silica gel flash column chromatography (hexane/EtOAc = 5:1) to give (*R*)-**17** (17 mg, 74%, 99% ee).

(*R*)-5,5,5-Trifluoro-4-hydroxy-4-phenylpentan-2-one ((*R*)-17)[89]



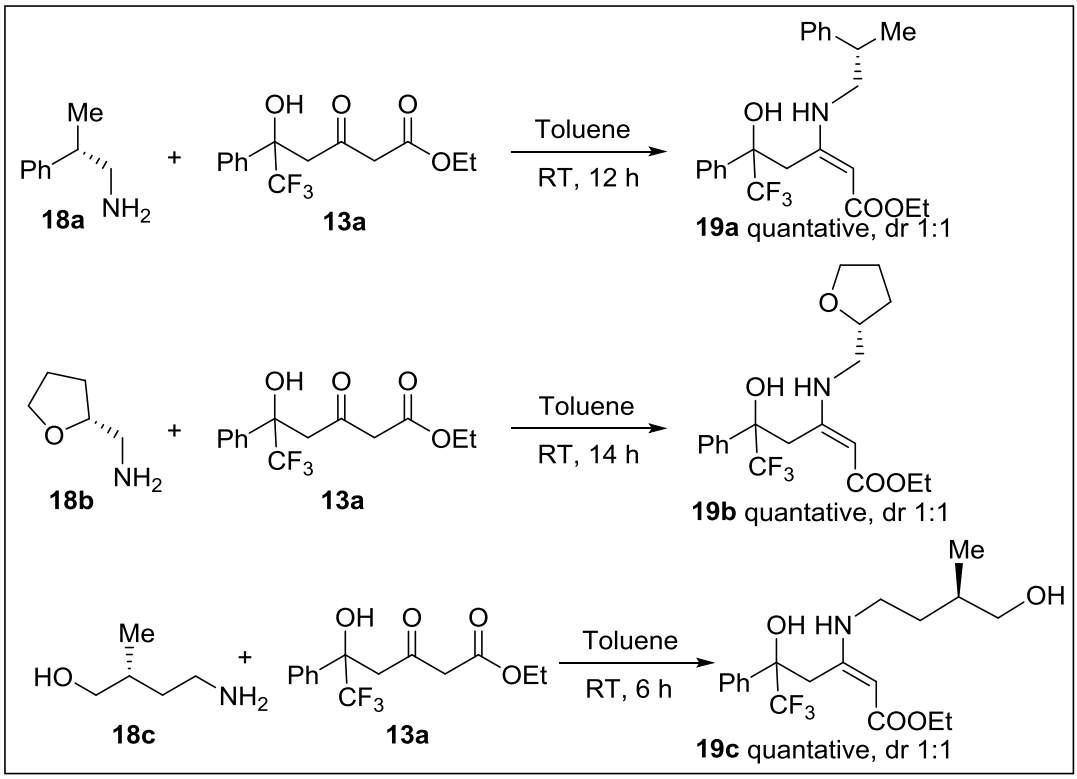
(*R*)-**17**

$[\alpha]_D^{25}$ –20.8 (c = 0.40, $CHCl_3$, 99% ee). Lit. $[\alpha]_D^{20}$ +24.1 (c = 1.0, $CHCl_3$, 92% ee) for (*S*)-**17**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H, C$\underline{H}_3$), 3.20 (d, *J* = 17.2 Hz, 1H, C(OH)C$\underline{H}$H), 3.37 (d, *J* = 17.2 Hz, 1H, C(OH)C$\underline{H}$H), 5.43 (s, 1H, O$\underline{H}$), 7.34-7.42 (m, 3H, Ar$\underline{H}$), 7.55-7.57 (m, 2H, Ar$\underline{H}$) ppm. HPLC (Daicel Chiralpak IB, hexane/2-PrOH = 95:5, 0.6 mL/min, λ = 220 nm): t_R (major, (*R*)-**17**) =11.4 min, t_R (miner, (*S*)-**17**) =13.5 min.

Formation of 19 from 13a and 18

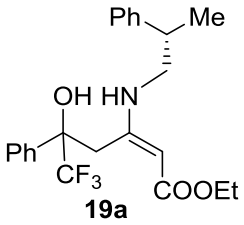
Synthesis of 19. To a solution of (±)-**13a** (30.4 mg, 0.1 mmol) in toluene (150 μL), amine **18** (0.11 mmol) was added, and the mixture was stirred at rt (25 °C) until **13a** was consumed (monitored by TLC). The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography to give **19** as diastereomer mixtures in quantative yield.

Synthesis of single diasteromer of 19. To a solution of (*R*)-**13a** (15.2 mg, 0.05 mmol) in toluene (100 μL), amine **18** (0.055 mmol) was added, and the mixture was stirred at rt (25 °C) until **13a** was consumed (monitored by TLC). The reaction mixture was diluted with hexane-EtOAc and purified by silica gel flash column chromatography to give **19** as mostly single diastereomer in quantative yield.



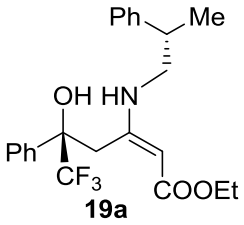
Scheme 6.1. Amines **18** tested to form enamines **19**.

Compound 19a



Compound **19a** (dr 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (d, J = 6.8 Hz, 3H×1/2, PhCHC$\underline{H}_3$), 0.99 (d, J = 6.8 Hz, 3H×1/2, PhCHC$\underline{H}_3$), 1.27 (t, J = 7.2 Hz, 3H×1/2, $OCH_2C\underline{H}_3$), 1.28 (t, J = 7.2 Hz, 3H×1/2, $OCH_2C\underline{H}_3$), 2.16-2.25 (m, 1H×1/2, PhC$\underline{H}CH_3$), 2.50 (d, J = 13.6 Hz, 1H×1/2, C(OH)C$\underline{H}$H), 2.54-2.64 (m, 2H×1/2, C$\underline{H}CH_3$, C(OH)C$\underline{H}$H), 2.73-2.81 (m, 1H, NC$\underline{H}$HCH), 2.87-2.97 (m, 1H, NC$\underline{H}$HCH), 3.22-3.28 (m, 1H×1/2, C=C$\underline{H}$COOEt), 3.45-3.51 (m, 1H×1/2, C=C$\underline{H}$COOEt), 4.04-4.22 (m, 3H, C(OH)C$\underline{H}$H, $OC\underline{H}_2CH_3$), 4.68 (s, 1H×1/2, O$\underline{H}$), 4.73 (s, 1H×1/2, O$\underline{H}$), 6.87 (s, 1H×1/2, N$\underline{H}$), 6.92-6.98 (m, 2H, Ar$\underline{H}$; 1H×1/2, N$\underline{H}$), 7.22-7.36 (m, 3H+3H×1/2, Ar$\underline{H}$), 7.40-7.44 (m, 3H×1/2, Ar$\underline{H}$), 7.57-7.61 (m, 2H, Ar$\underline{H}$). ^{13}C

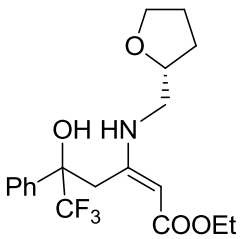
NMR (100 MHz, $CDCl_3$): 14.4, 18.8, 19.9, 38.0, 38.7, 38.8, 38.9, 50.0, 50.2, 59.86, 59.90, 76.8 (q, $J_{C,F}$ = 28 Hz), 86.29, 86.33, 125.7 (q, $J_{C,F}$ = 285 Hz), 125.8, 125.9, 126.76, 126.84, 126.9, 127.1, 128.4, 128.5, 128.56, 128.63, 128.8, 137.5, 137.8, 143.0, 143.1, 156.2, 156.3, 172.1, 172.2. HRMS (ESI) calcd for $C_{23}H_{27}NO_3F_3$ ($[M + H]^+$) 422.1938, found 422.1917.



19a

Single diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (d, J = 6.8 Hz, 3H, PhCHC$\underline{H}_3$), 1.27 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.16-2.25 (m, 1H, PhC$\underline{H}CH_3$), 2.50 (d, J = 13.6 Hz, 1H, C(OH)C$\underline{H}$H), 2.72-2.78 (m, 1H, NC$\underline{H}$HCH), 2.87-2.94 (m, 1H, NC$\underline{H}$HCH), 3.22-3.28 (m, 1H, C=C$\underline{H}$COOEt), 4.08 (d, J = 13.6 Hz, 1H, C(OH)C$\underline{H}$H), 4.10-4.22 (m, 2H, $OC\underline{H}_2CH_3$), 4.68 (s, 1H, O$\underline{H}$), 6.87 (s, 1H, N$\underline{H}$), 6.91-6.95 (m, 2H, Ar$\underline{H}$), 7.21-7.32 (m, 3H, Ar$\underline{H}$), 7.40-7.45 (m, 3H, Ar$\underline{H}$), 7.57-7.62 (m, 2H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 19.9, 38.6, 38.8, 49.9, 59.9, 76.8 (q, $J_{C,F}$ = 29 Hz), 86.2, 125.7 (q, $J_{C,F}$ = 285 Hz), 125.9, 126.8, 127.1, 128.4, 128.6, 128.8, 137.8, 143.0, 156.2, 172.1.

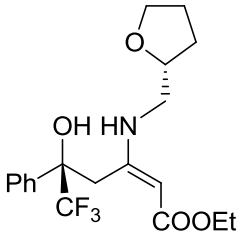
Compound 19b



19b

Compound **19b** (dr 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 1.23-1.32 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H×1/2), 1.27 (t, J = 7.2 Hz, 3H×1/2), 1.57-1.82 (m, 3H), 2.56-2.75 (m, 2H+1H×1/2), 2.93 (dt, J = 12.8 Hz, 4.4 Hz, 1H×1/2), 3.20-3.27 (m, 1H×1/2), 3.47-3.51 (m, 1H×1/2), 3.56-3.62 (m, 1H), 3.67-3.81 (m, 1H+1H×1/2), 3.90-3.95 (m, 1H×1/2), 4.11-4.21 (m, 3H), 4.64 (s, 1H),

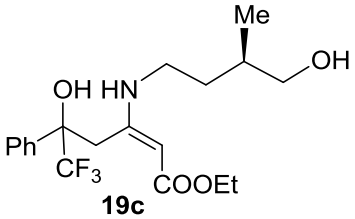
4.68 (s, 1H×1/2), 6.97 (s, 1H×1/2), 6.99 (s, 1H×1/2), 7.32-7.36 (m, 1H), 7.38-7.42 (m, 2H), 7.64-7.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 25.4, 28.3, 28.9, 38.7, 38.9, 46.0, 47.2, 59.8, 59.9, 67.7, 67.8, 75.4, 76.0, 77.0 (q, $J_{C,F}$ = 28 Hz), 86.0, 86.2, 125.8 (q, $J_{C,F}$ = 285 Hz), 125.95, 125.96, 126.00, 126.01, 128.2, 128.3, 128.5, 128.6, 137.6, 137.7, 156.6, 172.20, 172.23. HRMS (ESI) calcd for $C_{19}H_{25}NO_4F_3$ ($[M + H]^+$) 388.1730, found 388.1714.



19b

Single diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (t, J = 7.2 Hz, 3H), 1.72-1.82 (m, 3H), 2.61-2.75 (m, 3H), 3.20-3.27 (m, 1H), 3.56-3.63 (m, 1H), 3.67-3.73 (m, 1H), 3.77-3.82 (m, 1H), 4.09-4.22 (m, 3H), 4.65 (s, 1H), 6.98 (s, 1H), 7.32-7.42 (m, 3H), 7.65 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 25.4, 28.8, 38.9, 47.2, 59.9, 67.8, 76.0, 76.9 (q, $J_{C,F}$ = 28 Hz), 86.0, 125.8 (q, $J_{C,F}$ = 285 Hz), 125.91, 125.92, 128.3, 128.5, 137.7, 156.6, 172.2.

Compound 19c

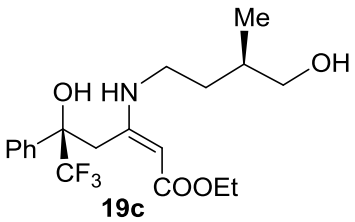


19c

Compound **19c** (dr 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 0.70 (d, J = 6.8 Hz, 3H×1/2), 0.75 (d, J = 6.8 Hz, 3H×1/2), 0.85-1.23 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.56-2.86 (m, 3H), 3.21-3.33 (m, 2H), 3.58-3.65 (m, 1H), 4.09-4.22 (m, 3H), 4.66 (s, 1H×1/2), 4.67 (s, 1H×1/2), 7.03 (s, 1H×1/2), 7.04 (s, 1H×1/2), 7.33-7.42 (m, 3H), 7.65-7.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 16.3, 16.5, 31.3, 31.4, 32.9, 33.1, 38.9, 41.0, 41.3, 59.9, 67.3, 67.5, 76.9 (q, $J_{C,F}$ = 28 Hz), 85.78, 85.83, 125.8 (q, $J_{C,F}$ = 285 Hz), 126.06, 126.08, 128.3, 128.4, 128.5, 137.87,

137.91, 156.4, 156.5, 172.29, 172.31. HRMS (ESI) calcd for $C_{19}H_{27}NO_4F_3$ ($[M + H]^+$) 390.1887, found 390.1869.

Compound **19c** (dr 1:1). ^{1}H NMR (400 MHz, CD_3CN): 0.65 (d, J = 6.4 Hz, 3H×1/2), 0.70 (d, J = 6.4 Hz, 3H×1/2), 0.84-0.96 (m, 1H), 1.03-1.23 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 2.52-2.54 (m, 1H), 2.56-2.83 (m, 2H), 2.97 (d, J = 14.0 Hz, 1H×1/2), 2.99 (d, J = 14.0 Hz, 1H×1/2), 3.13-3.18 (m, 2H), 3.90 (d, J = 14.0 Hz, 1H×1/2), 3.92 (d, J = 14.0 Hz, 1H×1/2), 4.04-4.16 (m, 2H), 4.56 (s, 1H×1/2), 4.57 (s, 1H×1/2), 4.58 (br, 1H), 7.34-7.43 (m, 3H), 7.62-7.64 (m, 2H).



19c

Single diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 0.70 (d, J = 6.4 Hz, 3H), 0.83-1.24 (m, 3H), 1.28 (t, J = 7.4 Hz, 3H), 2.57-2.65 (m, 2H), 2.79-2.87 (m, 1H), 3.21-3.31 (m, 2H), 3.58-3.63 (m, 1H), 4.10-4.22 (m, 3H), 4.67 (s, 1H), 7.03 (s, 1H), 7.33-7.43 (m, 3H), 7.66 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 16.3, 31.2, 32.8, 38.9, 41.0, 59.9, 67.5, 76.9 (q, $J_{C,F}$ = 28 Hz), 85.7, 125.8 (q, $J_{C,F}$ = 285 Hz), 126.1, 128.3, 128.5, 137.9, 156.4, 172.3.

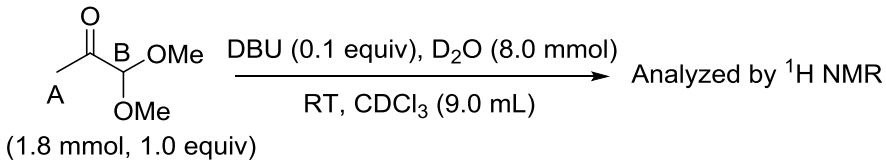
^{1}H NMR analyses during the progress of the reaction to form 19. To a solution of (±)-**13a** (30.4 mg, 0.1 mmol) in $CDCl_3$ (300 μL), enantiomerically pure amine **18** (0.11 mmol) was added, and the mixture was stirred at rt (25 °C). At 5 min, 30 min, 60 min, and 120 min, 360 min an aliquot was taken from the mixture, diluted with $CDCl_3$ or CD_3CN, and analyzed by ^{1}H NMR. Conversion of **18** at different time points was summarized in **Table 6.2**. In all cases, both of the enamine diastereomers were seen clearly within 30 min to 1 h. The dr of the formed enamine **19** was 1:1 at all of the time points analyzed with each of **18a**, **18b** and **18c**.

Table 6.2. Conversion of **18** at different time points during the formation of **19**.

Time (min)	Conversion of **18a**	Conversion of **18b**	Conversion of **18c**
5	--	--	--
30	--	--	46%
60	25%	13 %	67%
120	45%	22%	83%
360	65%	54%	100%

6.3 Experimental Section for Chapter 3

Deuteration of Pyruvic Aldehyde Derivative 1



Deuteration of pyruvic aldehyde derivative **1** in the presence of DBU: To a solution of **1** (212.7 μL, 1.80 mmol) in $CDCl_3$ (8.25 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 5 min before adding premade DBU solution in $CDCl_3$ (0.24 mmol/mL, 0.75 mL, 0.18 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.3. Deuteration of pyruvic aldehyde derivative **1** in the presence of DBU.

