Improvement of thiourea-mediated organocatalytic reactions

Thesis by
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Abbreviations

Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bzl	benzoyl
cat	catalyst
CDC	cross-dehydrogenative coupling
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
ee	enantiomeric excess
eq	equivalent
ESI-TOF	electrospray ionization-time-of-flight
Et	ethyl
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethoxycarbonyl
GABA	4-aminobutanoic acid
Gly	glycine
Hex	hexane
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
*i*Pr	isopropyl
IR	infrared spectroscopy
LPPS	liquid-phase peptide synthesis
Me	methyl
MeCN	acetonitrile
mp	melting point
MS	mass spectrometry
N.D.	not detected
NMR	nuclear magnetic resonance

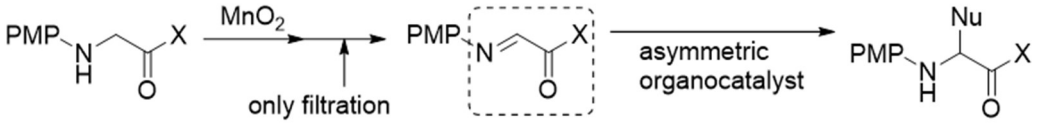
N.R.	no reaction
PEG	polyethylene glycol
PyBOP®	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PMP	*p*-methoxyphenyl
quant.	quantitative
rt.	room temperature
*t*Bu	*tert*-butyl
TCDI	1,1'-thiocarbonyldiimidazole
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Trt	triphenylmethyl
UV	ultraviolet

Contents

Preface

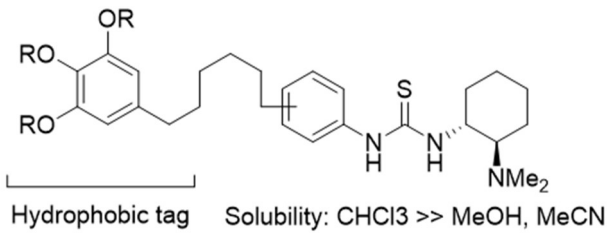
α-Amino acid moiety is often seen in biologically important compounds. In addition, this motif can be used as a chiral building block for the construction of more complex structures. Although the canonical α-amino acids are readily available from nature, most of the unnatural amino acids can be prepared only by derivatization of readily available chiral starting materials, or *de novo* synthesis in asymmetric manner. Among them, stereoselective Mannich reaction of nucleophiles and α-imino ester is a useful method for the synthesis of unnatural amino acids, because varieties of derivatives can be obtained simply by changing the nucleophile alone. However, the substrate of this reaction, α-imino ester, is unstable and difficult to synthesized. In chapter 1, A practical method for the synthesis of α-imino carboxylic acid derivatives including conventional α-imino esters, amides, and more electrophilic novel types of derivatives, and the application for the synthesis of unnatural amino acid in combination with the chiral thiourea organocatalyst are described.

Chapter 1



As described in Chapter 1, the chiral organocatalyst is a powerful tool for preparation of chiral compounds. However, they often present a problem of high catalyst loading. In this context, the development of a novel organocatalyst that can be recovered and reused after each asymmetric reaction is focused on. In Chapter 2, the synthesis of a novel recyclable organocatalyst that contains long alkyl chains as hydrophobic tag and evaluation of the utility of the novel catalyst for asymmetric reaction are described.

Chapter 2



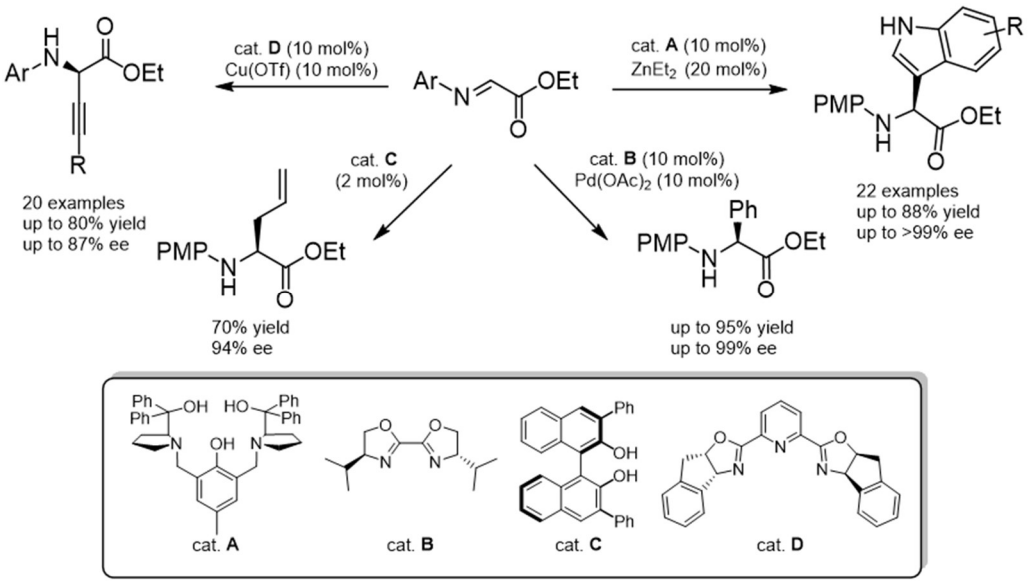
Chapter 1

A convenient method for preparation of α-imino carboxylic acid derivatives and synthesis of α-amino acid derivatives

1.1 Introduction

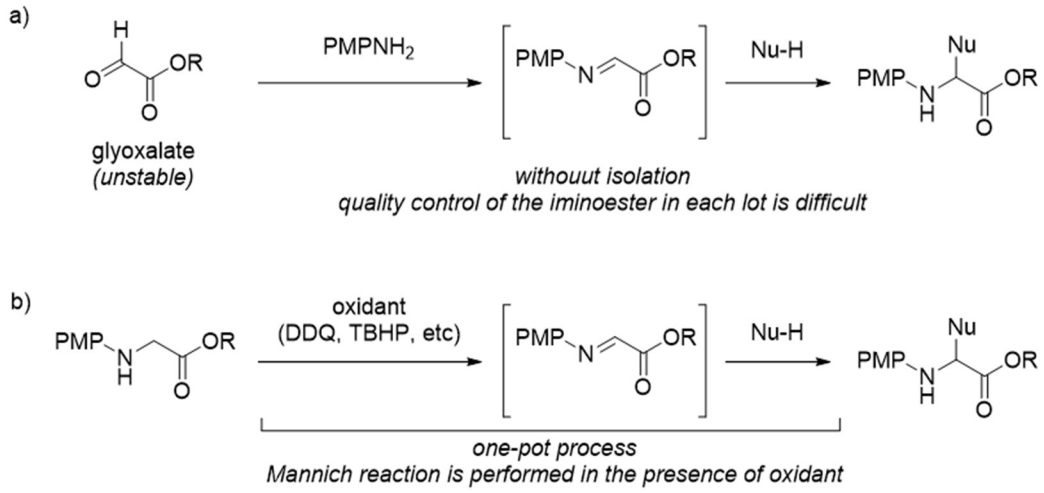
Unnatural α-amino acids are often seen in varieties of biologically active compounds,[1] including pharmaceuticals and have been used as indispensable chiral building blocks for the synthesis of such active compounds.[2] Additionally, increasing utility of unnatural amino acids as a key structural element has also been shown in fields of chemical biology and asymmetric transformation.[3] These contexts evoke much interest of synthetic chemists in asymmetric synthesis of the structural unit. [4] To enable easy access to diverse α-amino acids simply by changing the nucleophiles employed, Mannich-type reaction of α-imino ester has been widely used for the asymmetric synthesis.[5] α-Imino ester is a practical precursor of various α-amino acid derivatives and plays an important role in the synthesis of wide varieties of compounds including natural products and pharmaceuticals. Also, in the asymmetric Mannich reaction of α-imino esters, α-imino ester is used for the preparation of several unnatural amino acids having a wide range of biological activities (Scheme 1.1).