Experiment 1:

Time (min)	1	6	10	16	24	30.5
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.89	2.79	2.74	2.63	2.48	2.37

Integration of CH_3 at A/3	0.963	0.930	0.913	0.877	0.826	0.790

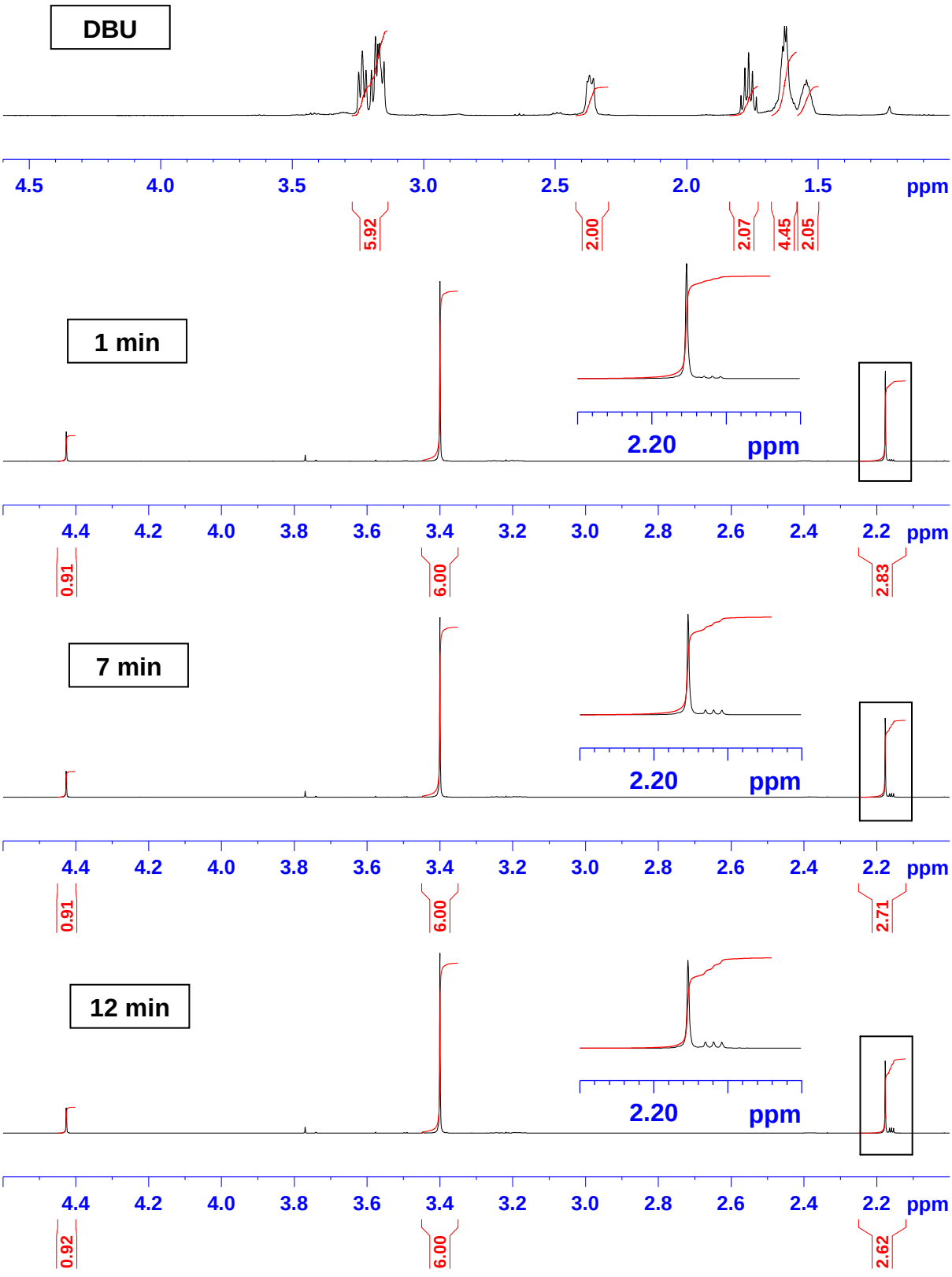
Time (min)	51	67
Integration of the dimethoxy group	6.00	6.00
Integration of CH_3 at A	2.02	1.85
Integration of CH_3 at A/3	0.673	0.617

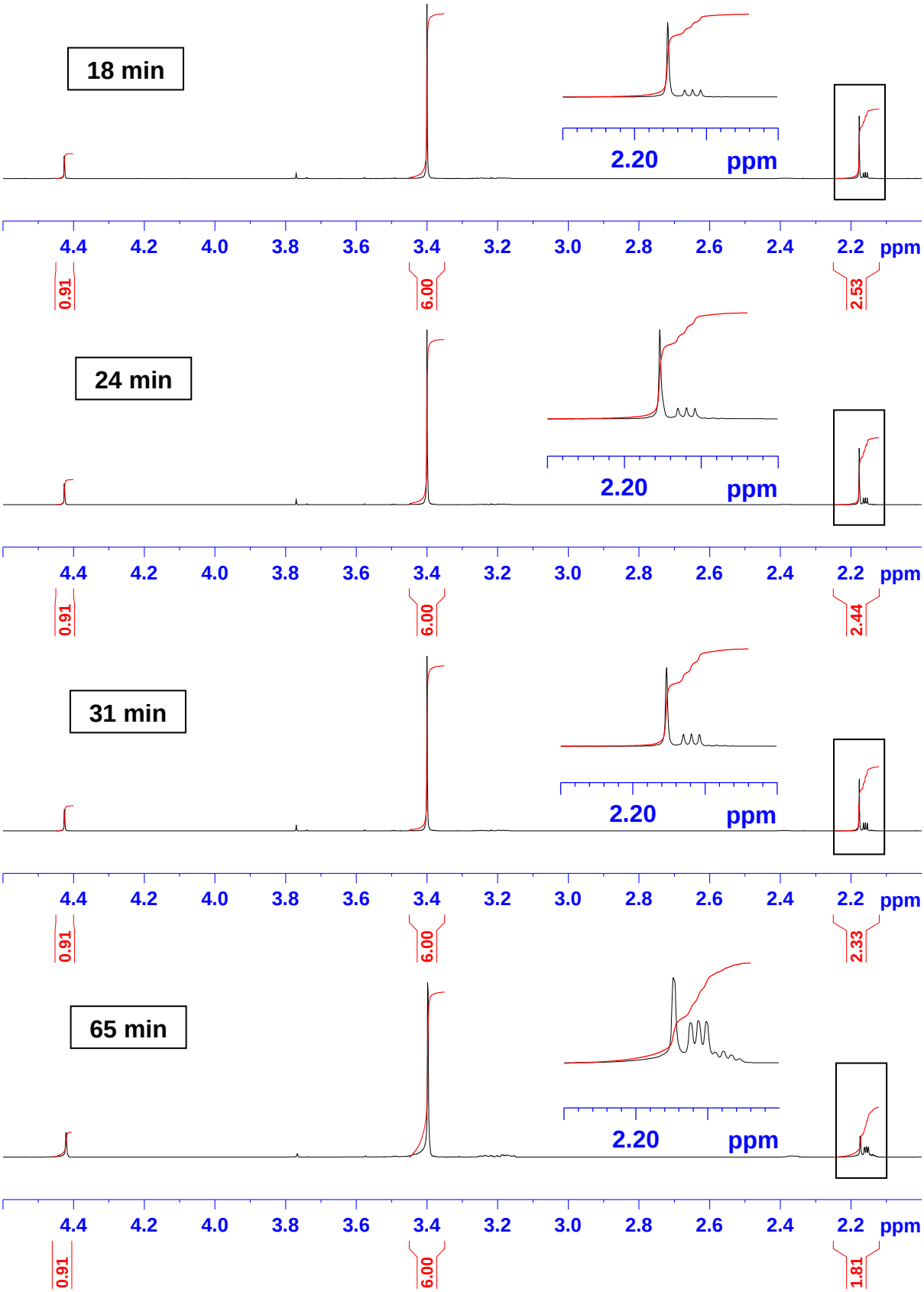
Experiment 2:

Time (min)	1	7	12	18	24	31
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.83	2.71	2.62	2.53	2.44	2.33
Integration of CH_3 at A/3	0.943	0.903	0.873	0.843	0.813	0.777

Time (min)	65	110	240
Integration of the dimethoxy group	6.00	6.00	6.00
Integration of CH_3 at A	1.81	1.39	0.78
Integration of CH_3 at A/3	0.603	0.463	0.26

Figure 6.2. NMR spectra of pyruvic aldehyde derivative **1** in the presence of DBU at different time points.

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4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 ppm
0.91
6.00
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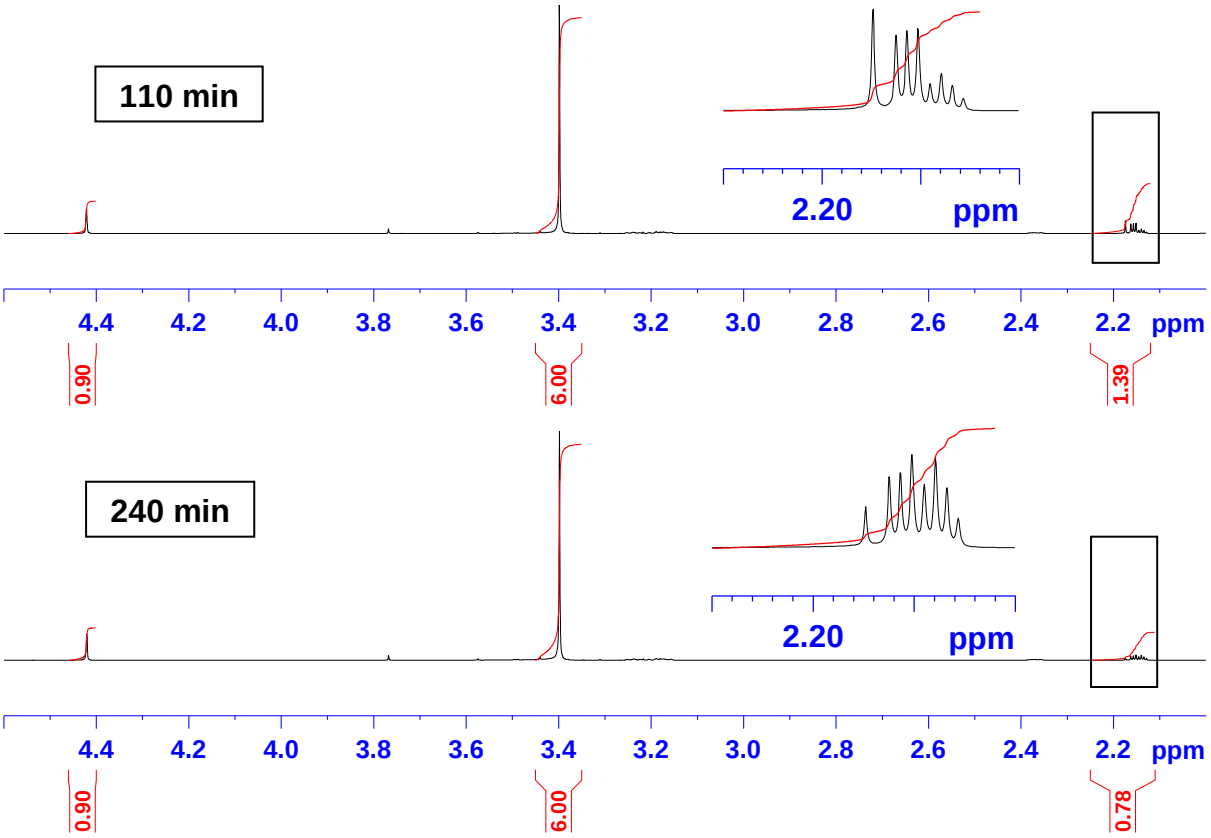
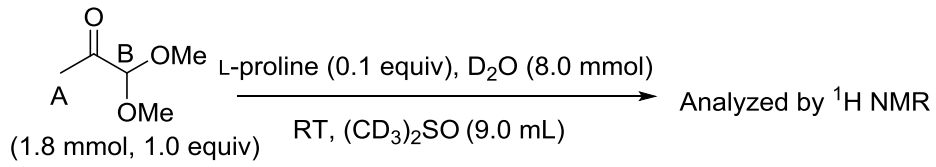
1.81





Deuteration of pyruvic aldehyde derivative **1** in the presence of L-proline: To a solution of L-proline (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding **1** (212.7 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.4. Deuteration of pyruvic aldehyde derivative **1** in the presence of L-proline.

Experiment 1:

Time (min)	3	40	63	96	175

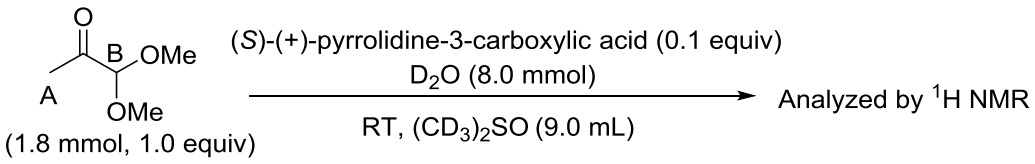
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.8455	2.8303	2.8239	2.8117	2.7847
Integration of CH_3 at A/3	0.9485	0.9434	0.9413	0.9372	0.928

Time (min)	245	760	2184	3635	5084
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.7626	2.6268	2.3715	2.1508	2.0298
Integration of CH_3 at A/3	0.9209	0.8756	0.7905	0.7169	0.6766

Experiment 2:

Time (min)	15	35	61	129	165	689
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.8345	2.8294	2.8173	2.7956	2.7828	2.6365
Integration of CH_3 at A/3	0.9448	0.9431	0.9391	0.9319	0.9276	0.8788

Time (min)	2105	3556	5005	6447	10090
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.352	2.1451	2.0312	1.9453	1.8642
Integration of CH_3 at A/3	0.784	0.7150	0.6771	0.6484	0.6214



Deuteration of pyruvic aldehyde derivative **1** in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid: To a solution of (*S*)-(+)-pyrrolidine-3-carboxylic acid (20.7 mg, 0.18 mmol)

in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding **1** (212.7 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^1H NMR. The experiments were performed twice.

Table 6.5. Deuteration of pyruvic aldehyde derivative **1** in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid.

Experiment 1:

Time (min)	1	6	11	16	21	38
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.8341	2.678	2.5096	2.3477	2.2405	1.8291
Integration of CH_3 at A/3	0.9447	0.8927	0.8365	0.7826	0.7468	0.6097

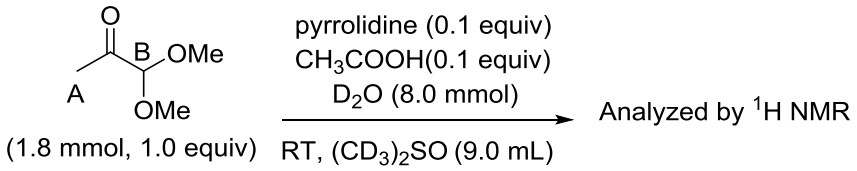
Time (min)	86	327
Integration of the dimethoxy group	6.00	6.00
Integration of CH_3 at A	1.2162	0.8596
Integration of CH_3 at A/3	0.4054	0.2865

Experiment 2:

Time (min)	1	6	10	18	23	35
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.8696	2.6936	2.6084	2.3293	2.1989	1.9396
Integration of CH_3 at A/3	0.9565	0.8979	0.8695	0.7764	0.7330	0.6465

Time (min)	85	308

Integration of the dimethoxy group	6.00	6.00
Integration of CH_3 at A	1.308	0.9089
Integration of CH_3 at A/3	0.436	0.3030



Deuteration of pyruvic aldehyde derivative **1** in the presence of pyrrolidine-CH_3COOH: To a solution of pyrrolidine (14.8 μL, 0.18 mmol) and CH_3COOH (10.3 μL, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding **1** (212.7 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^1H NMR. The experiments were performed twice.

Table 6.6. Deuteration of pyruvic aldehyde derivative **1** in the presence of pyrrolidine-CH_3COOH.

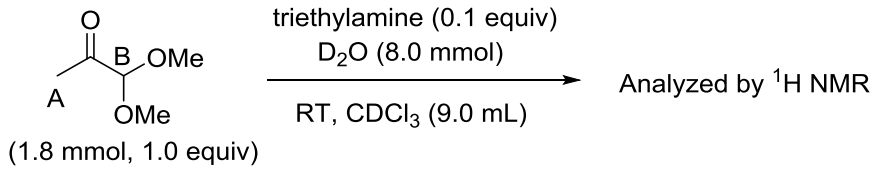
Experiment 1:

Time (min)	5	23	44	60	81	144	333
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Integration of CH_3 at A	2.6170	2.1945	1.7857	1.5735	1.3632	1.0706	0.8969
Integration of CH_3 at A/3	0.8723	0.7315	0.5952	0.5245	0.4544	0.3569	0.2990

Experiment 2:

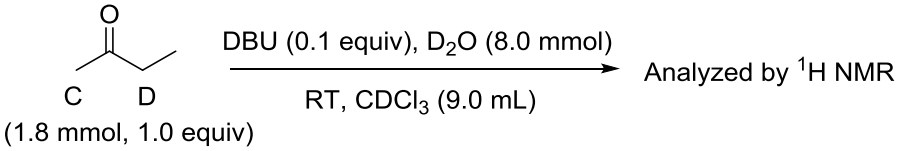
Time (min)	6	23	44	60	81	145	333
Integration of the dimethoxy group	6.00	6.00	6.00	6.00	6.00	6.00	6.00

Integration of CH_3 at A	2.6611	2.1897	1.7655	1.5379	1.3318	1.0111	0.8532
Integration of CH_3 at A/3	0.8870	0.7299	0.5885	0.5126	0.4439	0.3370	0.2844



Deuteration of pyruvic aldehyde derivative **1** in the presence of triethylamine: To a solution of **1** (212.7 μL, 1.80 mmol) in $CDCl_3$ (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 5 min before adding triethyl amine (25.1 μL, 0.18 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^1H NMR.

Deuteration of Methyl Ethyl Ketone



Deuteration of methyl ethyl ketone in the presence of DBU: To a solution of methyl ethyl ketone (161.2 μL, 1.80 mmol) in $CDCl_3$ (8.25 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 5 min before adding premade DBU solution in $CDCl_3$ (0.24 mmol/mL, 0.75 mL, 0.18 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^1H NMR. The experiments were performed twice.

Table 6.7. Deuteration of methyl ethyl ketone in the presence of DBU.

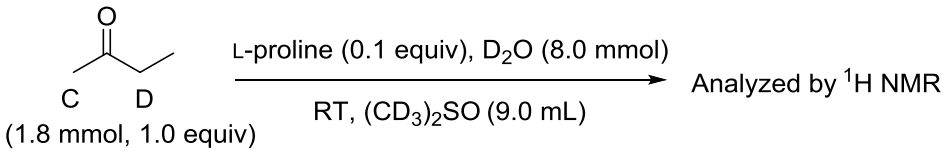
Experiment 1:

Time (min)	5*	30	90	147	229	297	359
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	2.9868	2.9623	2.9272	2.8981	2.8570	2.8257	2.7962
Integration of CH_3 at C/3	0.9956	0.9874	0.9757	0.9660	0.9523	0.9419	0.9321
Integration of CH_2 at D	1.9435	1.9493	1.9268	1.9039	1.8751	1.8472	1.8242
Integration of CH_2 at D/2	0.9718	0.9747	0.9634	0.9520	0.9376	0.9236	0.9121

*Not included in the graph.