Scheme 1.1 Asymmetric synthesis of unnatural amino acids using α-imino ester as substrate.

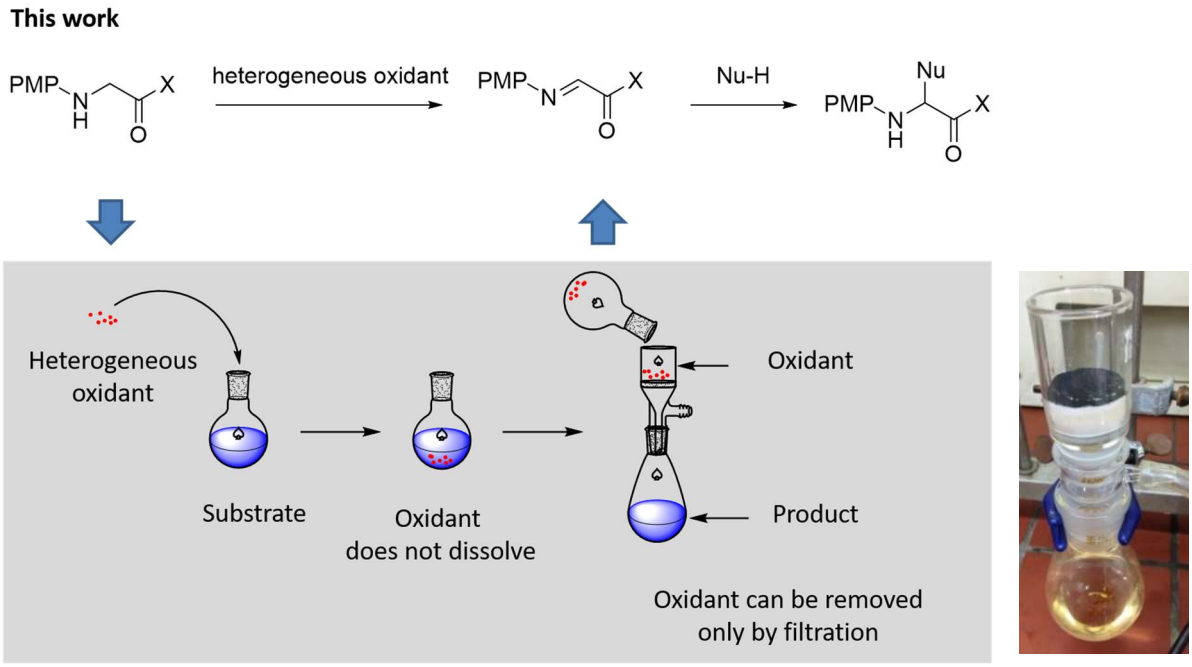


Conventionally α-imino esters were synthesized by condensation of glyoxalate and primary amine (Scheme 1.2 a). However, the unstable glyoxalate suffers easy hydrolysis or polymerization at room temperature. Additionally, high susceptibility of the resulting α-imino ester to silica gel has forced us to use the imino esters directly in the Mannich reaction without purification. Recently, research has been conducted on the synthesis of α-functionalized amino acids using cross-dehydrogenative coupling (CDC)[6] (Scheme 1.2 b). The CDC protocol features a one-pot, oxidative preparation and Mannich reaction of α-imino ester from glycinates with the use of an oxidants such as DDQ, CuOAc, $Ru(bpy)_3Cl_2$ / light (or *N*-oxyl radical), or Cu(I) / molecular oxygen. Although these CDC examples do not require the use of unstable glyoxalates, removal of the oxidant from reaction mixture is difficult. Therefore, easy removal of the oxidant from the reaction mixture for the Mannich reaction following has been desired.

Scheme 1.2 Conventional methods for imino esters and Mannich reactions.



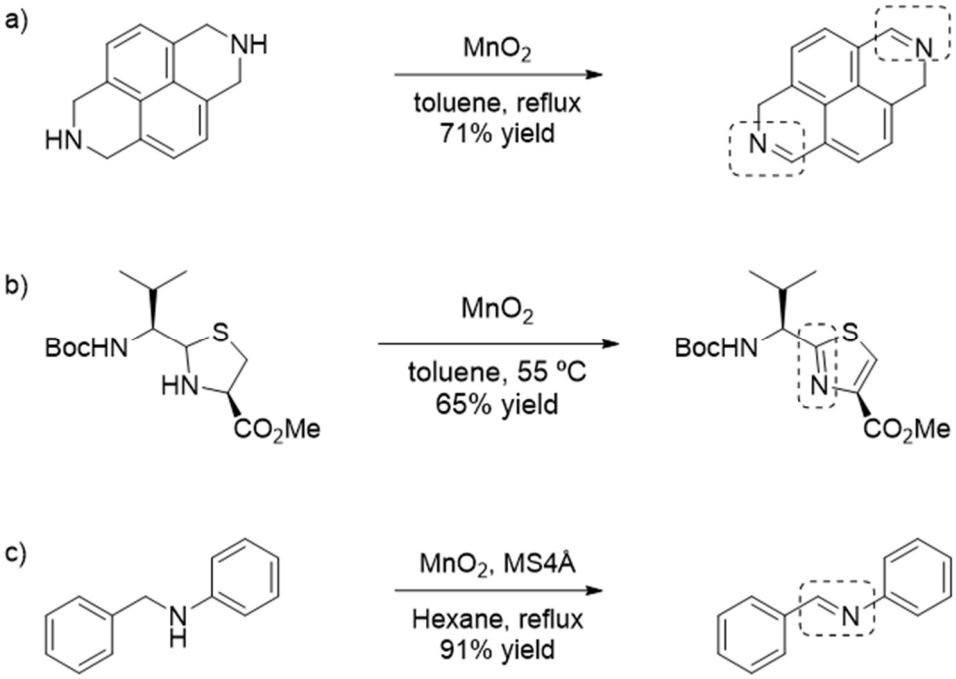
In this context, a heterogeneous oxidation system that allows for the facile removal of an insoluble oxidant by filtration should readily yield desired imino esters, which can thereby be subsequently subjected to Mannich reaction under oxidant-free conditions (Scheme 1.3).



Scheme 1.3 Synthesis of α-imino carboxylic acid derivatives.

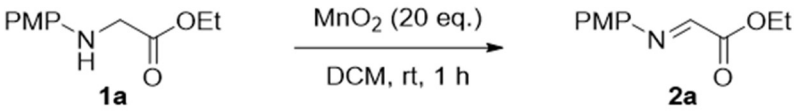
1.2 Screening of heterogeneous oxidant

Among wide varieties of oxidants, manganese(IV) oxide is a potential choice of heterogeneous oxidant.[7] The mild oxidative potential and readily separable properties make it possible to use manganese(IV) oxides for oxidative transformations at near final stage of complex molecules such as natural products. Although manganese(IV) oxidation emission conversion of aliphatic amines to the corresponding imines based on *N*-heteroaromatization of cyclic amines has been reported (Scheme 1.4), application of *α*-imino ester to the synthesis has yet to be reported.



Scheme 1.4 Oxidation by chemical Manganese oxide.

One of the non-negligible problems associated with oxidation using manganese(IV) oxide is the quality of the reagent. Generally, activated manganese(IV) oxide is reported to be suitable for MnO_2-mediated oxidative conversion. Thus, we initially attempted oxidation of *N*-*p*-methoxyphenyl (PMP) glycine ethyl ester **1a** in DCM using 20 equivalents of activated manganese(IV) oxide. The attempted reaction resulted in complete disappearance of **1a** within 1 hour and the desired imine **2a** was obtained simply by filtration through Celite®. However, some byproducts from overoxidation were detected. On the other hand, the use of less expensive and non-activated powdered manganese(IV) oxide gave the desired imine **2a** with good purity (Figure 1.1).



a)

b)

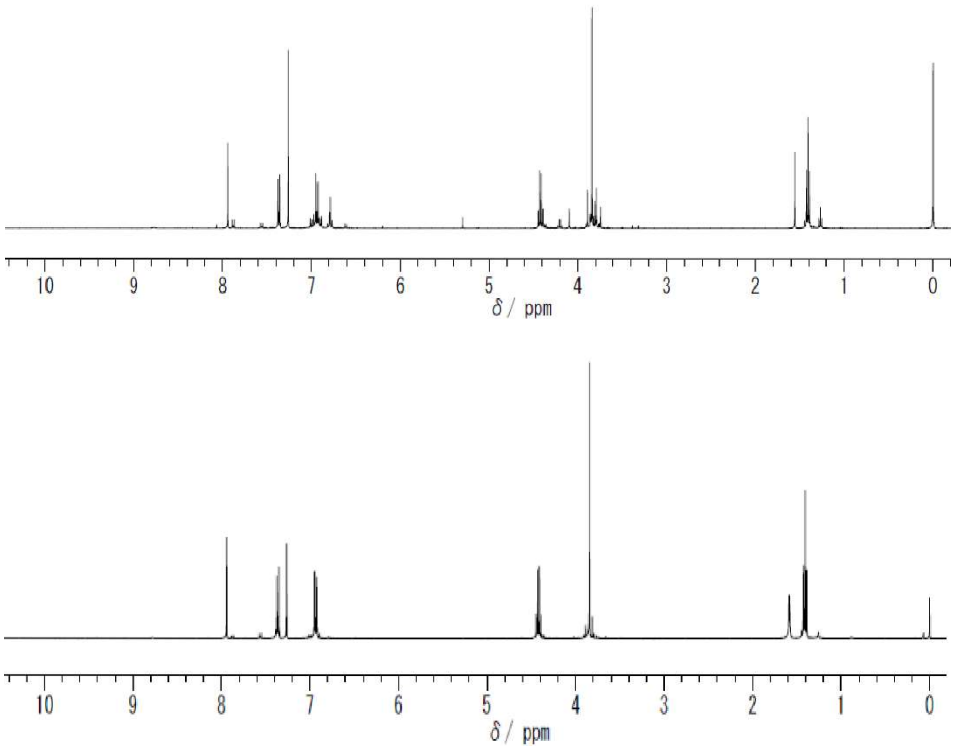


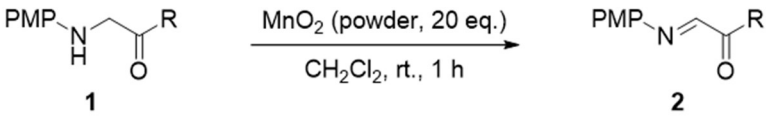
Figure 1.1

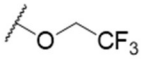
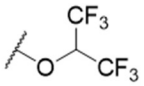
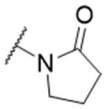
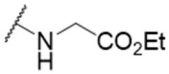
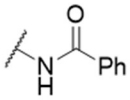
a) The ^{1}H NMR chart of the crude mixture of oxidation mediated by activated MnO_2 (purchased from Sigma-Aldrich Co, technical, activated, ≥90%).
b) The ^{1}H NMR chart of the crude mixture of oxidation mediated by MnO_2 powder (purchased from Wako Pure Chemical Industries, Ltd, ≥85%).

1.3 Preparation of α-amino acids derivatives

Next, applicability of the oxidation system to various carboxylic acid derivatives was investigated. Oxidation of ethyl, methyl, *t*-butyl, benzyl or allyl glycinate **1a-e** with nonactivated manganese(IV) oxide in DCM at room temperature for 1 h efficiently proceeded and the corresponding imins **2a-e** were obtained in high yields with good purities. (Table 1.1, entries 1–5). The resulting imino esters **2a-e** can be converted to carboxylic acids using acidic reagents[8], hydrogenation[9], or Pd-catalyzed[10] reactions, respectively. These substrate were highly useful for the asymmetric Mannich reaction that followed. We next attempted to synthesize imino amides **2f** and **g** with great value in the Petasis reaction using boric acid or boronate reagent. Although laborious and time-consuming steps were required for the preparation of such imino amides using the conventional addition-dehydration sequence, dipeptide-type compound PMP-Gly-Gly-OEt **1f** and glycyl N-ethyl anilide **1g** were successfully converted to the corresponding imino amides **2f** and **g** by the action of manganese(IV) oxide. Petasis reaction of the resulting imino amide **2f** with aryl boric acid has been reported to give aryl glycine derivatives[11]. Furthermore, Takemoto *et al.* describe an asymmetric Petasis reaction between a substrate such as **2g** and vinyl borate using a thiourea-type organic catalyst[12]. Next, we tried to synthesize a novel imine derivative that cannot be obtained by the conventional method using heterogeneous manganese(IV) oxide oxidation. The novel imines **2h-j** with highly activated ester moieties such as phenyl, trifluoroethyl or hexafluoroisopropyl ester could be prepared by our strategy (entries 8–10). In addition, this reaction formed the desired imino imides **2k** and **1** with high purity (entries 11, 12). Surprisingly, even thioester **2m**, susceptible to an oxidant, could be prepared without any problems (entry 13). This process is preferably applicable to large scale synthesis. When we conducted the oxidation of 15 mmol (3.0 g) of **1b**, the reaction proceeded in a manner similar to that performed using 1 mmol of the substrate (Scheme 1.5).

Table 1.1 Synthesis of α-imino carboxylic acid derivatives.

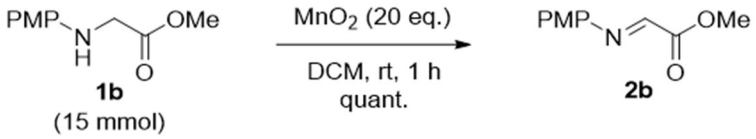


entry[a]	R	1	time (min)	2	yield (%)[b]	entry[a]	R	1	time (min)	2	yield (%)[b]
1		**1a**	60	**2a**	93	8		**1h**	30	**2h**	92
2		**1b**	60	**2b**	92	9		**1i**	60	**2i**	98
3		**1c**	60	**2c**	98	10		**1j**	60	**2j**	88
4		**1d**	60	**2d**	90	11		**1k**	45	**2k**	96
5		**1e**	60	**2e**	87						
6[c]		**1f**	60	**2f**	95	12		**1l**	60	**2l**	91
7		**1g**	60	**2g**	99	13		**1m**	30	**2m**	quant.