Experiment 2:

Time (min)	34	92	151	232	299	362
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	2.9568	2.9212	2.8875	2.8516	2.8184	2.7918
Integration of CH_3 at C/3	0.9856	0.9737	0.9625	0.9505	0.9395	0.9306
Integration of CH_2 at D	1.9434	1.9245	1.8982	1.8705	1.8439	1.8253
Integration of CH_2 at D/2	0.9717	0.9623	0.9491	0.9353	0.9220	0.9127



Deuteration of methyl ethyl ketone in the presence of L-proline: To a solution of L-proline (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding methyl ethyl ketone (161.2 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.8. Deuteration of methyl ethyl ketone in the presence of L-proline.

Experiment 1:

Time (min)	5*	40	130	180	268	354	433
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	3.0730	3.0723	3.032	3.0157	2.9738	2.9413	2.8978
Integration of CH_3 at C/3	1.0238	1.0241	1.0107	1.0052	0.9913	0.9804	0.9659

Time (min)	593	1472	2930	4360	8900
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	2.8397	2.6209	2.3926	2.2816	2.1661
Integration of CH_3 at C/3	0.9466	0.8736	0.7975	0.7605	0.7220

* Not included in the graph. There may be a lag for enamine formation.

Time (min)	40*	180*	268*	593	1472	2930	4360
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at D	1.9929	2.0047	1.9909	1.9386	1.9111	1.8302	1.7968
Integration of CH_2 at D/2	0.9965	1.0023	0.9955	0.9693	0.9556	0.9151	0.8984

* Not included in the graph. There may be a lag for enamine formation.

Experiment 2:

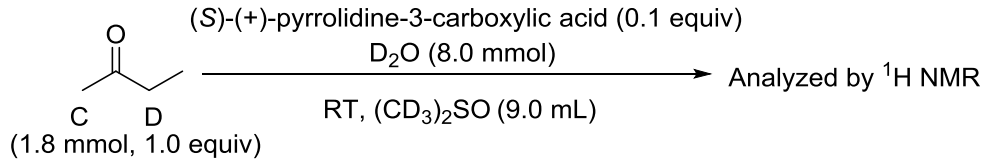
Time (min)	44	134	184	285.5	370	600
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	3.0784	3.0365	3.0126	2.9752	2.9352	2.8324
Integration of CH_3 at C/3	1.0261	1.0122	1.0042	0.9917	0.9784	0.9441

Time (min)	1477	2899	4330
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00

Integration of CH_3 at C	2.5882	2.3438	2.2392
Integration of CH_3 at C/3	0.8627	0.7813	0.7464

Time (min)	44*	134*	184*	600	1477	2889	4330
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at D	2.0143	1.9982	1.9993	1.9443	1.9051	1.8252	1.7784
Integration of CH_2 at D/2	1.007	0.9991	0.9997	0.9722	0.9526	0.9126	0.8892

* Not included in the graph. There may be a lag for enamine formation.



Deuteration of methyl ethyl ketone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid: To a solution of (*S*)-(+)-pyrrolidine-3-carboxylic acid (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding methyl ethyl ketone (161.2 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.9. Deuteration of methyl ethyl ketone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid.

Experiment 1:

Time (min)	6	21	41	55	70	91
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	2.6979	2.4299	2.086	1.8943	1.7431	1.5603
Integration of CH_3 at C/3	0.8993	0.8100	0.6953	0.6314	0.5810	0.5201

Time (min)	133	240
Integration of $CH_2C\underline{H_3}$	3.00	3.00
Integration of CH_3 at C	1.3287	1.1607
Integration of CH_3 at C/3	0.4429	0.3869

Time (min)	6	21	41	55	70	91
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at D	1.8464	1.7732	1.606	1.5131	1.4656	1.353
Integration of CH_2 at D/2	0.9232	0.8866	0.803	0.7566	0.7328	0.6765

Time (min)	133	240	370
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00
Integration of CH_2 at D	1.1981	1.0296	0.8975
Integration of CH_2 at D/2	0.5991	0.5148	0.4488

Experiment 2:

Time (min)	7	27	43	57	72	92
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at C	2.6988	2.3072	2.0482	1.8661	1.7077	1.5625
Integration of CH_3 at C/3	0.8996	0.76907	0.6827	0.6220	0.5692	0.5208

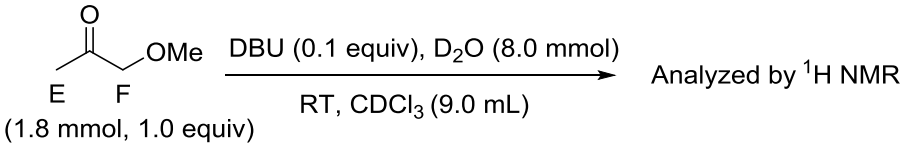
Time (min)	134	241
Integration of $CH_2C\underline{H_3}$	3.00	3.00
Integration of CH_3 at C	1.3325	1.1677

Integration of CH_3 at C/3	0.4442	0.3892

Time (min)	7	27	43	57	72	92
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at D	1.8377	1.7006	1.5959	1.5091	1.4271	1.3577
Integration of CH_2 at D/2	0.9189	0.8503	0.7980	0.7546	0.7136	0.6789

Time (min)	134	241	371
Integration of $CH_2C\underline{H_3}$	3.00	3.00	3.00
Integration of CH_2 at D	1.1933	1.0246	0.9037
Integration of CH_2 at D/2	0.5967	0.5123	0.4519

Deuteration of Methoxyacetone



Deuteration of methoxyacetone in the presence of DBU: To a solution of methoxyacetone (167.0 μL, 1.80 mmol) in $CDCl_3$ (8.25 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 5 min adding premade DBU solution in $CDCl_3$ (0.24 mmol/mL, 0.75 mL, 0.18 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.10. Deuteration of methoxyacetone 3 in the presence of DBU.

Experiment 1:

Time (min)	2	9	16	24	32	41
Integration of OCH_3	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at E	2.84	2.79	2.73	2.67	2.62	2.55
Integration of CH_3 at E/3	0.947	0.93	0.91	0.89	0.873	0.85

Time (min)	58	76	106	147	720
Integration of OCH3	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at E	2.44	2.34	2.19	2.03	1.03
Integration of CH_3 at E/3	0.814	0.78	0.73	0.678	0.344

Time (min)	2	9	16	32	41
Integration of OCH_3	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at F	1.9068	1.8909	1.8784	1.8493	1.8321
Integration of CH_2 at F/2	0.9534	0.9455	0.9392	0.9247	0.9161

Time (min)	76	106	147	720
Integration of OCH_3	3.00	3.00	3.00	3.00
Integration of CH_2 at F	1.7774	1.7393	1.6949	1.2653
Integration of CH_2 at F/2	0.8887	0.8697	0.8475	0.6327

Experiment 2:

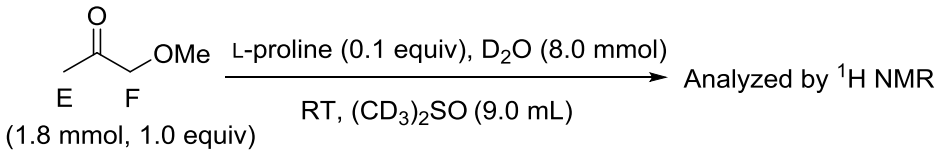
Time (min)	2	9	19	27	37	45

Integration of $OC\underline{H_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at E	2.84	2.77	2.69	2.63	2.56	2.51
Integration of CH_3 at E/3	0.947	0.923	0.897	0.877	0.853	0.837

Time (min)	55	78	111	682
Integration of OCH3	3.00	3.00	3.00	3.00
Integration of CH_3 at E	2.45	2.32	2.17	1.09
Integration of CH_3 at E/3	0.815	0.772	0.723	0.363

Time (min)	2	27	37	45	55
Integration of $OC\underline{H_3}$	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at F	1.9015	1.8596	1.8408	1.8265	1.8057
Integration of CH_2 at F/2	0.9508	0.9298	0.9204	0.9133	0.9029

Time (min)	78	111	682
Integration of $OC\underline{H_3}$	3.00	3.00	3.00
Integration of CH_2 at F	1.7735	1.7351	1.3079
Integration of CH_2 at F/2	0.8868	0.9676	0.6540



Deuteration of methoxyacetone in the presence of L-proline: To a solution of L-proline (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min

before adding internal standard CH_2Br_2 (62.6 μL, 0.9 mmol) and methoxyacetone (167.0μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^1H NMR. The experiments were performed twice.

Table 6.11. Deuteration of methoxyacetone in the presence of L-proline.

Experiment 1:

Time (min)	5*	46	113	172	251	310
Integration of internal standard $C\underline{H_2}Br_2$	1.158	1.158	1.158	1.158	1.158	1.158
Integration of CH_3 at E	3.00	2.9916	2.9023	2.8478	2.7500	2.7040
Integration of CH_3 at E/3	1.00	0.9972	0.9674	0.9493	0.9167	0.9013

Time (min)	360	421	566	661	2202	3752
Integration of internal standard $C\underline{H_2}Br_2$	1.158	1.158	1.158	1.158	1.158	1.158
Integration of CH_3 at E	2.6526	2.5894	2.5015	2.4681	1.9115	1.7233
Integration of CH_3 at E/3	0.8842	0.8631	0.8338	0.8227	0.6372	0.5744

* Not included in the graph. There may be a lag for enamine formation.

Time (min)	46	78	172	310
Integration of internal standard $C\underline{H_2}Br_2$	1.158	1.158	1.158	1.158
Integration of CH_2 at F	1.9482	1.945	1.9242	1.8953
Integration of CH_2 at F/2	0.9471	0.9725	0.9621	0.9476

Time (min)	360	661	2202	3752
Integration of internal standard $C\underline{H_2}Br_2$	1.158	1.158	1.158	1.158
Integration of CH_2 at F	1.8823	1.8279	1.6994	1.5687
Integration of CH_2 at F/2	0.9411	0.9139	0.8497	0.7844

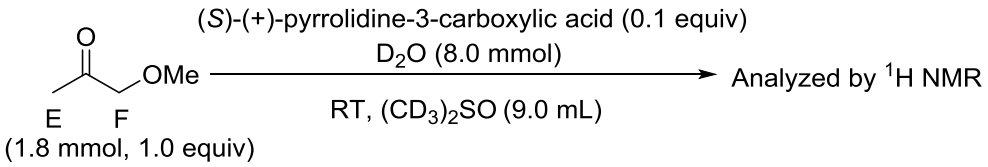
Experiment 2:

Time (min)	3*	35	105	165	242	302
Integration of internal standard $C\underline{H_2}Br_2$	1.1486	1.1486	1.1486	1.1486	1.1486	1.1486
Integration of CH_3 at E	3.00	2.9941	2.9219	2.8426	2.7838	2.7045
Integration of CH_3 at E/3	1.00	0.9980	0.9740	0.9475	0.9279	0.9015

Time (min)	353	413	556
Integration of internal standard $C\underline{H_2}Br_2$	1.1486	1.1486	1.1486
Integration of CH_3 at E	2.6593	2.6050	2.5171
Integration of CH_3 at E/3	0.8864	0.9683	0.8390

* Not included in the graph. There may be a lag for enamine formation.

Time (min)	35	105	242	302	353	556
Integration of internal standard $C\underline{H_2}Br_2$	1.1486	1.1486	1.1486	1.1486	1.1486	1.1486
Integration of CH_2 at F	1.9523	1.9395	1.9115	1.8937	1.8803	1.8445
Integration of CH_2 at F/2	0.9762	0.9698	0.9557	0.9468	0.9402	0.9223



Deuteration of methoxyacetone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid : To a solution of (*S*)-(+)-pyrrolidine-3-carboxylic acid (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding methoxyacetone **3** (167.0μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.12. Deuteration of methoxyacetone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid.

Experiment 1:

Time (min)	1	6	19	27	37	57
Integration of $O\underline{CH_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at E	2.9075	2.6671	2.1099	1.8865	1.6187	1.3431
Integration of CH_3 at E/3	0.9692	0.88903	0.7033	0.6288	0.5396	0.4477

Time (min)	145
Integration of $O\underline{CH_3}$	3.00
Integration of CH_3 at E	1.1374
Integration of CH_3 at E/3	0.3791

Time (min)	1	6	19	27	37	57
Integration of $O\underline{CH_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at F	2.0485	1.9835	1.7913	1.7528	1.5875	1.4417
Integration of CH_2 at F/2	1.0243	0.9918	0.8957	0.9864	0.7938	0.7209

Time (min)	145	268
Integration of $O\underline{CH_3}$	3.00	3.00
Integration of CH_2 at F	1.0427	0.8862
Integration of CH_2 at F/2	0.5214	0.4431

Experiment 2:

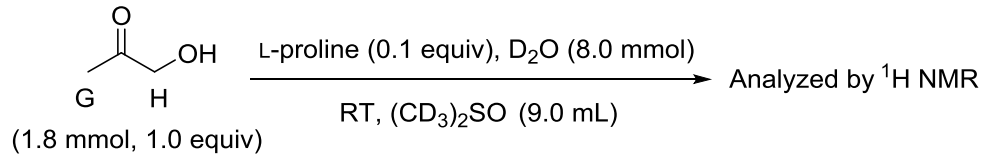
Time (min)	1.5	6	14	23	33	57
Integration of $O\underline{CH_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_3 at E	2.9015	2.6522	2.2763	1.9524	1.6923	1.3456
Integration of CH_3 at E/3	0.9672	0.8841	0.7588	0.6508	0.5641	0.4485

Time (min)	142
Integration of $O\underline{CH_3}$	3.00
Integration of CH_3 at E	1.1442
Integration of CH_3 at E/3	0.3814

Time (min)	1.5	6	14	23	33	57
Integration of $O\underline{CH_3}$	3.00	3.00	3.00	3.00	3.00	3.00
Integration of CH_2 at F	2.0604	1.9726	1.8453	1.7278	1.6294	1.4397
Integration of CH_2 at F/2	1.0302	0.9863	0.9227	0.8639	0.8147	0.7199

Time (min)	142	264
Integration of $O\underline{CH_3}$	3.00	3.00
Integration of CH_2 at F	1.053	0.9035
Integration of CH_2 at F/2	0.5265	0.4518

Deuteration of Hydroxyacetone



Deuteration of hydroxyacetone in the presence L-proline: To a solution of L-proline (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding internal standard CH_2Br_2 (62.6 μL, 0.9 mmol) and hydroxyacetone (125.8 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.13. Deuteration of hydroxyacetone in the presence of L-proline.

Experiment 1:

Time (min)	3*	39	177	248	791
Integration of internal standard $C\underline{H_2}Br_2$	0.982	0.982	0.982	0.982	0.982
Integration of CH_3 at G	3.00	3.0019	2.9681	2.9420	2.7742
Integration of CH_3 at G/3	1.00	1.001	0.9894	0.9807	0.9247

Time (min)	1222	2421	2784	4200
Integration of internal standard $C\underline{H_2}Br_2$	0.982	0.982	0.982	0.982
Integration of CH_3 at G	2.6550	2.4764	2.4468	2.3489
Integration of CH_3 at G/3	0.885	0.8255	0.8156	0.7830

* Integration of CH_3 at position G was adjusted to be 3.00. Not included in the graph. There may be a lag for enamine formation.

Time (min)	117	1222	2421	4200
Integration of internal standard $C\underline{H_2}Br_2$	0.982	0.982	0.982	0.982

Integration of CH_2 at H	2.0314	2.0276	1.9795	1.9157
Integration of CH_2 at H/2	1.0157	1.0138	0.9898	0.9579

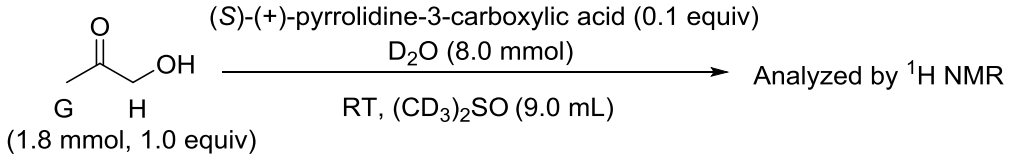
Experiment 2:

Time (min)	3*	47	113	191	251	795
Integration of internal standard $C\underline{H_2}Br_2$	0.9568	0.9568	0.9568	0.9568	0.9568	0.9568
Integration of CH_3 at G	3.00	2.9996	2.9780	2.9611	2.9282	2.7492
Integration of CH_3 at G/3	1.00	0.9999	0.9927	0.9870	0.9761	0.9164

Time (min)	2431	2795	4205
Integration of internal standard $C\underline{H_2}Br_2$	0.9568	0.9568	0.9568
Integration of CH_3 at G	2.4821	2.4362	2.3752
Integration of CH_3 at G/3	0.8274	0.8121	0.7917

* Integration of CH_3 at position G was adjusted to be 3.00. Not included in the graph. There may be a lag for enamine formation.

Time (min)	113	795	2431	4205
Integration of internal standard $C\underline{H_2}Br_2$	0.982	0.982	0.982	0.982
Integration of CH_2 at H	2.0443	2.0237	1.9830	1.9475
Integration of CH_2 at H/2	1.0222	1.0119	0.9915	0.9738



Deuteration of hydroxyacetone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid: To a solution of (*S*)-(+)-pyrrolidine-3-carboxylic acid (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding internal standard CH_2Br_2 (62.6 μL, 0.9 mmol) and hydroxyacetone (125.8 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

Table 6.14. Deuteration of hydroxyacetone in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid.