[a] The reaction was conducted with **1** (1.0 mmol) and MnO_2 (20.0 mmol) in DCM (100 ml) at room temperature.

[b] Yield of the crude product after filtration though Celite®.

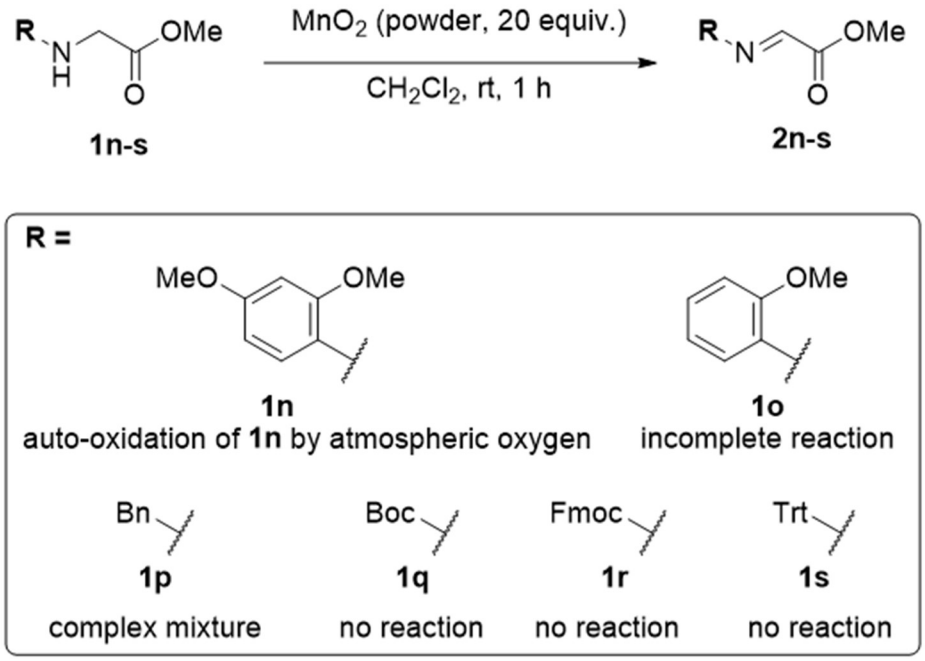
[c] For this entry, 25.0 mmol of MnO_2 was used.



Scheme 1.5 Gram scale synthesis.

1.4 Screening of the N-protected glycinates having protective groups other than PMP

Protective groups other than PMP were examined (Scheme 1.6). The derivative **1n** with electron donating methoxy substituents at both the *para* and *ortho* positions of the aryl ring underwent autoxidation by atmospheric oxygen. The ortho methoxy phenyl protected derivative **1o** probably caused oxidation to proceed slower than the PMP protected substrate due to steric hindrance and caused an incomplete reaction. As the amount of oxidant increased, a complex mixture was formed. Other protections including benzyl (Bn), tert-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc) and triphenylmethyl (Trt) also failed to offer the corresponding imines. Thus, we decided to investigate further applicability using *N*-PMP protection.

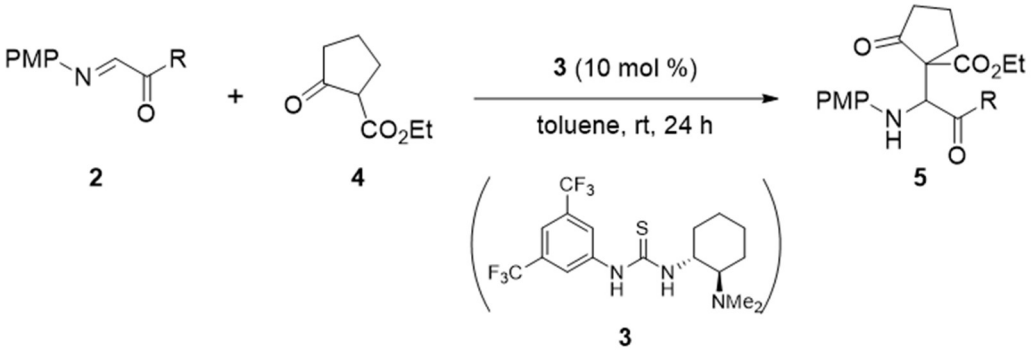


Scheme 1.6 Failed attempts at oxidation of the *N*-protected glycinates having protective groups other than PMP.

1.5 Application for the asymmetric Mannich reaction of α-amino acid derivatives

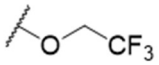
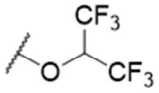
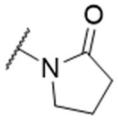
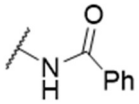
The asymmetric Mannich reaction of the obtained imine was conducted in the presence of Takemoto chiral bifunctional thiourea catalyst **3**[13]. First, asymmetric Mannich reaction of ethyl *α*-imino carboxylate **2a** and *β*-keto ester **4** gave the corresponding Mannich adduct **5a** in low yield as a diastereomeric mixture. The enantiomeric excess of one of the diastereomers was good (entry 1). The reaction of phenyl ester type imine **2h** also produced the adduct **5b** with low enantioselectivity (entry 2). Surprisingly, the perfluoroalkyl ester imines **2i** and **j** did not give any adducts (entries 3, 4). Further examination revealed that the reaction using imino imide **2k** proceeded smoothly to yield the corresponding adduct **5e** with higher yield and enantioselectivity compared to that using **2a** as substrate (entry 5). On the other hand, the reaction of the benzimide-type substrate **2l** did not proceed (entry 6). Unfortunately, the reaction with imino thioester **2m** resulted in low chemical yield (entry 7). As a result, the reaction rate of **2k** was superior to that of the known compound **2a**. Although the mechanisms of these reactions are not yet clear, it is presumed that the interaction between the carbonyl group of the 5-membered ring and the thiourea catalyst contributes by promoting the reaction with high enantioselective reaction outcome. The two carbonyl groups of benzimide-type substrate **2l** may have different orientations than those of 5-membered ring substrate **2k**, which may cause differences in substrate reactivity.

Table 1.2 Asymmetric mannich reaction of α-imino carboxylic acid derivatives.



2 **4** **5**

3

entry[a]	R	5	yield (%)[b]	dr[c]	ee of each diastereomer (%)[d]
1		**5a**	25	57:43	84, 36
2		**5b**	31	51:49	51, 7
3		**5c**	0	--	--
4		**5d**	0	--	--
5		**5e**	77	61:39	95, 52
6		**5f**	0	--	--
7		**5g**	40	51:49	82, 56

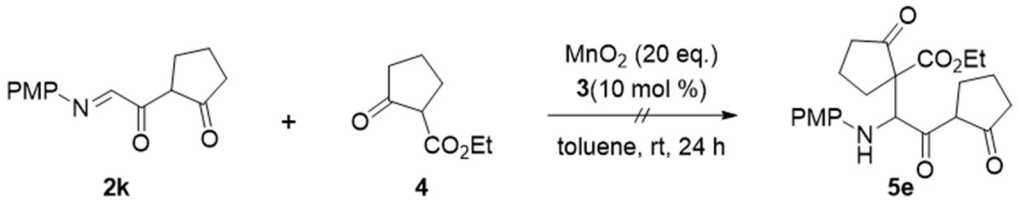
[a] The reaction was conducted with **2** (1.0 eq.), **4** (2.0 eq.) and **3** (10 mol%) in toluene at room temperature for 24 h.