Experiment 1:

Time (min)	1*	6	11	19	29	40
Integration of internal standard $C\underline{H_2}Br_2$	0.9879	0.9879	0.9879	0.9879	0.9879	0.9879
Integration of CH_3 at G	2.6838	2.4935	2.2923	1.9635	1.7089	1.5055
Integration of CH_3 at G/3	0.8946	0.8312	0.7641	0.6545	0.5696	0.5018

Time (min)	62	111	219
Integration of internal standard $C\underline{H_2}Br_2$	0.9879	0.9879	0.9879
Integration of CH_3 at G	1.301	1.2372	1.2038
Integration of CH_3 at G/3	0.4337	0.4124	0.4013

* Integration of CH_2 at position H was adjusted to be 2.00.

Time (min)	1*	6	11	19	29	40

Integration of internal standard $C\underline{H_2}Br_2$	0.9879	0.9879	0.9879	0.9879	0.9879	0.9879
Integration of CH_2 at H	2	1.9966	1.9522	1.901	1.8657	1.7691
Integration of CH_2 at H/2	1	0.9983	0.9761	0.9505	0.9329	0.8846

Time (min)	62	111	219	342
Integration of internal standard $C\underline{H_2}Br_2$	0.9879	0.9879	0.9879	0.9879
Integration of CH_2 at H	1.6859	1.5557	1.4645	1.4394
Integration of CH_2 at H/2	0.8430	0.7779	0.7323	0.7197

* Integration of CH_2 at position H was adjusted to be 2.00. Not included in the graph. There may be a lag for enamine formation.

Experiment 2:

Time (min)	1*	5.5	14	24	35	58
Integration of internal standard $C\underline{H_2}Br_2$	1.0121	1.0121	1.0121	1.0121	1.0121	1.0121
Integration of CH_3 at G	2.6878	2.5001	2.1354	1.8316	1.6078	1.3261
Integration of CH_3 at G/3	0.8959	0.8334	0.7118	0.6105	0.5359	0.4420

Time (min)	96	214
Integration of internal standard $C\underline{H_2}Br_2$	1.0121	1.0121
Integration of CH_3 at G	1.2365	1.2194
Integration of CH_3 at G/3	0.4122	0.4065

* Integration of CH_2 at position H was adjusted to be 2.00.

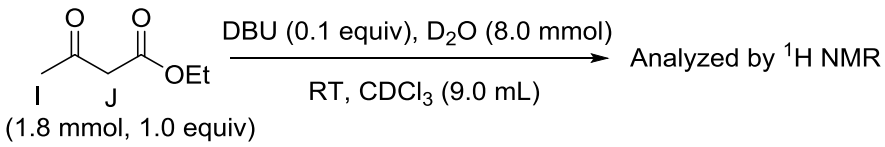
Time (min)	1*	5.5	14	24	35	58
Integration of internal standard $C\underline{H_2}Br_2$	1.0121	1.0121	1.0121	1.0121	1.0121	1.0121
Integration of CH_2 at H	2	2.0165	1.942	0.9213	1.8158	1.7006

Integration of CH_2 at H/2	1	1.0083	0.971	0.9607	0.9229	0.8503

Time (min)	96	214	337
Integration of internal standard $C\underline{H_2}Br_2$	1.0121	1.0121	1.0121
Integration of CH_2 at H	1.5725	1.4996	1.4489
Integration of CH_2 at H/2	0.7863	0.7498	0.7245

* Integration of CH_2 at position H was adjusted to be 2.00. Not included in the graph. There may be a lag for enamine formation.

Deuteration of Ethyl Acetoacetate



(1.8 mmol, 1.0 equiv)

Deuteration of ethyl acetoacetate in the presence of DBU: To a solution of ethyl acetoacetate (227.4 μL, 1.80 mmol) in $CDCl_3$ (8.25 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 5 min before adding premade DBU solution in $CDCl_3$ (0.24 mmol/mL, 0.75 mL, 0.18 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^1H NMR. The experiments were performed twice.

Table 6.15. Deuteration of ethyl acetoacetate in the presence of DBU.

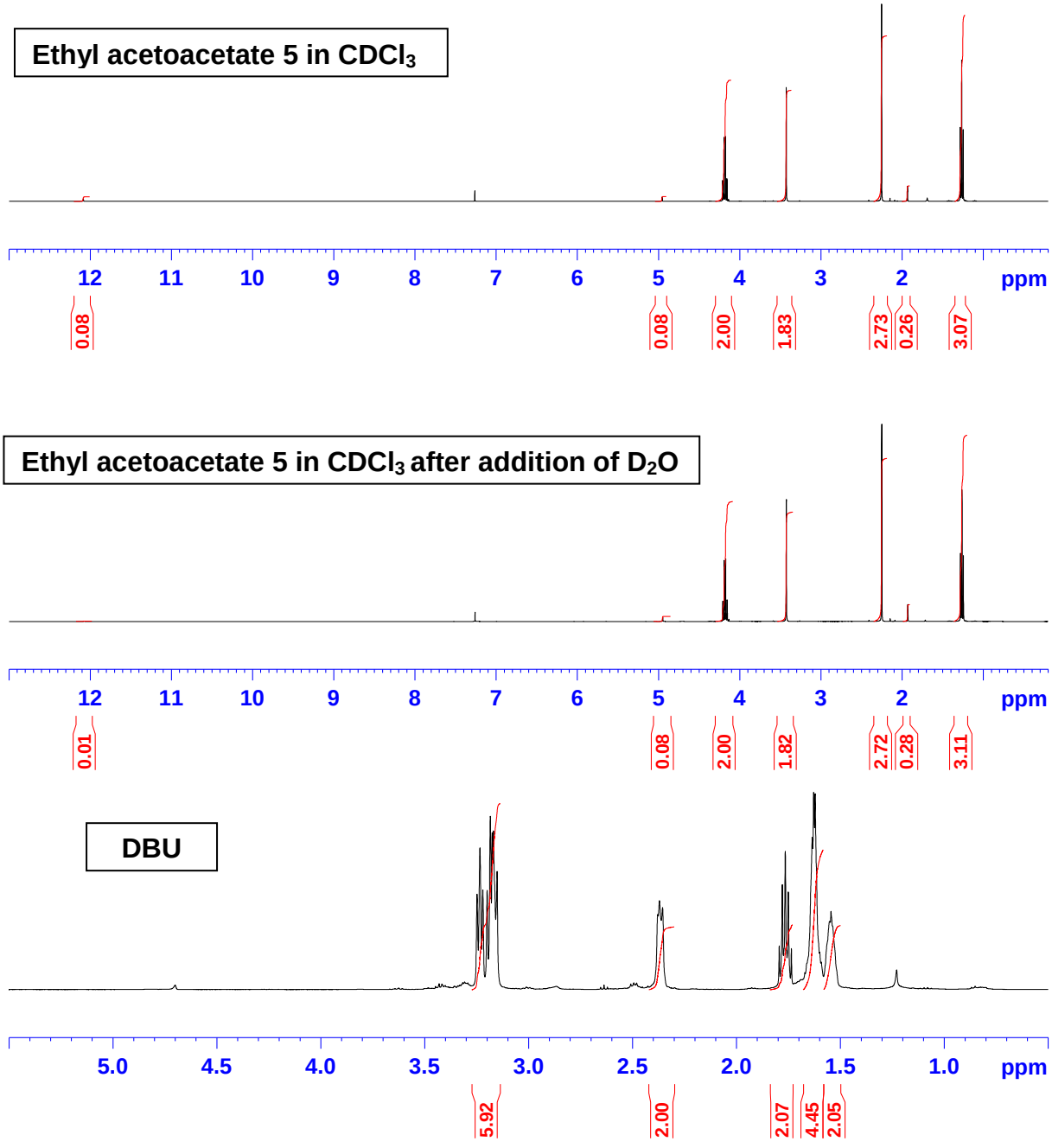
Experiment 1:

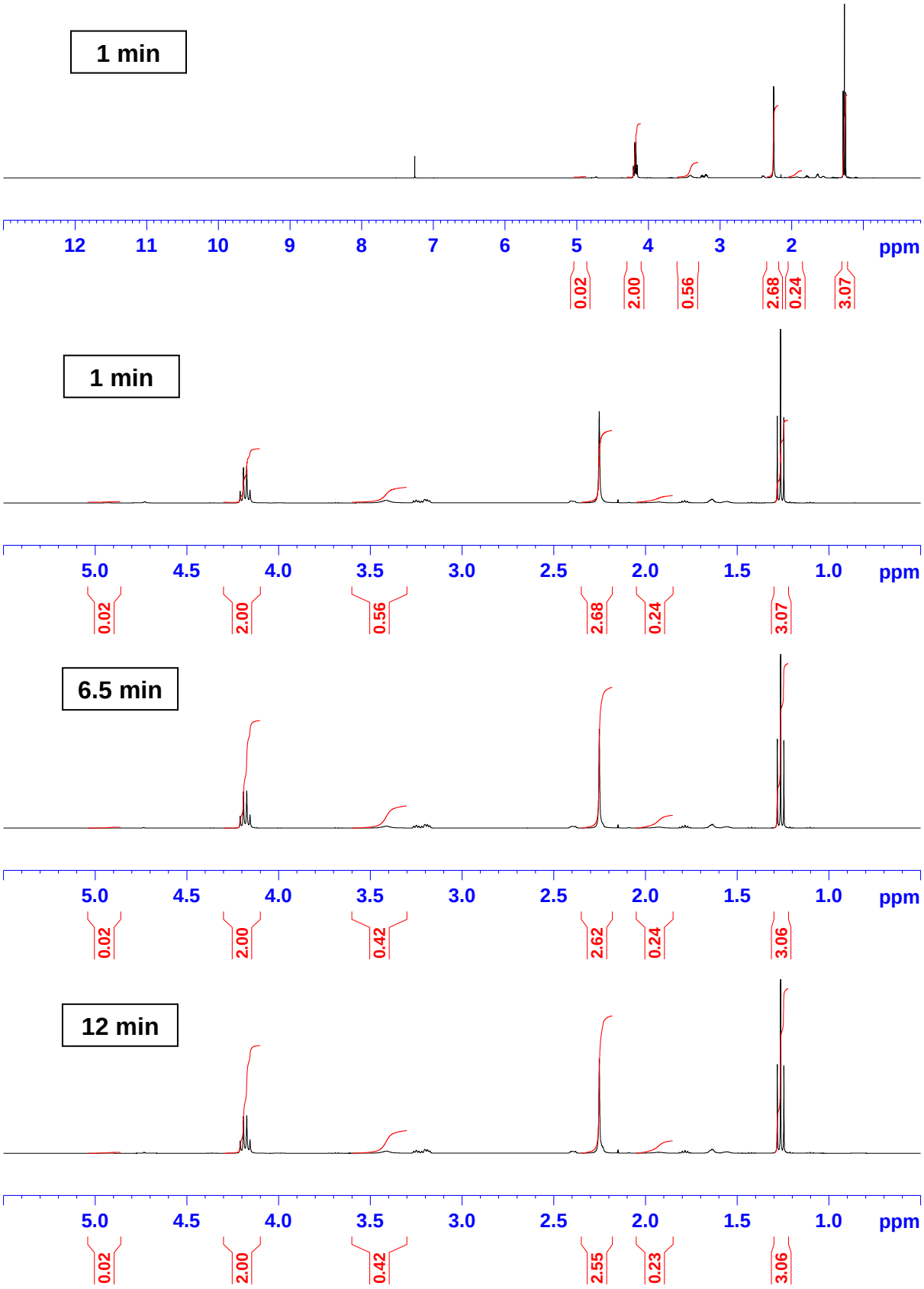
Time (min)	1	7	12.5	18	25	31
Integration of $OC\underline{H_2}CH_3$	2.00	2.00	2.00	2.00	2.00	2.00
Integration of CH_3 at I	2.66	2.60	2.54	2.49	2.43	2.38
Integration of CH_3 at I/3	0.887	0.867	0.847	0.83	0.81	0.793

Experiment 2:

Time (min)	1	6.5	12	18	25	32
Integration of $OC\underline{H_2}CH_3$	2.00	2.00	2.00	2.00	2.00	2.00
Integration of CH_3 at I	2.68	2.62	2.55	2.50	2.43	2.38
Integration of CH_3 at I/3	0.893	0.873	0.85	0.833	0.81	0.793

Figure 6.3. NMR spectra of ethyl acetoacetate in the presence of DBU at different time points.

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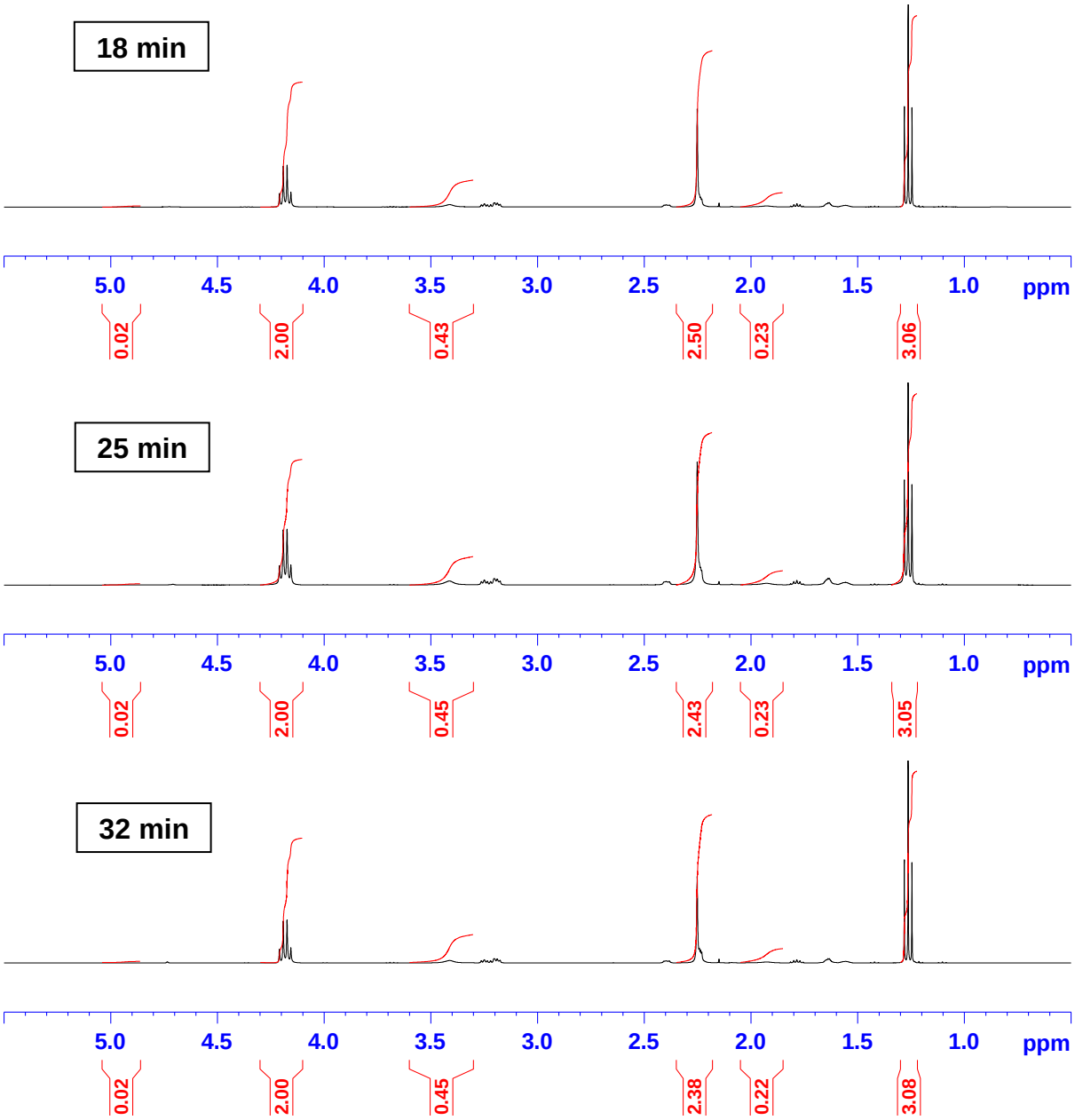
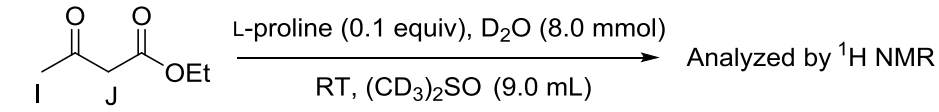
0.02 2.00 0.56 2.68 0.24 3.07
1 min
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.02 2.00 0.56 2.68 0.24 3.07
6.5 min
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.02 2.00 0.42 2.62 0.24 3.06
12 min
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.02 2.00 0.42 2.55 0.23 3.06

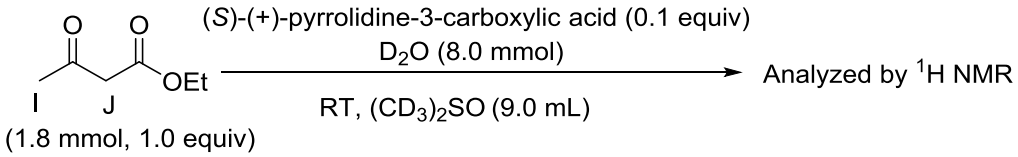




(1.8 mmol, 1.0 equiv)

Deuteration of ethyl acetoacetate in the presence of L-proline: To a solution of L-proline (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding ethyl acetoacetate (227.4 μL, 1.80 mmol). At time points indicated, a

portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.



Deuteration of ethyl acetoacetate in the presence of (*S*)-(+)-pyrrolidine-3-carboxylic acid: To a solution of (*S*)-(+)-pyrrolidine-3-carboxylic acid (20.7 mg, 0.18 mmol) in deuterated DMSO (9.0 mL), D_2O (144.0 μL, 8.0 mmol) was added at room temperature (25 °C). The mixture was stirred at the same temperature for 30 min before adding ethyl acetoacetate (227.4 μL, 1.80 mmol). At time points indicated, a portion (0.5 mL) of the mixture was taken out and analyzed by ^{1}H NMR. The experiments were performed twice.

6.4 Experimental Section for Chapter 4

6.4.1. Experimental Section for Chapter 4.2

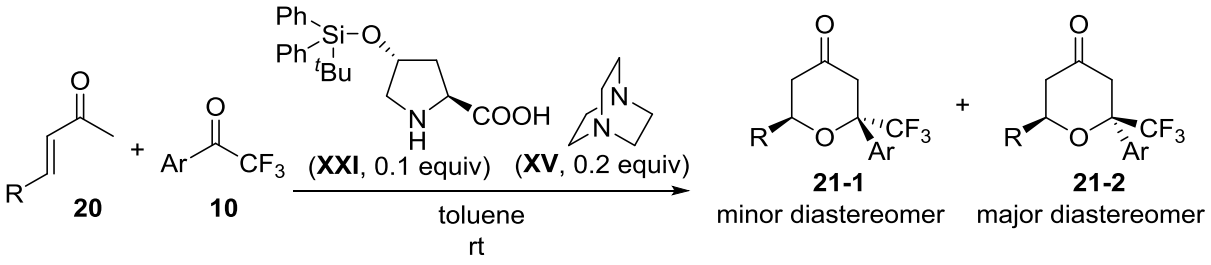
Synthesis of Catalysts and Enones

Amine catalysts **IX**[53, 128] and **XVIII** [129] were synthesized by reported procedures.[53,128,129] Enones were purchased or synthesized by reported procedures[53] or by modified methods of the reported procedures.[130]

4-(4-Bromophenyl)but-3-en-2-one

To a mixture of water (10.0 mL), acetone (8.0 mL), and 4-bromobenzaldehyde (3.7 g, 20 mmol), NaOH solution (10% in water, 5 mL) was added at room temperature (25 ^{o}C), and the mixture was stirred at the same temperature for 1 h.[130] Generated precipitate was collected by filtration, washed with hexane, dried under vacuum to give 4-(4-bromophenyl)but-3-en-2-one (4.3g, 95%). The ^{1}H and ^{13}C NMR of this product matched to the reported data.[131]

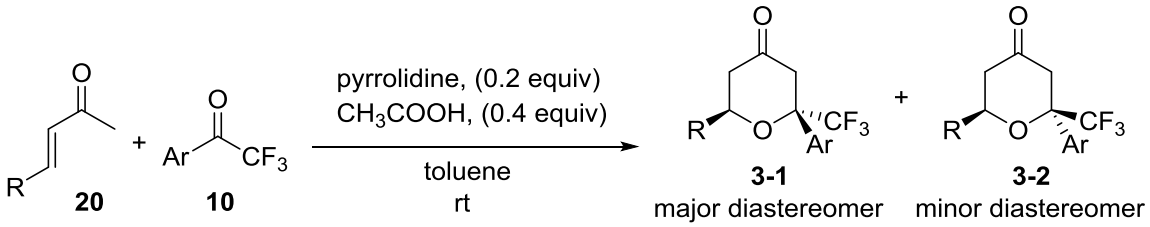
Oxa-Hetero-Diels-Alder Reactions



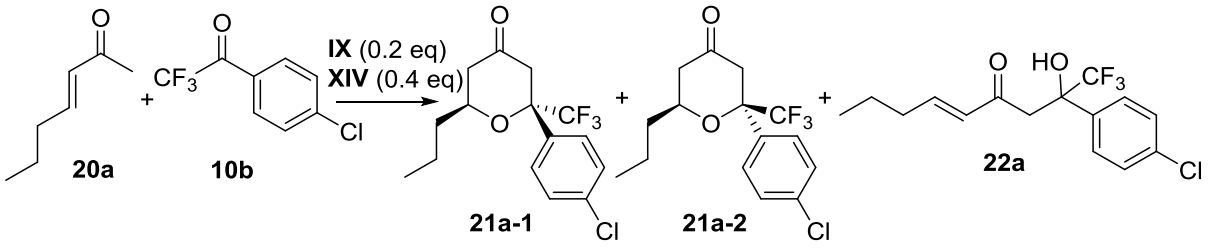
General procedure for the catalytic enantioselective oxa-hetero-Diels-Alder reactions (Table 4.2) To a solution of enone **20** (1.0 mmol) and aryl trifluomethyl ketone **10** (0.2 mmol) in toluene (super dehydrated, 0.4 mL), (2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)pyrrolidine-2-carboxylic acid (**XXI**) (7.4 mg, 0.02 mmol) and DABCO (**XV**) (4.49 mg, 0.04 mmol) were added at room temperature (25 ^{o}C), and the mixture was stirred at the same temperature until **10** was consumed (monitored by TLC and crude ^{1}H NMR). The mixture was purified by flash column chromatography (hexane/CH_2Cl_2 = 3:1 to 2:1) to give product **3** (**3-1** and **3-2**). For all the cases using catalyst system **XXI**-**XV**, isomer **21-2** was the major diastereomer and **21-1** was the minor diastereomer. R_f values of **21-1** and **21-2** were the same or similar. The dr was determined by ^{1}H NMR analysis before purification, and the value was retained after purification except a large-scale reaction (i.e., a 1.0 mmol-scale reaction to afford **3j-2**). The ee was determined by chiral-phase HPLC analysis after purification. The ratio of **21**/**22** (**21** = **21-1** and **21-2**, **22** = aldol product) was determined by ^{1}H NMR analysis before purification.

Relative stereochemistries of **21a** (**21a-1** and **21a-2**) were deduced from the relative stereochemistries of **25-1** and **25-2**, which were determined by ^{1}H NMR *J* values and NOESY experiments (see compounds **25-1** and **25-2**). Relative stereochemistries of **21g** (**21g-1** and **21g-2**) were determined by ^{1}H NMR *J* values and NOESY experiments (see compound **21g**). Relative stereochemistries of compound **21** other than **21a** and **21g** were determined by

analogy. The absolute stereochemistry of **21** was tentatively assigned by the deduction from the previously suggested transition states[54] and the product[53] of the [4+2] cycloaddition of the *in situ*-formed enamine of **20a** with isatin under catalyst system **IX**-**X**.



General procedure for the synthesis of racemic standards of 3. To a solution of enone **20** (1.0 mmol) and aryl trifluomethyl ketone **10** (0.2 mmol) in toluene (super dehydrated, 0.4 mL), pyrrolidine (3.2 μL, 0. 04 mmol) and acetic acid (**XIV**) (4.6 μL, 0.08 mmol) were added at room temperature (25 ^{o}C), and the reaction mixture was stirred at the same temperature until **10** was consumed (monitored by TLC and crude ^{1}H NMR). The mixture was purified by flash column chromatography (hexane/CH_2Cl_2 = 3:1 to 2:1) to give racemic product **21-1** and **21-2** as a diastereomer mixture. Among all the products except **21i** and **21j**, isomer **21-1** was the major diastereomer and **21-2** was the minor diastereomer. **21**:**22** > 95:5.

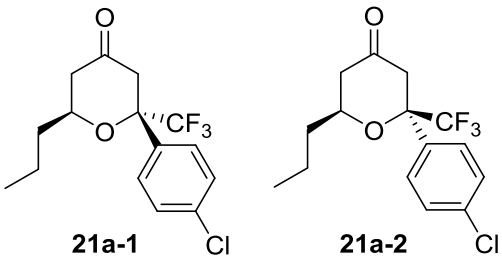


Synthesis of compound 22a with 21a. To a solution of enone **20a** (56.0 μL, 0.5 mmol) and 4-chlorophenyl trifluoromethyl ketone (**10b**) (15.0 μL, 0.1 mmol) in toluene (super dehydrated, 0.2 mL), amine catalyst **IX** (5.87 mg, 0.02 mmol) and acetic acid (**XIV**) (2.3 μL, 0.04 mmol) were added at room temperature (25 ^{o}C), and the mixture was stirred at the same temperature until **10b** was consumed (monitored by TLC and crude ^{1}H NMR). The

mixture was purified by flash column chromatography (hexane/CH_2Cl_2 = 3:1 to 2:1) to give **21a** and **22a** (21.0 mg, **21a-1**:**21a-2**:**22a** = 62:8:30). Compound **22a** was eluted with **21a** in usual silica gel flash column chromatography. The ratio of **21a**/**22a** and the dr of **21a** were determined by ^{1}H NMR analysis.

A 2 mmol-scale reaction to afford 21a. To a solution of **20a** (1.3 mL, 10.0 mmol) and **10b** (417.0 mg, 2.0 mmol) in toluene (super dehydrated, 2.0 mL), (2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)pyrrolidine-2-carboxylic acid (**XXI**) (74.0 mg, 0.2 mmol,) and DABCO (**XV**) (44.8 mg, 0.4 mmol) were added at room temperature (25 ^{o}C) and the reaction mixture was stirred at the same temperature for 24 h. The reaction mixture was purified by flash column chromatography (hexane/CH_2Cl_2 = 3:1 to 2:1) to give product **21a-1** and **21a-2** as a diastereomer mixture (320.0 mg, 50%, **21a-1**:**21a-2** =1:1.9, **21a-2** er 96:4).

2-(4-Chlorophenyl)-6-propyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21a)

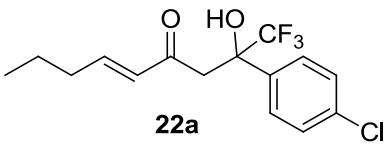


Synthesized by the general procedure; 24 h, 37.6 mg (59%), dr **21a-1**:**21a-2** = 1:1.9, **21a-2** er 97:3.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H × 1.9/2.9, C$\underline{H}_3$), 1.01 (t, *J* = 7.2 Hz, 3H × 1/2.9, C$\underline{H}_3$), 1.35-1.81 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 2.21 (dd, *J* = 11.6 Hz, 16.0 Hz, 1H × 1/2.9, CHC$\underline{H}$HC=O), 2.26 (ddd, *J* = 1.6 Hz, 2.4 Hz, 14.7 Hz, 1H × 1.9/2.9, CHC$\underline{H}$HC=O), 2.39 (dd, *J* = 11.6 Hz, 14.7 Hz, 1H × 1.9/2.9, CHC$\underline{H}$HC=O), 2.49 (dd, *J* = 2.4 Hz, 16.0 Hz, 1H × 1/2.9, CHC$\underline{H}$HC=O), 2.85 (d, *J* = 15.6 Hz, 1H × 1/2.9, CF$_3$CC$\underline{H}$HC=O), 3.01 (d, *J* = 14.3 Hz, 1H × 1.9/2.9, CF$_3$CC$\underline{H}$HC=O), 3.19 (d, *J* = 14.3 Hz, 1H × 1.9/2.9, CF$_3$CC$\underline{H}$HC=O), 3.29 (d, *J* = 15.6 Hz, 1H × 1/2.9, CF$_3$CC$\underline{H}$HC=O), 3.65-3.71 (m, 1H ×

1.9/2.9, OC<u>H</u>), 4.39-4.44 (m, 1H × 1/2.9, OC<u>H</u>), 7.35-7.49 (m, 4H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.4, 38.1, 38.4, 42.7, 43.8, 45.7, 46.8, 72.1, 73.2, 78.5 (q, $J_{C,F}$ = 28 Hz), 80.5 (q, $J_{C,F}$ = 30 Hz), 123.6 (q, $J_{C,F}$ = 282 Hz), 124.9 (q, $J_{C,F}$ = 287 Hz), 127.8, 128.6, 129.1, 129.8, 132.0, 135.3, 135.9, 136.2, 202.9, 203.1. HRMS (ESI): calcd for $C_{15}H_{15}O_2ClF_3$ ($[M - H]^-$) 319.0707, found 319.0713. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 11.6 min, t_R (major diastereomer, minor enantiomer) = 13.5 min. t_R (minor diastereomer) = 19.4 min and 20.3 min.

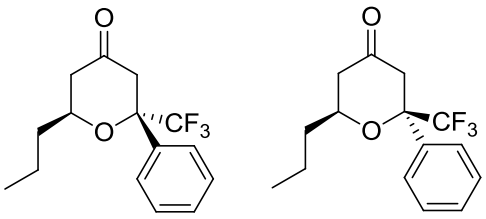
Compound 22a



22a

Data of **22a** extracted from the data of a mixture of **22a** with **21a** (**21a-1**:**21a-2**:**22a** = 62:8:30 and 64:18:18): ^{1}H NMR (400 MHz, $CDCl_3$): peaks separated from **21a**: δ 3.23 (d, *J* = 16.8 Hz, 1H, $CF_3CC\underline{H}HC{=}O$), 3.46 (d, *J* = 16.8 Hz, 1H, $CF_3CC\underline{H}HC{=}O$), 6.08 (dd, *J* = 4.0 Hz, 16.0 Hz, 1H, $C\underline{H}{=}CHCH_2$), 6.95 (dt, *J* = 6.8 Hz, 16.0 Hz, 1H, $CH{=}C\underline{H}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 21.1, 34.6, 41.3, 76.1 (q, $J_{C,F}$ = 29 Hz), 124.4 (q, $J_{C,F}$ = 283 Hz), 127.9, 128.7, 130.4, 134.9, 136.3, 151.4, 199.3.

2-Phenyl-6-propyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21b)

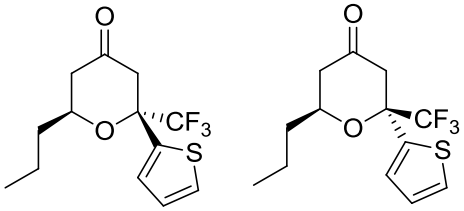


21b-1 **21b-2**

Synthesized by the general procedure; 48 h, 31.4 mg (55%), dr **21b-1**:**21b-2** = 1:1.3, **21b-2** er 96:4.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H × 1.3/2.3, C<u>H</u>$_3$), 1.02 (t, *J* = 7.2 Hz, 3H × 1/2.3, C<u>H</u>$_3$), 1.34-1.82 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 2.22 (dd, *J* = 12.0 Hz, 16.4 Hz, 1H × 1/2.3, CHC<u>H</u>HC=O), 2.25 (ddd, *J* = 1.6 Hz, 2.8 Hz, 14.9 Hz, 1H × 1.3/2.3, CHC<u>H</u>HC=O), 2.38 (ddd, *J* = 0.8 Hz, 11.5 Hz, 14.9 Hz, 1H × 1.3/2.3, CHC<u>H</u>HC=O), 2.48 (ddd, *J* = 0.8 Hz, 2.8 Hz, 16.4 Hz, 1H × 1/2.3, CHC<u>H</u>HC=O), 2.90 (d, *J* = 15.6 Hz, 1H × 1/2.3, CF_3CC<u>H</u>HC=O), 3.01 (dd, *J* = 0.8 Hz, 14.8 Hz, 1H × 1.3/2.3, CF_3CC<u>H</u>HC=O), 3.26 (dd, *J* = 0.8 Hz, 14.8 Hz, 1H × 1.3/2.3, CF_3CC<u>H</u>HC=O), 3.31 (dd, *J* = 0.8 Hz, 15.6 Hz, 1H × 1/2.3, CF_3CC<u>H</u>HC=O), 3.68-3.75 (m, 1H × 1.3/2.3, OC<u>H</u>), 4.39-4.44 (m, 1H × 1/2.3, OC<u>H</u>), 7.36-7.56 (m, 5H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.4, 18.5, 38.2, 38.5, 42.8, 44.0, 45.8, 46.8, 71.9, 73.1, 78.7 (q, $J_{C,F}$ = 28 Hz), 80.8 (q, $J_{C,F}$ = 29 Hz), 123.9 (q, $J_{C,F}$ = 282 Hz), 125.1 (q, $J_{C,F}$ = 287 Hz), 126.3, 128.3, 128.8, 129.0, 129.5, 133.4, 137.7, 203.4, 203.6 ppm; HRMS (ESI): calcd for $C_{15}H_{18}O_2F_3$ ($[M + H]^+$) 287.1253, found 287.1258. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 11.7 min, t_R (major diastereomer, minor enantiomer) = 18.9 min. t_R (minor diastereomer) = 20.6 min and 21.4 min.

6-Propyl-2-(thiophen-2-yl)-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21c)



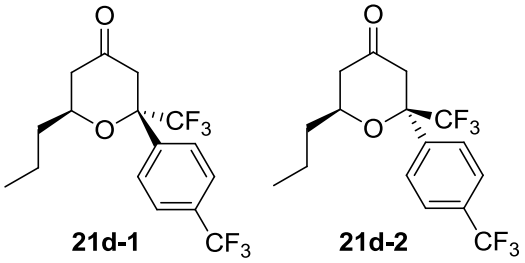
21c-1 **21c-2**

Synthesized by the general procedure; 28 h, 30.1 mg (52%), dr **21c-1**:**21c-2** = 1:1.4, **21c-2** er 91:9.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H × 1.4/2.4, C<u>H</u>$_3$), 0.99 (t, *J* = 7.2 Hz, 3H × 1/2.4, C<u>H</u>$_3$), 1.34-1.80 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 2.27-2.40 (m, 1H × 1/2.4, CHC<u>H</u>HC=O, 2H × 1.4/2.4, CHC<u>HH</u>C=O), 2.48 (dd, *J* = 2.7 Hz, 17.3 Hz, 1H × 1/2.4,

CHC<u>H</u>HC=O), 2.96 (d, *J* = 15.6 Hz, 1H × 1/2.4, CF_3CC<u>H</u>HC=O), 2.99 (d, *J* = 14.7 Hz, 1H × 1.4/2.4, CF_3CC<u>H</u>HC=O), 3.14 (dd, *J* = 0.7 Hz, 14.7 Hz, 1H × 1.4/2.4, CF_3CC<u>H</u>HC=O), 3.29 (d, *J* = 15.6 Hz, 1H × 1/2.4, CF_3CC<u>H</u>HC=O), 3.76-3.82 (m, 1H × 1.4/2.4, OC<u>H</u>), 4.39-4.44 (m, 1H × 1/2.4, OC<u>H</u>), 6.99-7.05 (m, 1H × 1.4/2.4, 2H × 1/2.4, Ar<u>H</u>), 7.13 (dd, *J* = 1.2 Hz, 3.7 Hz, 1H × 1.4/2.4, Ar<u>H</u>), 7.34 (dd, *J* = 1.2 Hz, 5.2 Hz, 1H × 1/2.4, Ar<u>H</u>), 7.44 (dd, *J* = 1.2 Hz, 5.2 Hz, 1H × 1.4/2.4, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.2, 18.3, 38.0, 43.9, 44.6, 45.4, 46.9, 72.2, 73.5, 78.1 (q, $J_{C,F}$ = 30 Hz), 79.4 (q, $J_{C,F}$ = 31 Hz), 123.4 (q, $J_{C,F}$ = 282 Hz), 124.5 (q, $J_{C,F}$ = 286 Hz), 125.5, 126.8, 127.0, 127.2, 128.7, 130.0, 137.1, 141.8, 202.9, 203.0. HRMS (ESI): calcd for $C_{13}H_{14}O_2F_3S$ ([M - H]$^-$) 291.0661, found 291.0663. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 13.49 min, t_R (major diastereomer, minor enantiomer) = 20.6 min. t_R (minor diastereomer) = 23.1 min and 25.4 min.