[b] Yield of isolated product.

[c] Estimated by chiral HPLC analysis.

[d] Determined by chiral HPLC analysis.

To demonstrate the usefulness of this method, we decided to investigat the reaction using asymmetric organocatalyst in the presence of manganese(IV) oxidant. When thiourea **4**-catalyzed Mannich reactions of **2k** and **3** were carried out in the presence of manganese(IV) oxide which is a mild oxidant, the catalyst used was decomposed and the reaction did not proceed. This result indicates that removal of oxidant after imine formation is essential for the success of this reaction (Scheme 1.7).



Scheme 1.7 Influence of MnO_2 in asymmetric Mannich reaction.

1.6 Conclusion

A novel and facile approach to α-imino carboxylic acid derivatives was developed where the oxidation of *N*-protected glycine derivatives in the presence of manganese(IV) oxide under mild conditions was involved. This procedure tolerates the synthesis of various compounds including such as phenyl ester, perfluoroalkyl esters, imides, or thioester functionalities which could not be prepared by conventional synthetic protocol, and extends of the substrate scopes for the synthesis of unnatural α-amino acid derivatives.

Chapter 2

Development of Recyclable organocatalyst using Hydrophobic Tag

2.1 Introduction

In the field of the development of novel drugs, stereocontrol of the chiral compounds is essential because most of the compounds possess chirality and it drastically affects the biological activities of those compounds. Many researchers have devoted much effort to develop asymmetric catalysis for the preparation of optically active species. Recently, the organocatalysts are attracting much attention because of their low cost, low toxicity, easy operation and high efficiency compared with the conventional asymmetric metal catalysts. In light of these advantages, Jacobsen *et al.* reported[17] a catalytic asymmetric Strecker reaction with a thiourea catalyst **6** in 1998 (Figure 2.1). It is considered that the thiourea activates the imine by hydrogen bonding with its two NH protons and the reaction progresses. Many other groups have also developed various thioureas and their analogue, urea catalysts[18] (Figure 2.1). Among them, Takemoto *et al.* developed a bifunctional organocatalyst **3**[19] having thiourea and tertiary amino group in one molecule. In this catalyst, the thiourea moiety activates the electrophile and the tertiary amino group activates the nucleophile, respectively, and the asymmetric reaction proceeds efficiently (Figure 2.2). This catalyst catalyzes a variety of asymmetric reactions, such as aza-Henry reaction of *N*-Boc imines and nitroalkenes, and Michael addition of nitroolefins and 1,3-dicarbonyl nucleophiles.

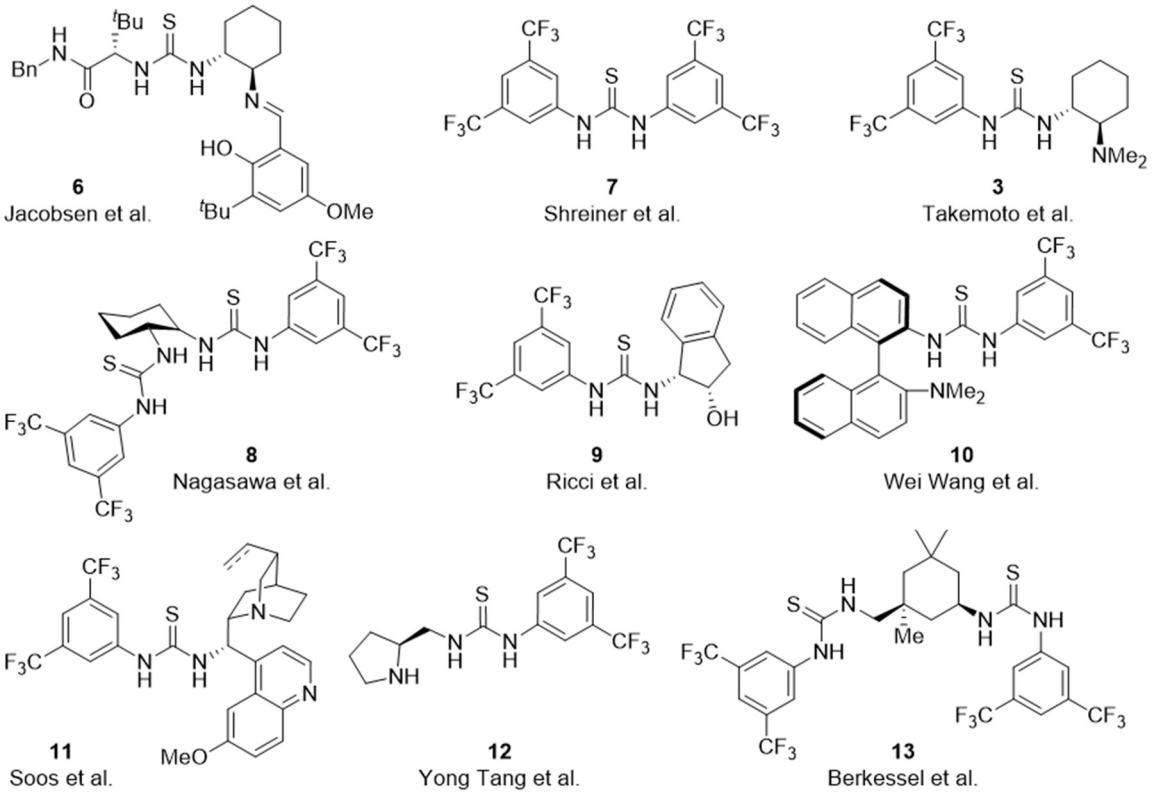


Figure 2.1 Structures of thiourea organocatalysts.

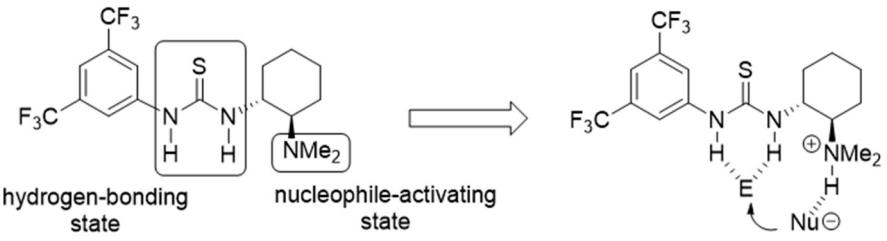


Figure 2.2 Bifunctional thiourea organocatalyst.

Although unlimited amounts of optically active compounds can theoretically generated from a small amount of the catalyst as an asymmetric source, supply of such compounds is in fact limited since the catalysts are discarded after completion of each reaction in most cases. If the catalyst can be readily recovered and reused after the asymmetric reactions (recyclable), it can generate chiral compounds infinitely (Figure 2.3).