6-Propyl-2-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)dihydro-2*H*-pyran-4(3*H*)-one (21d)

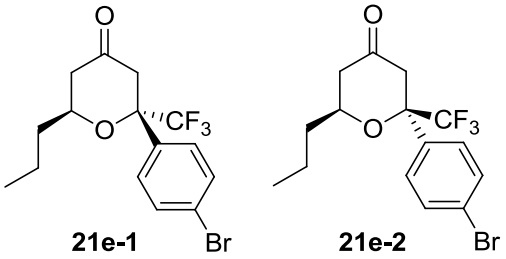


Synthesized by the general procedure; 18 h, 30.2 mg (43%), dr **21d-1**:**21d-2** = 1:1.7, **21d-2** er 97:3.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.2 Hz, 3H × 1.7/2.7, C<u>H</u>$_3$), 1.02 (t, *J* = 7.1 Hz, 3H × 1/2.7, C<u>H</u>$_3$), 1.37-1.83 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 2.17-2.31 (m, 1H, CHC<u>H</u>HC=O), 2.42 (dd, *J* = 11.5 Hz, 15.0 Hz, 1H × 1.7/2.7, CHC<u>H</u>HC=O), 2.52 (dd, *J* = 2.1 Hz, 16.6 Hz, 1H × 1/2.7, CHC<u>H</u>HC=O), 2.88 (d, *J* = 15.6 Hz, 1H × 1/2.7, CF_3CC<u>H</u>HC=O), 3.08 (dd, *J* = 0.7 Hz, 14.7 Hz, 1H × 1.7/2.7, CF_3CC<u>H</u>HC=O), 3.24 (d, *J* = 14.7 Hz, 1H ×

1.7/2.7, $CF_3CC\underline{H}HC{=}O$), 3.34 (dd, J = 0.6 Hz, 15.6 Hz, 1H × 1/2.7, $CF_3CC\underline{H}HC{=}O$), 3.65-3.72 (m, 1H × 1.7/2.7, $OC\underline{H}$), 4.42-4.47 (m, 1H × 1/2.7, $OC\underline{H}$), 7.63-7.71 (m, 4H, $Ar\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.4, 38.1, 38.4, 42.8, 43.9, 45.8, 46.7, 72.4, 73.4, 78.6 (q, $J_{C,F}$ = 28 Hz), 80.6 (q, $J_{C,F}$ = 30 Hz), 123.57 (q, $J_{C,F}$ = 282 Hz), 123.66 (q, $J_{C,F}$ = 271 Hz), 123.8 (q, $J_{C,F}$ = 271 Hz), 124.8 (q, $J_{C,F}$ = 287 Hz), 125.4 (q, $J_{C,F}$ = 4 Hz), 125.8 (q, $J_{C,F}$ = 4 Hz), 126.9, 128.8, 131.3 (q, $J_{C,F}$ = 33 Hz), 131.8 (q, $J_{C,F}$ = 32 Hz), 137.6, 141.5, 202.6, 202.8. HRMS (ESI): calcd for $C_{16}H_{15}O_2F_6$ ([M - H]$^-$) 353.0971, found 353.0990. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, minor enantiomer) = 13.4 min, t_R (major diastereomer, major enantiomer) = 14.1 min. t_R (minor diastereomer) = 15.8 min and 20.4 min.

2-(4-Bromophenyl)-6-propyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21e)

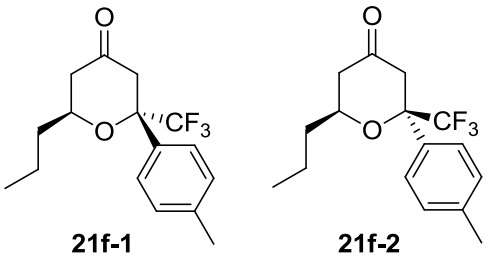


Synthesized by the general procedure; 24 h, 44.0 mg (59%), dr **21e-1**:**21e-2** = 1:2.4, er of **21e-2** 97:3.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J = 7.2 Hz, 3H × 2.4/3.4, $C\underline{H}_3$), 1.01 (t, J = 7.1 Hz, 3H × 1/3.4, $C\underline{H}_3$), 1.35-1.81 (m, 4H × 3.4/3.4, $C\underline{H}_2C\underline{H}_2CH_3$), 2.17-2.29 (m, 1H, $CHC\underline{H}HC{=}O$), 2.39 (dd, J = 11.5 Hz, 14.8 Hz, 1H × 2.4/3.4, $CHC\underline{H}HC{=}O$), 2.49 (dd, J = 2.3 Hz, 16.4 Hz, 1H × 1/3.4, $CHC\underline{H}HC{=}O$), 2.85 (d, J = 15.6 Hz, 1H × 1/3.4, $CF_3CC\underline{H}HC{=}O$), 3.01 (d, J = 14.8 Hz, 1H × 2.4/3.4, $CF_3CC\underline{H}HC{=}O$), 3.19 (d, J = 14.8 Hz, 1H × 2.4/3.4, $CF_3CC\underline{H}HC{=}O$), 3.28 (d, J = 15.6 Hz, 1H × 1/3.4, $CF_3CC\underline{H}HC{=}O$), 3.65-3.71 (m, 1H × 2.4/3.4, $OC\underline{H}$), 4.39-4.43 (m, 1H × 1/3.4, $OC\underline{H}$), 7.35-7.58 (m, 4H, $Ar\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.4, 38.1, 38.4, 42.7, 43.8, 45.7, 46.8, 72.1, 73.3, 78.5 (q, $J_{C,F}$ =

28 Hz), 80.6 (q, $J_{C,F}$ = 30 Hz), 123.5, 123.6 (q, $J_{C,F}$ = 282 Hz), 124.2, 124.8 (q, $J_{C,F}$ = 287 Hz), 128.1, 130.1, 131.6, 132.1, 132.5, 136.8, 202.9, 203.1. HRMS (ESI): calcd for $C_{15}H_{15}O_2BrF_3$ ($[M - H]^-$) 363.0202, found 363.0208. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 11.5 min, t_R (major diastereomer, minor enantiomer) = 12.6 min. t_R (minor diastereomer) = 18.2 min and 19.7 min.

6-Propyl-2-(p-tolyl)-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21f)

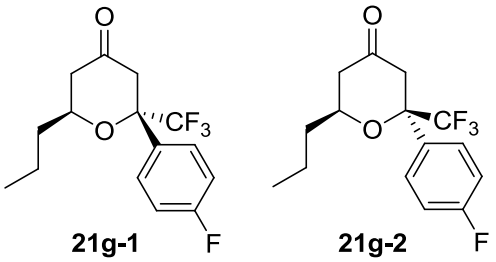


Synthesized by the general procedure; 72 h (**2** was not consumed), 17.6 mg (29%), dr **21f-1**:**21f-2** = 1:1.3, **21f-2** er 94:6.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H × 1.3/2.3, C$\underline{H}_3$), 1.01 (t, *J* = 7.2 Hz, 3H × 1/2.3, C$\underline{H}_3$), 1.36-1.82 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 2.18-2.26 (m, 1H, CHC$\underline{H}$HC=O), 2.32-2.39 (m, 1H×1.3/2.3, CHC$\underline{H}$HC=O), 2.36 (s, 3H, ArC$\underline{H}_3$), 2.47 (ddd, *J* = 0.8 Hz, 2.4 Hz, 16.4 Hz, 1H × 1/2.3, CHC$\underline{H}$HC=O), 2.89 (d, *J* = 15.6 Hz, 1H × 1/2.3, CF$_3$CC$\underline{H}$HC=O), 2.98 (dd, *J* = 0.8 Hz, 14.6 Hz, 1H × 1.3/2.3, CF$_3$CC$\underline{H}$HC=O), 3.25 (dd, *J* = 0.8 Hz, 14.6 Hz, 1H × 1.3/2.3, CF$_3$CC$\underline{H}$HC=O), 3.29 (dd, *J* = 0.8 Hz, 15.6 Hz, 1H × 1/2.3, CF$_3$CC$\underline{H}$HC=O), 3.67-3.74 (m, 1H × 1.3/2.3, OC$\underline{H}$), 4.37-4.42 (m, 1H × 1/2.3, OC$\underline{H}$), 7.18-7.23 (m, 2H, Ar$\underline{H}$), 7.36-7.44 (m, 2H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.4, 18.5, 21.0, 21.1, 38.2, 38.5, 42.9, 44.0, 45.8, 46.9, 71.7, 73.0, 78.7 (q, $J_{C,F}$ = 28 Hz), 80.7 (q, $J_{C,F}$ = 29 Hz), 123.9 (q, $J_{C,F}$ = 282 Hz), 125.2 (q, $J_{C,F}$ = 287 Hz), 126.2, 128.3, 129.0, 129.5, 130.2, 134.8, 139.0, 139.6, 203.65, 203.73. HRMS (ESI): calcd for $C_{16}H_{20}O_2F_3$ ($[M + H]^+$) 301.1410, found 301.1408. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99.5:0.5, 0.6

mL/min, λ = 220 nm): t_R (major diastereomer, minor enantiomer) = 13.3 min, t_R (major diastereomer, major enantiomer) = 13.9 min. t_R (minor diastereomer) = 15.3 min and 18.5 min.

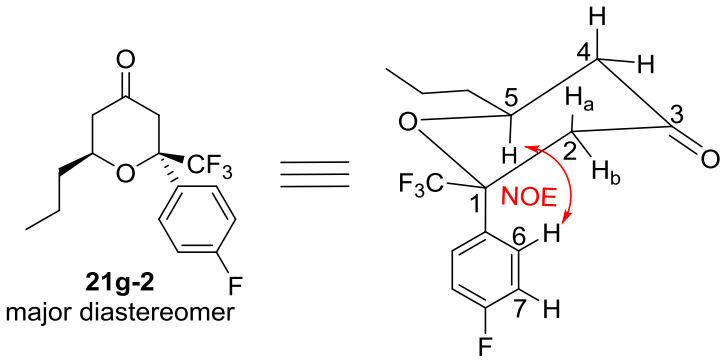
2-(4-Fluorophenyl)-6-propyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21g)



Synthesized by the general procedure; 26 h, 33.4 mg (55%), dr **21g-1**:**21g-2** = 1:2.2, **21g-2** er 96:4.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H × 2.2/3.2, C$\underline{H}_3$), 1.01 (t, *J* = 7.2 Hz, 3H × 1/3.2, C$\underline{H}_3$), 1.35-1.81 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 2.22 (dd, *J* = 11.6 Hz, 16.6 Hz, 1H × 1/3.2, CHC$\underline{H}$HC=O), 2.27 (ddd, *J* = 1.6 Hz, 2.8 Hz, 14.8 Hz, 1H × 2.2/3.2, CHC$\underline{H}$HC=O), 2.39 (ddd, *J* = 0.7 Hz, 11.4 Hz, 14.8 Hz, 1H × 2.2/3.2, CHC$\underline{H}$HC=O), 2.49 (ddd, *J* = 0.6 Hz, 2.8 Hz, 16.6 Hz, 1H × 1/3.2, CHC$\underline{H}$HC=O), 2.86 (d, *J* = 15.6 Hz, 1H × 1/3.2, CF$_3$CC$\underline{H}$HC=O), 3.02 (dd, *J* = 0.8 Hz, 14.6 Hz, 1H × 2.2/3.2, CF$_3$CC$\underline{H}$HC=O), 3.21 (dd, *J* = 0.7 Hz, 14.6 Hz, 1H × 2.2/3.2, CF$_3$CC$\underline{H}$HC=O), 3.30 (dd, *J* = 0.6 Hz, 15.6 Hz, 1H × 1/3.2, CF$_3$CC$\underline{H}$HC=O), 3.65-3.71 (m, 1H × 2.2/3.2, OC$\underline{H}$), 4.38-4.44 (m, 1H × 1/3.2, OC$\underline{H}$), 7.05-7.14 (m, 2H, Ar$\underline{H}$), 7.46-7.54 (m, 2H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.4, 38.1, 38.5, 42.9, 44.0, 45.8, 46.8, 72.0, 73.2, 78.5 (q, $J_{C,F}$ = 28 Hz), 80.5 (q, $J_{C,F}$ = 30 Hz), 115.3 (d, $J_{C,F}$ = 21 Hz), 115.9 (d, $J_{C,F}$ = 22 Hz), 123.7 (q, $J_{C,F}$ = 282 Hz), 125.0 (q, $J_{C,F}$ = 287 Hz), 128.3 (d, $J_{C,F}$ = 8 Hz), 129.2 (d, $J_{C,F}$ = 3 Hz), 130.4 (d, $J_{C,F}$ = 9 Hz), 133.5, 163.0 (d, $J_{C,F}$ = 247 Hz), 163.3 (d, $J_{C,F}$ = 248 Hz), 203.1, 203.3. HRMS (ESI): calcd for $C_{15}H_{15}O_2F_4$ ([M - H]$^-$) 303.1003, found 303.1013. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 10.6 min, t_R (major

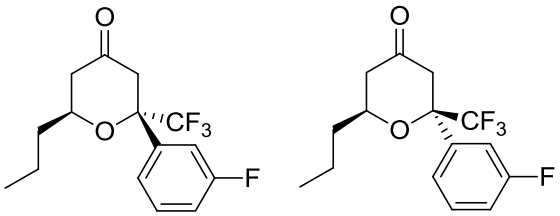
diastereomer, minor enantiomer) = 13.4 min. t_R (minor diastereomer) = 19.3 min and 20.9 min. The relative stereochemistry was determined by the NOESY experiment as shown below.



The inter-proton distance H5-H6 was estimated by the reported method.[127] The proton distance of the geminal protons H2a-H2b was used as the reference to be 1.75 Å.[127] Only F2-slices were usded to determine the NOE intensity.[127]

	Relative NOE Intensity	Proton distance[127]
H2a-H2b	49.84 (a_{ref})	1.75 Å (r_{ref})
H5-H6	2.16 (a_{5-6})	2.95 Å (r_{5-6})

2-(3-Fluorophenyl)-6-propyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21h)

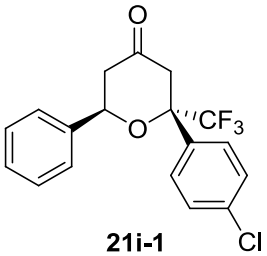


Synthesized by the general procedure; 24 h, 33.0 mg (54%), dr **21h-1**:**21h-2** = 1:2.2, **21h-2** er 95:5.

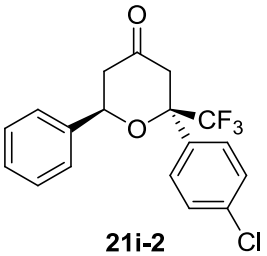
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.2 Hz, 3H × 2.2/3.2, C<u>H</u>$_3$), 1.02 (t, *J* = 7.0 Hz, 3H × 1/3.2, C<u>H</u>$_3$), 1.36-1.82 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 2.23 (dd, *J* = 11.6 Hz, 16.6 Hz, 1H × 1/3.2, CHC<u>H</u>HC=O), 2.28 (ddd, *J* = 1.6 Hz, 2.7 Hz, 15.0 Hz, 1H × 2.2/3.2, CHC<u>H</u>HC=O), 2.40 (ddd, *J* = 0.6 Hz, 11.5 Hz, 15.0 Hz, 1H × 2.2/3.2, CHC<u>H</u>HC=O), 2.50

(ddd, *J* = 0.7 Hz, 2.7 Hz, 16.6 Hz, 1H × 1/3.2, CHC<u>H</u>HC=O), 2.86 (d, *J* = 15.6 Hz, 1H × 1/3.2, CF_3CC<u>H</u>HC=O), 3.02 (dd, *J* = 0.8 Hz, 14.8 Hz, 1H × 2.2/3.2, CF_3CC<u>H</u>HC=O), 3.10 (dd, *J* = 0.6 Hz, 14.8 Hz, 1H × 2.2/3.2, CF_3CC<u>H</u>HC=O), 3.29 (dd, *J* = 0.7 Hz, 15.6 Hz, 1H × 1/3.2, CF_3CC<u>H</u>HC=O), 3.69-3.75 (m, 1H × 2.2/3.2, OC<u>H</u>), 4.39-4.45 (m, 1H × 1/3.2, OC<u>H</u>), 7.05-7.42 (m, 4H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 18.38, 18.44, 38.1, 38.4, 42.8, 44.0, 45.8, 46.7, 72.2, 73.3, 78.4 (q, $J_{C,F}$ = 28 Hz), 80.4 (q, $J_{C,F}$ = 30 Hz), 114.0 (d, $J_{C,F}$ = 24 Hz), 115.6 (d, $J_{C,F}$ = 23 Hz), 116.1 (d, $J_{C,F}$ = 21 Hz), 116.7 (d, $J_{C,F}$ = 21 Hz), 121.9, 123.6 (q, $J_{C,F}$ = 282 Hz), 124.0 (d, $J_{C,F}$ = 3 Hz), 124.9 (q, $J_{C,F}$ = 287 Hz), 129.9 (d, $J_{C,F}$ = 8 Hz), 130.4 (d, $J_{C,F}$ = 8 Hz), 136.2 (d, $J_{C,F}$ = 7 Hz), 140.2 (d, $J_{C,F}$ = 7 Hz), 162.6 (d, $J_{C,F}$ = 245 Hz), 163.0 (d, $J_{C,F}$ = 246 Hz), 202.9, 203.1. HRMS (ESI): calcd for $C_{15}H_{17}O_2F_4$ ($[M + H]^+$) 305.1159, found 305.1158. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 14.3 min, t_R (major diastereomer, minor enantiomer) = 16.7 min. t_R (minor diastereomer) = 19.3 min and 25.2 min.