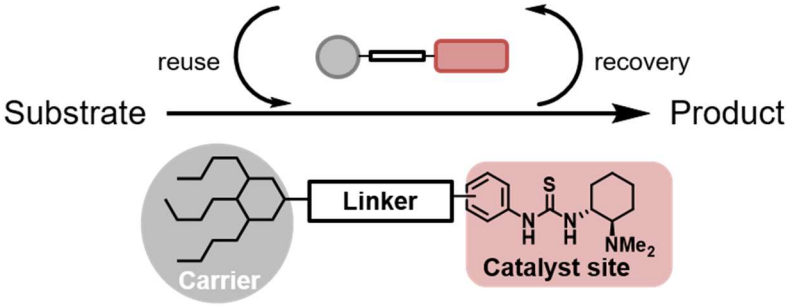
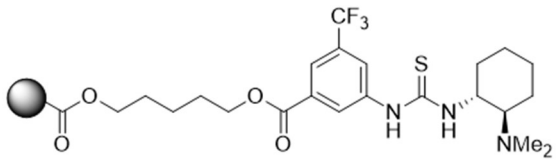


Figure 2.3 Diagram of recyclable organocatalyst.

Several types of catalysts bearing catalytic part and appropriate carrier moieties have been developed as recyclable catalysts (Figure 2.4). Takemoto *et al*. reported a resin-supported catalyst **14**.[20] After the reaction catalyzed by **14**, the resin-supported catalyst **14** can be easily separated from the reaction by filtration and reused in another trial. However, it is difficult to maintain the homogeneity of the catalyst, because resin polymers have a range of molecular weights, and therefore the catalytic activity can vary in each lot. In addition, compared with the parent catalysts, the efficacies of the reactions catalyzed by resin-supported catalysts are generally low since the resin catalyst is not dissolved in the reaction. Polyethyleneglycol (PEG) is another choice of polymer-type carrier. In contrast to the resin-type catalyst, pegylated catalyst is soluble in certain solvents. However, the recovery efficacies are sometimes low due to difficulty in control of the solubility. Recently, multi-substituted fluorine carrier-bearing catalysts were developed by Cai *et al*. as a new type of recyclable catalyst[21] (fluorous-tagged catalyst). The compounds having such tags have high solubility in fluorine-containing solvent and strongly interact with a silica gel containing fluorine.[22] Therefore, those catalysts can be separated from the reaction solution by extraction with a fluorine-containing solvent or by chromatography with a fluorine-containing solvent or carriers such as silica gel. This method is excellent but requires large amount of expensive fluorinated species.

a) Resin-bond thiourea organocatalyst.



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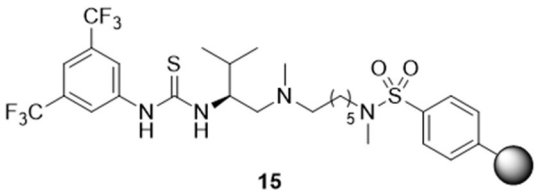
Miyabe, Takemoto et al



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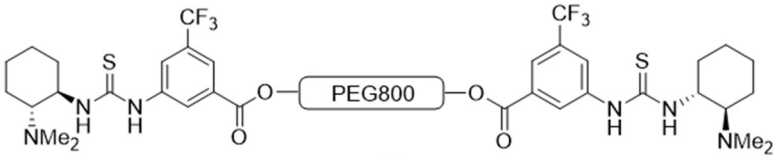
b) PEG support organocatalyst.



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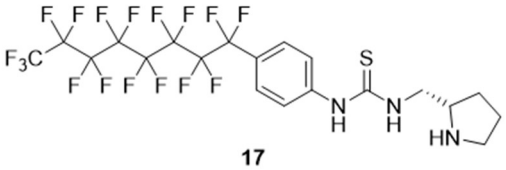
Miyabe, Takemoto et al

c) Flurous organocatalyst.



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Cai et al

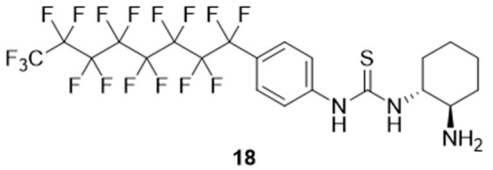

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Figure 2.4 Recyclable catalyst.

To develop novel recyclable catalysts that overcome the problems encountered in the use of conventional catalysts, in this study a hydrophobic tag consisting of a long alkyl chain was focused on. A compound bearing this tag moiety is soluble in less-polar solvents such as $CHCl_3$ and THF and precipitate in polar organic solvents such as MeOH and CH_3CN. Therefore, those compounds are homogeneous during the reaction in less-polar solvent and can be easily separated from the reaction mixture by changing the solvent to polar ones and filtration of the resulting precipitate. Tamiaki, Chiba and Takahashi have independently developed[23] such the hydrophobic tags and applied them to the synthesis of important biomolecules such as peptides and nucleic acids (Figure 2.5). It was considered that the hydrophobic tag would be an efficient carrier of recyclable catalyst since the catalyst bearing this tag moiety is expected to be soluble in the solvent generally used in asymmetric catalytic reactions and recovered simply by solvent-exchange and filtration (Scheme 2.1). In this study, as novel recyclable catalyst, **20** bearing the amino thiourea moiety as a catalytic part and hydrophobic tag as a carrier part

as novel recyclable catalyst was synthesized. The parent catalyst **3** and the resin-supported catalyst **19** were also prepared for evaluating the synthetic utility of novel recyclable catalysts (Figure 2.6).

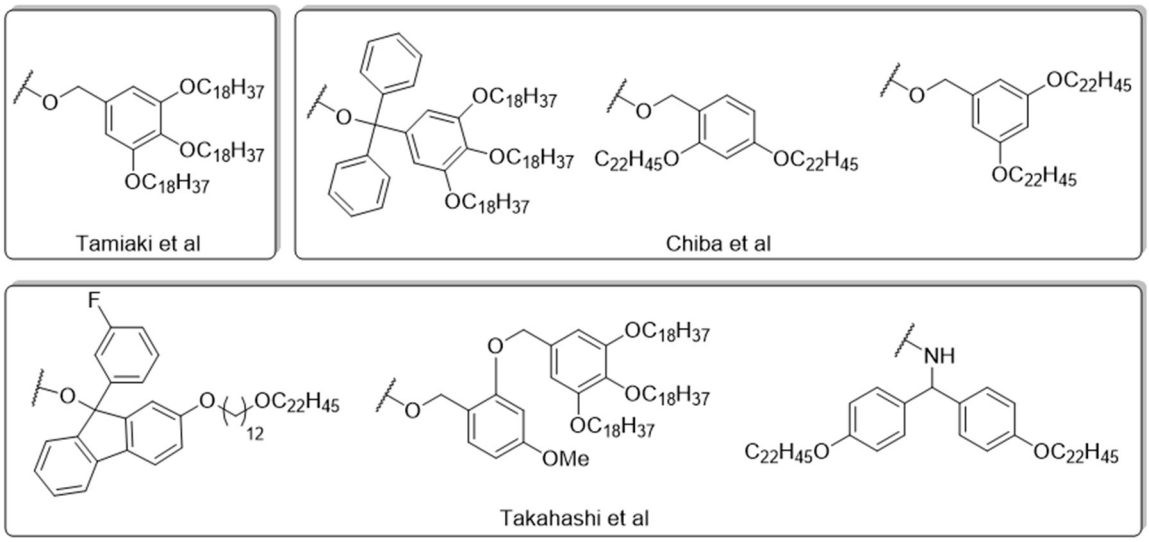
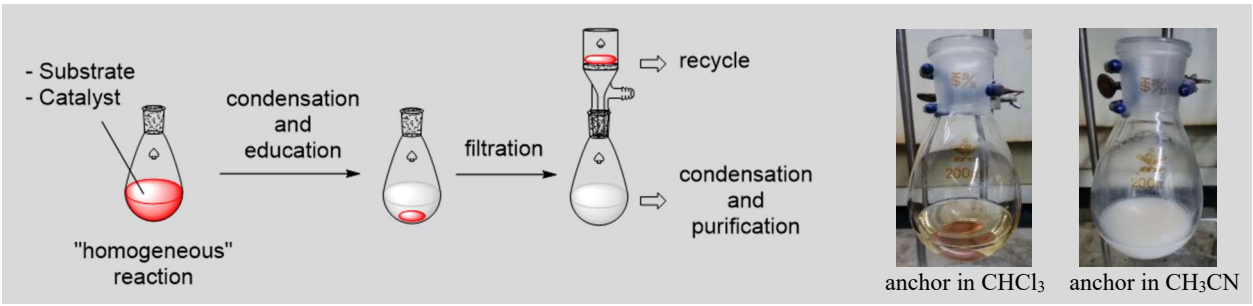