2-(4-Chlorophenyl)-6-phenyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21i)



21i-1



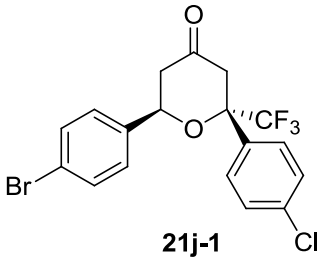
21i-2

Synthesized by the general procedure; 24 h, 58.1 mg (82%), dr **21i-1**:**21i-2** = 1:4.2, **21i-2** er 91:9.

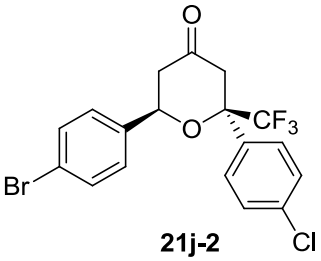
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (ddd, *J* = 1.6 Hz, 3.2 Hz, 15.2 Hz, 1H × 4.2/5.2, CHC<u>H</u>HC=O), 2.59 (dd, *J* = 11.6 Hz, 16.8 Hz, 1H × 1/5.2, CHC<u>H</u>HC=O), 2.72 (ddd, *J* = 0.7 Hz, 11.6 Hz, 15.2 Hz, 1H × 4.2/5.2, CHC<u>H</u>HC=O), 2.76 (ddd, *J* = 0.6 Hz, 2.8 Hz, 16.8 Hz, 1H × 1/5.2, CHC<u>H</u>HC=O), 3.02 (d, *J* = 15.6 Hz, 1H × 1/5.2, CF_3CC<u>H</u>HC=O), 3.18 (dd, *J* = 0.7 Hz, 14.7 Hz, 1H × 4.2/5.2, CF_3CC<u>H</u>HC=O), 3.32 (dd, *J* = 0.6 Hz, 14.7 Hz, 1H × 4.2/5.2,

$CF_3CC\underline{H}HC=O$), 3.44 (dd, J = 0.6 Hz, 15.6 Hz, 1H × 1/5.2, $CF_3CC\underline{H}HC=O$), 4.74 (dd, J = 3.2 Hz, 11.6 Hz, 1H × 4.2/5.2, $OC\underline{H}$), 5.46 (dm, J = 11.6 Hz, 1H × 1/5.2, $OC\underline{H}$), 7.35-7.57 (m, 9H, $Ar\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.7, 43.7, 47.3, 48.6, 73.9, 75.5, 79.0 (q, $J_{C,F}$ = 29 Hz), 80.9 (q, $J_{C,F}$ = 30 Hz), 123.6 (q, $J_{C,F}$ = 282 Hz), 124.9 (q, $J_{C,F}$ = 287 Hz), 125.7, 126.0, 127.9, 128.6, 128.7, 128.8, 128.9, 129.1, 129.3, 129.8, 131.47, 131.55, 135.5, 136.2, 139.1, 139.5, 202.0, 202.2. HRMS (ESI): calcd for $C_{18}H_{15}O_2ClF_3$ ($[M + H]^+$) 355.0707, found 355.0700. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 22.0 min, t_R (major diastereomer, minor enantiomer) = 25.9 min. t_R (minor diastereomer) = 35.6 min and 47.2 min.

6-(4-Bromophenyl)-2-(4-chlorophenyl)-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21j)



21j-1



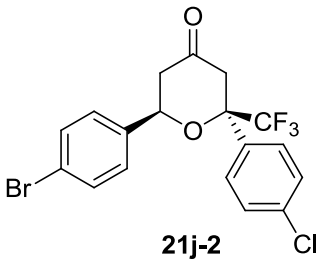
21j-2

Synthesized by the general procedure; 24 h, 54.2 mg (63%), dr **21j-1**:**21j-2** = 1:4.1, **21j-2** er 94:6.

Colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (ddd, J = 1.6 Hz, 3.2 Hz, 15.0 Hz, 1H × 4.1/5.1, $CHC\underline{H}HC=O$), 2.46 (dd, J = 11.6 Hz, 16.4 Hz, 1H × 1/5.1, $CHC\underline{H}HC=O$), 2.58 (ddd, J = 0.8 Hz, 11.6 Hz, 15.0 Hz, 1H × 4.1/5.1, $CHC\underline{H}HC=O$), 2.66 (ddd, J = 0.8 Hz, 2.8 Hz, 16.4 Hz, 1H × 1/5.1, $CHC\underline{H}HC=O$), 2.93 (d, J = 15.6 Hz, 1H × 1/5.1, $CF_3CC\underline{H}HC=O$), 3.09 (dd, J = 0.8 Hz, 14.8 Hz, 1H × 4.1/5.1, $CF_3CC\underline{H}HC=O$), 3.24 (dd, J = 0.8 Hz, 14.8 Hz, 1H × 4.1/5.1, $CF_3CC\underline{H}HC=O$), 3.35 (dd, J = 0.8 Hz, 15.6 Hz, 1H × 1/5.1, $CF_3CC\underline{H}HC=O$), 4.61 (dd, J = 3.2 Hz, 11.6 Hz, 1H × 4.1/5.1, $OC\underline{H}$), 5.34 (dd, J = 2.8 Hz, 11.6 Hz, 1H × 1/5.1, $OC\underline{H}$), 7.17-7.52 (m, 8H, $Ar\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.7, 43.6, 47.1, 48.4, 73.3, 74.9, 79.1 (q,

$J_{C,F}$ = 29 Hz), 81.0 (q, $J_{C,F}$ = 30 Hz), 122.55, 122.64, 123.5 (q, $J_{C,F}$ = 282 Hz), 124.8 (q, $J_{C,F}$ = 287 Hz), 127.3, 127.6, 127.8, 128.8, 129.4, 129.7, 131.2, 132.0, 132.1, 135.6, 136.3, 138.1, 138.5, 201.4, 201.7. HRMS (ESI): calcd for $C_{18}H_{14}O_2BrClF_3$ ($[M + H]^+$) 432.9812, found 432.9797. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, minor enantiomer) = 30.3 min, t_R (major diastereomer, major enantiomer) = 34.1 min.

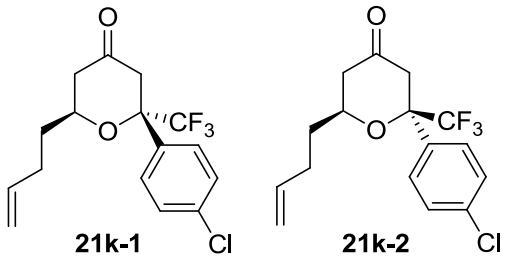
A 1 mmol-scale reaction to afford 21j-2. To a solution of 4-(4-bromophenyl)but-3-en-2-one (**20j**) (1.05g, 5.0 mmol) and 4-chlorophenyl trifluomethyl ketone (**10b**) (208.6 mg, 1.0 mmol) in toluene (super dehydrated, 2.0 mL), (2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)pyrrolidine-2-carboxylic acid (**XXI**) (37.0 mg, 0.1 mmol,) and DABCO (**XV**) (22.4 mg, 0.2 mmol) were added at room temperature (25 ^oC), and the mixture was stirred at the same temperature for 24 h. The dr was determined by ^1H NMR analysis before purification to be 1:4.1 (**21j-1**:**21j-2**). The mixture was purified by flash column chromatography (hexane/CH_2Cl_2 = 3:1 to 2:1) to give **21j-2** (255.0 mg, 61%, er 92:8).



21j-2

Colorless gum; er 92:8. ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (ddd, *J* = 1.6 Hz, 3.2 Hz, 15.0 Hz, 1H, CHC<u>H</u>HC=O), 2.58 (ddd, *J* = 0.8 Hz, 11.6 Hz, 15.0 Hz, 1H, CHC<u>H</u>HC=O), 3.08 (dd, *J* = 0.8 Hz, 14.6 Hz, 1H, CF_3CC<u>H</u>HC=O), 3.24 (dd, *J* = 0.8 Hz, 14.6 Hz, 1H, CF_3CC<u>H</u>HC=O), 4.61 (dd, *J* = 3.2 Hz, 11.6 Hz, 1H, OC<u>H</u>), 7.17-7.20 (m, 2H, Ar<u>H</u>), 7.33-7.39 (m, 4H, Ar<u>H</u>), 7.45-7.48 (m, 2H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.7, 48.4, 73.3, 81.0 (q, $J_{C,F}$ = 30 Hz), 122.6, 123.6 (q, $J_{C,F}$ = 282 Hz), 127.3, 129.4, 129.7, 131.3, 132.0, 136.3, 138.2, 201.5.

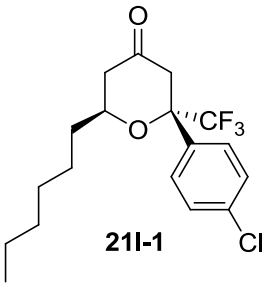
6-(But-3-en-1-yl)-2-(4-chlorophenyl)-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21k)



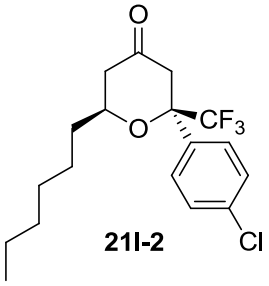
Synthesized by the general procedure; 29 h, 31.2 mg (47%), dr **21k-1**:**21k-2** = 1:1.7, **21k-2** er 96:4.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60-1.94 (m, 2H, $C\underline{H_2}CH_2CH=CH_2$), 2.11-2.52 (m, 4H, $CH_2C\underline{H_2}CH=CH_2$, $CHC\underline{H_2}C=O$), 2.86 (d, J = 15.6 Hz, 1H × 1/2.7, $CF_3CC\underline{H}HC=O$), 3.02 (dd, J = 0.5 Hz, 14.6 Hz, 1H × 1.7/2.7, $CF_3CC\underline{H}HC=O$), 3.20 (d, J = 14.6 Hz, 1H × 1.7/2.7, $CF_3CC\underline{H}HC=O$), 3.29 (d, J = 15.6 Hz, 1H × 1/2.7, $CF_3CC\underline{H}HC=O$), 3.67-3.37 (m, 1H × 1.7/2.7, $OC\underline{H}$), 4.40-4.46 (m, 1H × 1/2.7, $OC\underline{H}$), 4.95-5.14 (m, 2H, $CH_2CH=C\underline{H_2}$), 5.74-5.91 (m, 1H, $CH_2C\underline{H}=CH_2$), 7.36-7.51 (m, 4H, $Ar\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2, 29.3, 35.2, 35.5, 42.7, 43.8, 45.7, 46.7, 71.7, 72.8, 78.5 (q, $J_{C,F}$ = 28 Hz), 80.6 (q, $J_{C,F}$ = 30 Hz), 115.5, 115.7, 123.6 (q, $J_{C,F}$ = 282 Hz), 124.9 (q, $J_{C,F}$ = 287 Hz), 127.8, 128.6, 129.1, 129.8, 131.8, 135.3, 136.0, 137.2, 137.3, 202.6, 202.8. HRMS (ESI): calcd for $C_{16}H_{17}O_2ClF_3$ ($[M + H]^+$) 333.0864, found 333.0858. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, major enantiomer) = 16.6 min, t_R (major diastereomer, minor enantiomer) = 19.9 min. t_R (minor diastereomer) = 29.5 min and 55.9 min.

2-(4-Chlorophenyl)-6-hexyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one (21l)



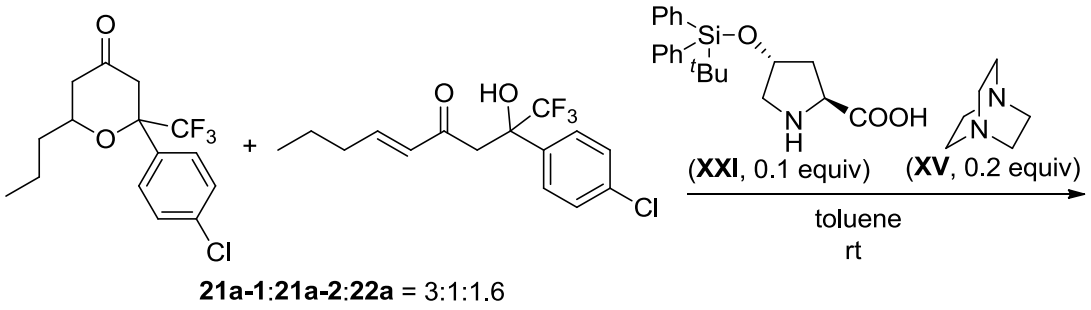
21l-1



21l-2

Synthesized by the general procedure; 26 h, 39.3 (51%), dr **21l-1**:**21l-2** = 1:2.3, **21l-2** er 95:5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86-1.80 (m, 13H, ($C\underline{H}_2$)$_5C\underline{H}_3$), 2.17-2.29 (m, 1H, CHC<u>H</u>HC=O), 2.38 (dd, *J* = 11.6 Hz, 14.9 Hz, 1H × 2.3/3.3, CHC<u>H</u>HC=O), 2.49 (dd, *J* = 2.8 Hz, 16.6 Hz, 1H × 1/3.3, CHC<u>H</u>HC=O), 2.85 (d, *J* = 15.6 Hz, 1H × 1/3.3, CF_3CC<u>H</u>HC=O), 3.01 (dd, *J* = 0.6 Hz, 14.6 Hz, 1H × 2.3/3.3, CF_3CC<u>H</u>HC=O), 3.19 (d, *J* = 14.6 Hz, 1H × 2.3/3.3, CF_3CC<u>H</u>HC=O), 3.29 (d, *J* = 15.6 Hz, 1H × 1/3.3, CF_3CC<u>H</u>HC=O), 3.63-3.70 (m, 1H × 2.3/3.3, OC<u>H</u>), 4.37-4.41 (m, 1H × 1/3.3, OC<u>H</u>), 7.33-7.51 (m, 4H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ =14.0, 22.6, 25.05, 25.06, 29.0, 29.1, 31.66, 31.68, 36.0, 36.3, 42.7, 43.8, 45.7, 46.8, 72.3, 73.6, 78.5 (q, $J_{C,F}$ = 28 Hz), 80.5 (q, $J_{C,F}$ = 30 Hz), 123.6 (q, $J_{C,F}$ = 282 Hz), 124.9 (q, $J_{C,F}$ = 287 Hz), 127.8, 128.6, 129.1, 129.8, 132.0, 135.9, 202.9, 203.1. HRMS (ESI): calcd for $C_{18}H_{23}O_2ClF_3$ ($[M + H]^+$) 363.1333, found 363.1326. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major diastereomer, minor enantiomer) = 10.8 min, t_R (major diastereomer, major enantiomer) = 11.5 min. t_R (minor diastereomer) = 12.9 min and 17.1 min.

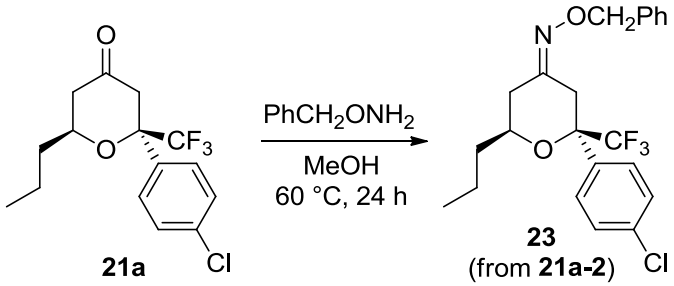
Analysis of the Stability of the Products under the Catalytic Conditions



21a-1:**21a-2**:**22a** = 3:1:1.6

To a mixture of racemic **21a** and racemic **22a** (**21a-1**:**21a-2**:**22a** = 3:1:1.6, 44.8 mg, **21a** 0.10 mmol, **22a** 0.04 mmol) in toluene (super dehydrated, 0.2 mL), proline derivative **XXI** (0.01 mmol, 3.7 mg) and DABCO (**XV**) (0.02 mmol, 2.3 mg) were added at room temperature (25 ^{o}C). At 30 min, 20 h, 44 h, and 115 h, an aliquot was taken from the mixture, diluted with $CDCl_3$, and analyzed by ^{1}H NMR. No decomposition of the compounds and no changes in the ratios were detected.

Transformations of the Oxa-Hetero-Diels-Alder Reaction Products



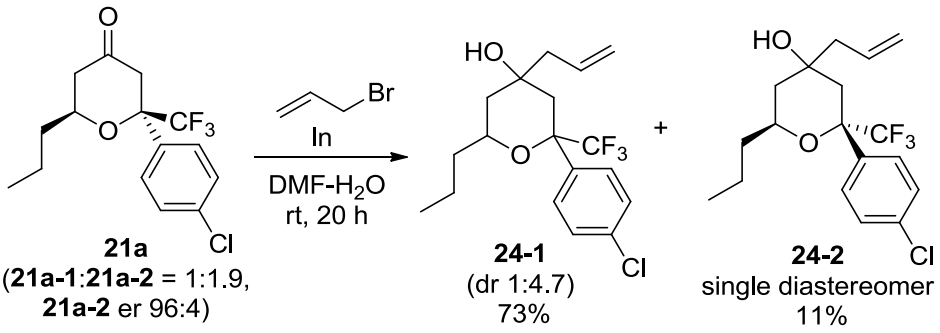
21a (**21a-1**:**21a-2** = 1:1.9, **21a-2** er 96:4)

23 (from **21a-2**) 61%

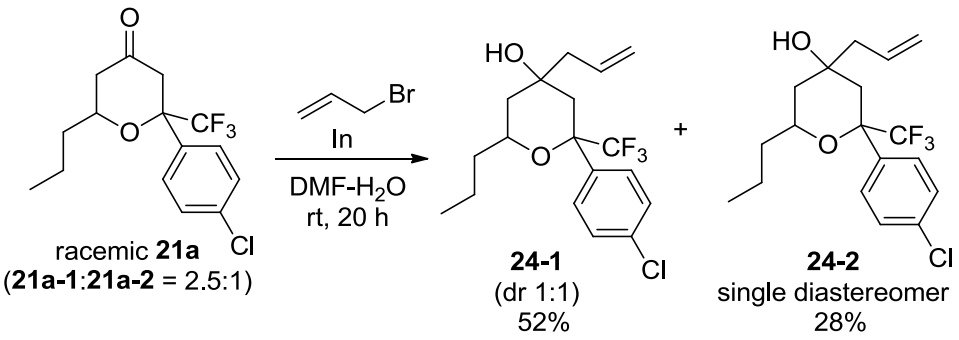
Transformation of 21a to 23. To a solution of **21a** (**21a-1**:**21a-2** = 1:1.9, **21a-2** er 96:4, 32.1 mg, 0.10 mmol) in MeOH (1.0 mL), $PhCH_2ONH_2$ (12.3 mg, 0.10 mmol) was added at room temperature (25 ^{o}C). The mixture was stirred at 60 ^{o}C for 24 h (consumption of **21a** was analyzed by TLC). After being cooled to room temperature, the mixture was purified by flash column chromatography (hexane/EtOAc = 15:1 to 10:1) to give **23** (major diastereomer from **21a-2**, 25.9 mg, 61%).