Figure 2.5 Hydrophobic tags for LPPS.

Scheme 2.1 Method for recovery and reuse.



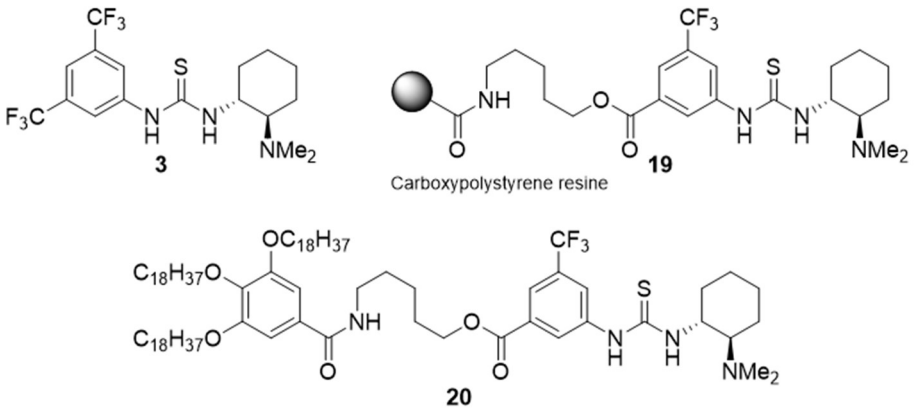
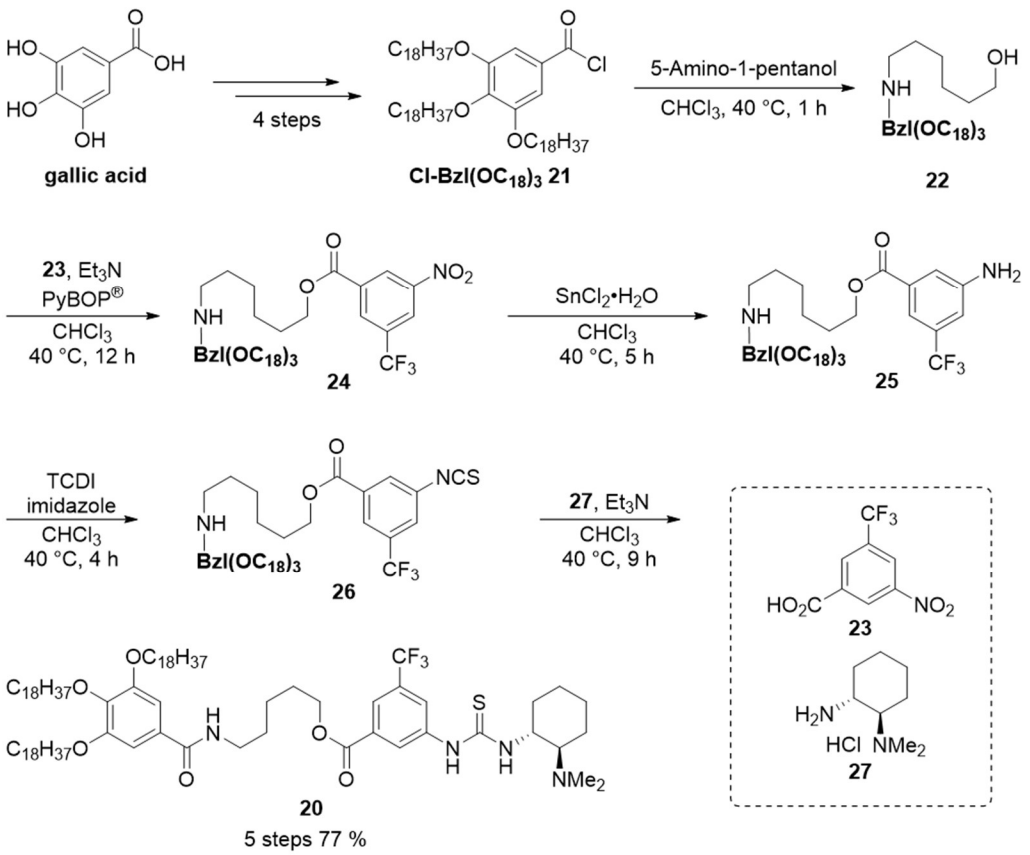


Figure 2.6 Three kinds of thiourea catalyst

2.2 Synthesis of hydrophobic tag thiourea catalyst and resin-bound thiourea organocatalyst

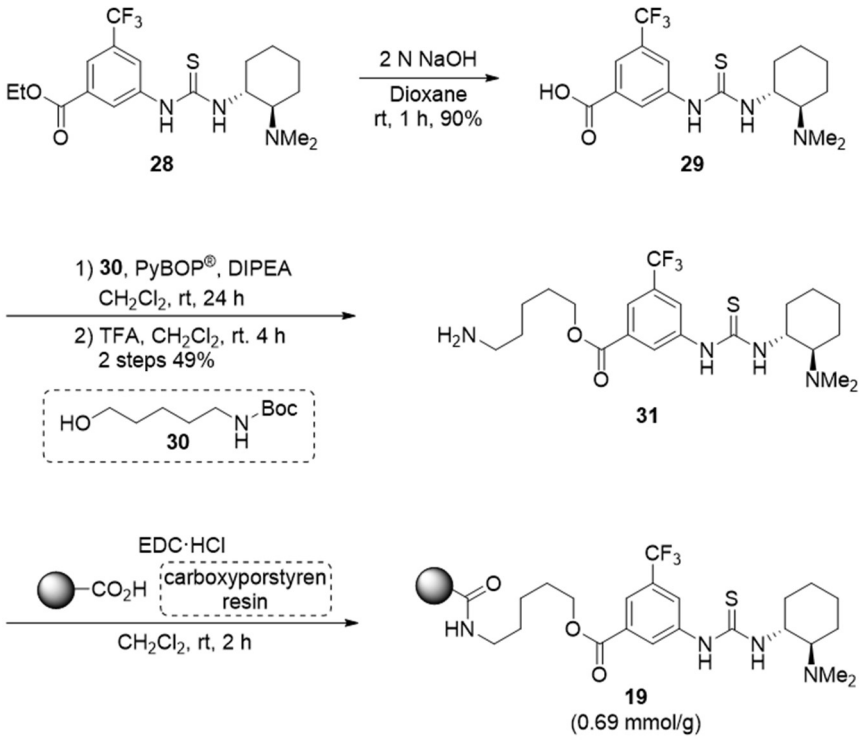
The thiourea catalyst having hydrophobic tag **20** was prepared from the known compound **21**[24] (Scheme 2). The acid chloride **21** was treated with the commercially available 5-amino-1-pentanol to yield the requisite hydroxyalkyl benzamide **22**. Condensation of **22** with the benzoic acid derivative **23** in the presence of (benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate (PyBOP®) yielded **24** and *nitro group of **24** was reduced* to give **25**. The amino group was converted to isothiocyanate group by 1,1'-thiocarbonyldiimidazole (TCDI). Finally, the synthesis of catalyst **20** was accomplished by the addition of optically active cyclohexyl diamine **27** to **26**. In each step, the excess reagents could be removed by precipitation of the desired compound and washing of the precipitate with excess MeOH or CH_3CN. To obtain the analytically pure catalyst **20**, silica gel chromatography was performed in final step. All of the reactions proceeded effectively and the desired catalyst **20** was obtained in 77% isolated yield over five steps from **21**.