2-(4-Chlorophenyl)-6-propyl-2-(trifluoromethyl)dihydro-2*H*-pyran-4(3*H*)-one *O*-benzyl oxime (23)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.2 Hz, 3H, C$\underline{H}_3$), 1.34-1.73 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 1.93 (dd, *J* = 11.6 Hz, 15.2 Hz, 1H, CHC$\underline{H}$HC=N), 2.87 (d, *J* = 14.8 Hz, 1H, CF_3CC$\underline{H}$HC=N), 3.00 (ddd, *J* = 0.4 Hz, 2.8 Hz, 15.2 Hz, 1H, CHC$\underline{H}$HC=N), 3.11 (d, *J* = 14.8 Hz, 1H, CF_3CC$\underline{H}$HC=N), 3.38-3.45 (m, 1H, OC$\underline{H}$), 5.05 (s, 2H, C$\underline{H}_2$Ph), 7.21-7.41 (m, 9H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.6, 31.5, 32.6, 38.1, 70.6, 75.6, 79.4 (q, $J_{C,F}$ = 29 Hz), 123.9 (q, $J_{C,F}$ = 282 Hz), 127.71, 127.73, 128.3, 128.7, 130.1, 132.4, 135.2, 137.8, 152.2. HRMS (ESI): calcd for $C_{22}H_{24}O_2NClF_3$ ([M + H]$^+$) 426.1430, found 426.1442.



Transformation of 21a to 24. A mixture of **21a** (**21a-1**:**21a-2** = 1:1.9, **21a-2** er 96:4, 32.1 mg, 0.10 mmol), allylbromide (86 μL, 1.0 mmol), and In (15.3 mg, 0.13 mmol) in DMF (0.8 mL)-H_2O (0.1 mL) was stirred at room temperature (25 ^{o}C) for 20 h. The mixture was added to aqueous saturated NH_4Cl and extracted with CH_2Cl_2 (x 3). Organic layers were combined, washed with brine, dried with $MgSO_4$, concentrated, and purified by flash column chromatography (hexane/EtOAc = 20:1 to 10:1) to give **24-1** (26.4 mg, 73%, a mixture of two diastereomers, **24-1a** from **21a-1**, **24-1b** from **21a-2**, **24-1a**:**24-1b** = 1:4.7) and **24-2** (from **21a-1**, 4.1 mg, 11%, single diastereomer).



A mixture of racemic **21a** (**21a-1**:**21a-2** = 2.5:1, 32.1 mg, 0.10 mmol), allylbromide (86 μL, 1.0 mmol), and In (15.3 mg, 0.13 mmol) in DMF (0.8 mL)-H_2O (0.1 mL) was stirred at room temperature (25 ^oC) for 20 h. The mixture was added to aqueous saturated NH_4Cl and extracted with CH_2Cl_2 (x 3). Organic layers were combined, washed with brine, dried with $MgSO_4$, concentrated, and purified by flash column chromatography (hexane/EtOAc = 20:1 to 10:1) to give **24-1** (18.8 mg, 52%, a mixture of two diastereomers, **24-1a** from **21a-1**, **24-1b** from **21a-2**, **24-1a**:**24-1b** = 1:1) and **24-2** (from **21a-1**, 10.1 mg, 28%, single diastereomer).

Compound 24-1

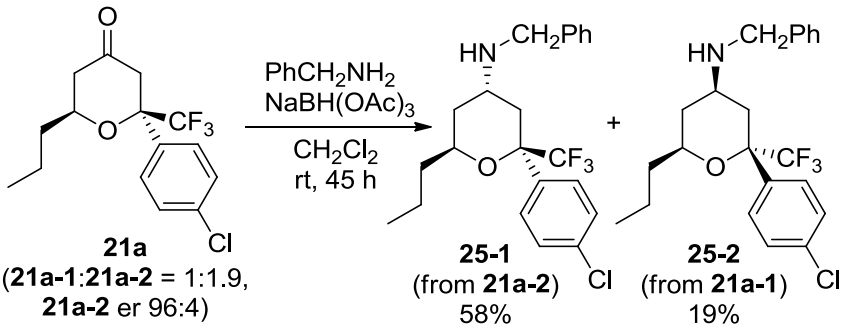
R_f = 0.38 (hexane/ EtOAc = 10:1).

Colorless oil. **24-1a**:**24-1b** = 1:4.7. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95-1.00 (m, 3H, C$\underline{H}_3$), 1.39-1.72 {m, (4H, C$\underline{H}_2$C$\underline{H}_2$CH$_3$), (2H × 4.7/5.7, OCHC$\underline{H}_2$COH), (1H × 1/5.7, OCHC$\underline{H}$HCOH)}, 1.90 (dd, *J* = 3.4 Hz, 14.5 Hz, 1H × 1/5.7, OCHC$\underline{H}$HCOH), 1.99 (d, *J* = 14.4 Hz, 1H × 4.7/5.7, CCF$_3$C$\underline{H}$HCOH), 2.22-2.32 (m, 2H, C$\underline{H}_2$CH=CH$_2$), 2.37 (s, 2H × 1/5.7, CCF$_3$C$\underline{H}_2$COH), 2.49 (d, *J* = 14.4 Hz, 1H × 4.7/5.7, CCF$_3$C$\underline{H}$HCOH), 3.75-3.81 (m, 1H × 4.7/5.7, OC$\underline{H}$), 3.92-3.99 (m, 1H × 1/5.7, OC$\underline{H}$), 5.13-5.26 (m, 2H, CH=C$\underline{H}_2$), 5.78-5.92 (m, 1H, C$\underline{H}$=CH$_2$), 7.34-7.39 (m, 2H, Ar$\underline{H}$), 7.48 (d, *J* = 8.6 Hz, 2H × 4.7/5.7, Ar$\underline{H}$), 7.57 (d, *J* = 8.4 Hz, 2H × 1/5.7, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): * donates **24-1b**, δ 13.8, *14.2, 18.5, *18.7, *35.6, 37.3, *38.0, 38.4, *41.9, 43.2, 47.9, *48.6, *67.7, *69.2, 69.5, 71.3, 77.0 (q, $J_{C,F}$ = 28 Hz), *78.1 (q, $J_{C,F}$ = 28 Hz), 119.8, *120.4, *124.4 (q, $J_{C,F}$ = 282 Hz), 125.3 (q, $J_{C,F}$ = 286 Hz), 128.2, *128.3, 128.4, *129.7, *131.8, 132.3, *133.8, 134.5, *134.7, 137.9.

Compound 24-2

R_f = 0.31 (hexane/ EtOAc = 10:1).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.2 Hz, 3H, C<u>H</u>$_3$), 1.35 (dd, *J* = 11.8 Hz, 14.1 Hz, 1H, OCHC<u>H</u>HCOH), 1.46-1.74 (m, 5H, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$, OCHC<u>H</u>HCOH), 1.93-2.04 (m, 2H, C<u>H</u>$_2$CH=CH$_2$), 2.08 (dd, *J* = 0.6 Hz, 14.5 Hz, 1H, CCF$_3$C<u>H</u>HCOH), 2.54 (dd, *J* = 0.9 Hz, 14.5 Hz, 1H, CCF$_3$C<u>H</u>HCOH), 4.29-4.33 (m, 1H, OC<u>H</u>), 5.05-5.11 (m, 1H, CH=C<u>H</u>H), 5.19-5.22 (m, 1H, CH=C<u>H</u>H), 5.72-5.83 (m, 1H, C<u>H</u>=CH$_2$), 7.32-7.35 (m, 2H, Ar<u>H</u>), 7.50 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 18.6, 38.2, 39.4, 42.5, 48.3, 68.4, 70.0, 76.2 (q, $J_{C,F}$ = 28 Hz), 120.6, 125.5 (q, $J_{C,F}$ = 287 Hz), 127.7, 128.2, 132.0, 134.3 ,139.1.



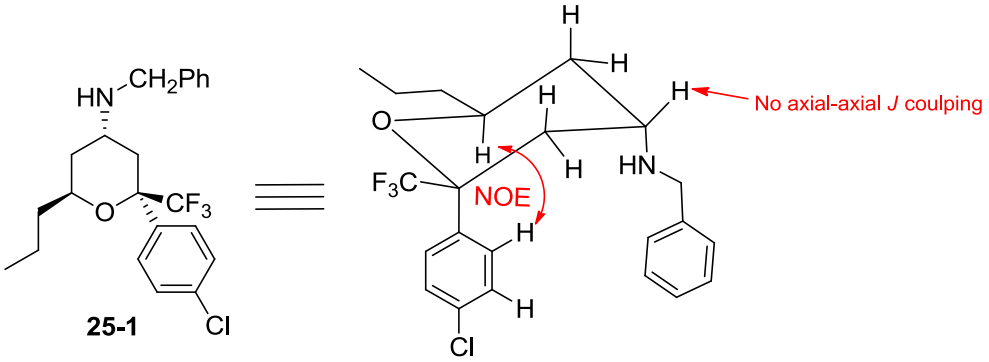
Transformation of 21a to 25. To a solution of **21a** (**21a-1**:**21a-2** = 1:1.9, **21a-2** er 96:4, 32.1 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL), benzylamine (32.7 μL, 0.30 mmol) and $NaBH(OAc)_3$ (64 mg, 0.30 mmol) were added at room temperature (25 ^{o}C), and the mixture was stirred at the same temperature for 45 h (consumption of **21a** was analyzed by TLC). After addition of aqueous NaOH (1 N, 0.6 mL), the mixture was extracted with CH_2Cl_2 (x 3). Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc = 20:1 to 6:1) gave **25-1** (from **21a-2**, 23.9 mg, 58%, single diastereomer, er 95:5) and **21-2** (from **21a-1**, 7.8 mg, 19%, single diastereomer).

Compound 25-1

R_f = 0.29 (hexane/ EtOAc = 10:1).

Colorless oil. $[\alpha]_D^{24}$ +31.7 (c = 1.93, $CHCl_3$, er 95:5 determined by the HPLC analysis). ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.2 Hz, 3H, CH_3), 1.31-1.72 (m, 6H, $CH_2CH_2CH_3$, $CH_2CH_2CH_3$, $CHCH_2CHNH$), 2.33-2.36 (m, 1H, CCF_3CHHCH), 2.45 (dd, *J* = 5.2 Hz, 14.4 Hz, 1H, CCF_3CHHCH), 3.23-3.26 (m, 1H, $CHNHCH_2Ph$), 3.67 (s, 2H, CH_2Ph), 3.74-3.81 (m, 1H, OCH), 7.06-7.07 (m, 2H, ArH), 7.22-7.38 (m, 5H, ArH), 7.49 (d, *J* = 8.8 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 18.6, 30.6, 35.1, 38.4, 48.8, 50.9, 67.2, 77.6 (q, $J_{C,F}$ = 28 Hz), 124.6 (q, $J_{C,F}$ = 282 Hz), 127.2, 127.8, 128.4, 128.9, 134.6 ,135.4. HRMS (ESI) calcd for $C_{22}H_{26}ONClF_3$ ($[M + H]^+$) 412.1650, found 412.1644. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major enantiomer) = 8.0 min, t_R (minor enantiomer) = 12.1 min.

Relative stereochemistry of **25-1** was determined by ^1H NMR and NOESY experiments as shown below.



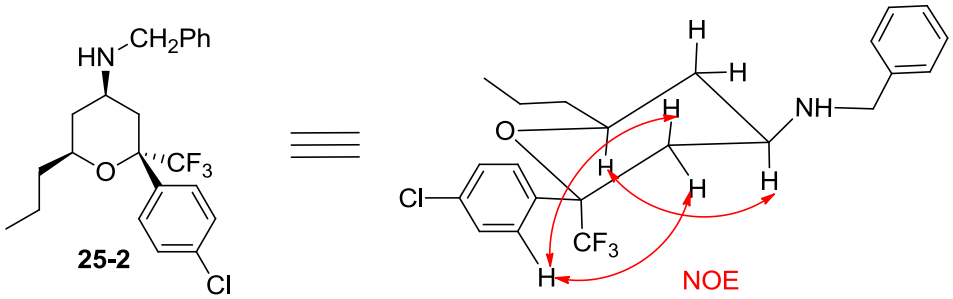
Compound 25-2

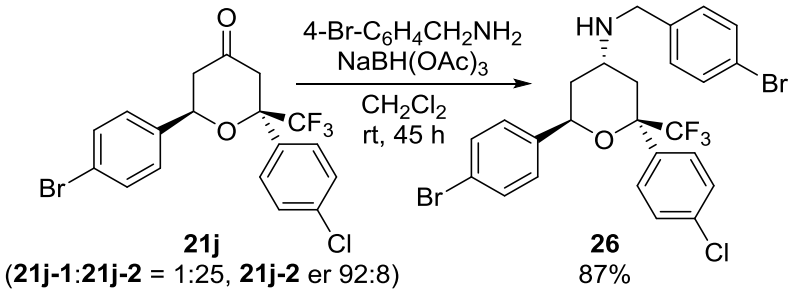
R_f = 0.24 (hexane/ EtOAc = 10:1).

Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H, CH_3), 1.06 (dt, *J* = 12.8 Hz, 11.6 Hz, 1H, $CHCHHCHCHNHBn$), 1.43-1.69 (m, 5H, $CH_2CH_2CH_3$, $CF_3CHHCHCHNH$), 2.01-2.06 (m, 1H, $CHCHHCH$), 2.87 (ddd, *J* = 1.6 Hz, 4.4 Hz, 13.8 Hz, 1H, CCF_3CHHCH),

3.19-3.24 (m, 1H, CHNH), 3.86 (d, J = 15.5 Hz, 1H, CHHPh), 3.89 (d, J = 15.5 Hz, 1H, CHHPh), 4.00-4.05 (m, 1H, OCH), 7.27-7.35 (m, 7H, ArH), 7.49 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 18.6, 37.4, 37.6, 38.8, 50.0, 50.6, 73.0, 76.7 (q, $J_{C,F}$ = 27 Hz), 125.9 (q, $J_{C,F}$ = 290 Hz), 127.3, 127.6, 128.0, 128.2, 128.6, 134.3, 139.0. HRMS (ESI) calcd for $C_{22}H_{26}ONClF_3$ ($[M + H]^+$) 412.1650, found 412.1637.

Relative stereochemistry of **25-2** was determined by ^{1}H NMR and NOESY experiments as shown below.





Transformation of 21j to 26. To a solution of **21j** (**21j-1:21j-2** = 1:25, **21j-2** er 92:8, 70.0 mg, 0.161 mmol) in CH_2Cl_2 (2.5 mL), 4-bromobenzylamine (93.0 mg, 0.50 mmol) and $NaBH(OAc)_3$ (106.8 mg, 0.50 mmol) were added at room temperature (25 ^{o}C) and the mixture was stirred at the same temperature for 45 h (consumption of **21j** was analyzed by TLC). After addition of aqueous NaOH (1 N, 1.5 mL), the mixture was extracted with CH_2Cl_2 (x 3). Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc = 10:1) to give **26** (97.1 mg, 87%, er 92:8, single diastereomer).

***N*-(4-Bromobenzyl)-6-(4-bromophenyl)-2-(4-chlorophenyl)-2 (trifluoromethyl)tetrahydro-2*H*-pyran-4-amine (26)**

Colorless oil. $[\alpha]_D^{25}$ –23.4 (c = 2.70, $CHCl_3$, er 92:8 determined by the HPLC analysis). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78-1.88 (m, 2H, CHC$\underline{H}_2$CHNH), 2.39 (dd, *J* = 4.0 Hz, 14.4 Hz, 1H, CF_3CC$\underline{H}$HC=O), 2.57 (dd, *J* = 3.2 Hz, 14.4 Hz, 1H, CF_3CC$\underline{H}$HC=O), 3.34 (m 1H, C$\underline{H}$NH), 3.60 (d, *J* = 14.0 Hz, 1H, C$\underline{H}$HPh), 3.66 (d, *J* = 14.0 Hz, 1H, C$\underline{H}$HPh), 4.87 (dd, *J* = 3.6 Hz, 10.6 Hz, 1H, OC$\underline{H}$), 6.86 (d, *J* = 8.0 Hz, 2H Ar$\underline{H}$), 7.23 (d, *J* = 8.4 Hz, 2H Ar$\underline{H}$), 7.36-7.40 (m, 4H, Ar$\underline{H}$), 7.47-7.52 (m, 4H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 37.5, 49.4, 50.6, 68.5, 78.3 (q, $J_{C,F}$ = 28 Hz), 120.8, 121.6, 124.5 (q, $J_{C,F}$ = 282 Hz), 127.4, 128.6, 129.3, 131.4, 131.6, 134.79, 134.80, 138.9, 140.6. HRMS (ESI) calcd for $C_{25}H_{22}ONBr_2ClF_3$ ([M + H]$^+$) 601.9678, found 601.9703. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 99:1, 0.6 mL/min, λ = 220 nm): t_R (major enantiomer) = 18.6 min, t_R (minor enantiomer) = 23.0 min.

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