Scheme 2.2 Synthesis of hydrophobic tag thiourea organocatalyst



To evaluate the utility of the hydrophobic tag-containing catalyst compared with that of the conventional recyclable catalyst, a resin-bound thiourea catalyst was prepared (Scheme 3). The thiourea **28** having ethyl ester moiety was synthesized in accordance with the method reported[20] by Miyabe and Takemoto. First, ethyl ester **28** was hydrolyzed to yield the corresponding carboxylic acid **29**. Next, amidation of commercially available 5-(Boc-amino)-1-pentanol **30** in the presence of PyBOP® and diisopropylethylamine (DIPEA) in CH_2Cl_2, followed by deprotection of amino group by TFA gave **31** in 49% yield over two steps. Thiourea **31** having the spacer moiety was introduced to carboxypolystyrene resin by condensation with EDC·HCl to give the resin-bound catalysts **19**. Unreacted carboxy group was capped with trimethylsilyl diazomethane to convert the corresponding methyl ester. The content of the catalyst loaded on the resin was determined to be 0.69 mmol/g by quantification of the content of nitrogen atom by elemental analysis.

Scheme 2.3 Synthesis of resin-bound thiourea organocatalyst



*2.3 Solubility of catalyst **20** in various solvents*

Solubility of catalyst **20** possessing the hydrophobic tag was tested in various solvents as shown Table 2.1. As anticipated, although the solubility in the absence of $CHCl_3$ was low below 20 °C, Catalyst **20** was soluble in $CHCl_3$, toluene, and THF, on the other hand, in polar solvents such as MeOH and MeCN catalyst **20** was insoluble. Based on these results, all subsequent reactions were conducted at 30 °C in less polar solvents with consideration for the recovery of **20** the addition of polar solvents.

Table 2.1 Solubility of catalyst **20** in various solvents.

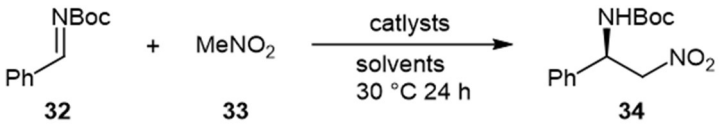
Entry	Solvent	Solubility [mM][a]		
		4 °C	20 °C	30 °C
1	$CHCl_3$	141.0	156.5	176.5
2	CH_2Cl_2	6.4	7.5	30.9
3	toluene	1.5	1.7	39.5
4	THF	4.5	4.7	32.4
5	MeOH	N.D.	N.D.	0.1
6	MeCN	N.D.	N.D.	0.1

[a] Determined from saturated solution of **20**

*2.4 aza-Henry reaction using catalyst **20** and recovery*

Having obtained the thiourea catalyst **20** bearing hydrophobic tag, the reaction efficacy of the catalyst was evaluated in comparison with that of the parent catalyst and with conventional recyclable catalyst by aza-Henry reaction of 0.1 mmol of *N*-Boc imine **32** with 10 eq. of nitromethane **33** in DCM at 30 °C for 24 h (Table 1). This reaction proceeded smoothly with the parent thiourea catalyst **3**, and the adduct **34** was obtained in 76% yield with 90% ee in favor of the (*R*) product (entry 1). Pleasingly, the newly synthesized hydrophobic tag thiourea catalyst **20** also showed comparable reactivity and enantioselectivity to those of the parent catalyst **5** (entry 2). On the other hand, the conventional recyclable catalyst, resin-supported thiourea **19** did not produce the product **34** at all (entry 3). When the reaction was carried out in 30 mol% of the catalyst **19**, the product **34** was obtained in with up to 15% yield even after prolonged reaction (entry 4). The other less-polar solvents were also screened, but toluene gave diminished chemical yield and the reaction in THF did not proceed at all (entries 5 and 6). Next, the same reaction was attempted in gram-scale and the reaction of 1.0 g (4.9 mmol) of **32** smoothly proceeded in a manner similar to that performed using 0.1 mmol of the substrate (Table 2.2, entry 7).

Table 2.2 aza-Henry reactions using catalyst **20** and recovery

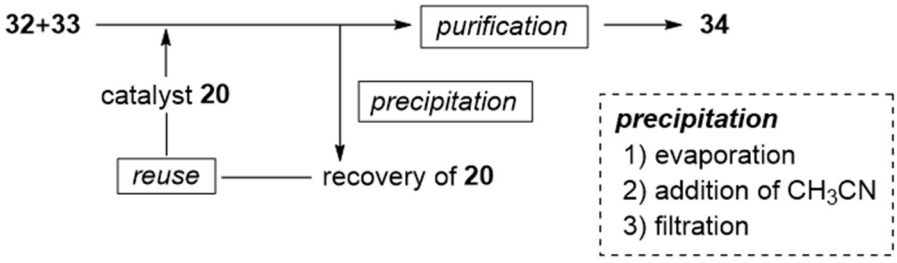


Entry[a]	Catalyst (mol%)	solvent	Recovered catalyst (%)[b]	Yield (%)[c]	Ee (%)[d]
1	**3** (10)	CH_2Cl_2	--	76	90
2	**20** (10)	CH_2Cl_2	99	77	91
3	**19** (10)	CH_2Cl_2	99	N.R.	--
4[e]	**19** (30)	CH_2Cl_2	99	15	89
5	**20** (10)	toluene	99	30	91
6	**20** (10)	THF	99	N.R.	--
7[f]	**20** (10)	CH_2Cl_2	99	81	91

[a] Reactions were carried out with **32** (1 eq.) and **33** (10 eq.) in solvent (0.1 M)
[b] Recovered by MeCN. [c] Isolated yield.
[d] Determined by chiral HPLC analysis. (IC-3, flow rate 1.0 ml/min, Hex:^{i}Pr = 85:15)
[e] Reaction was carried out for 6 days. [f] Reaction was carried out on a 1.0 g scale.

Next, the recyclability of the catalyst **16** was evaluated (Scheme 2.4 and Figure 2.7). After the aza-Henry reaction under the conditions described in Table 1, entry 2, the catalyst **20** was precipitated with the aid of CH_3CN and recovered from the reaction mixture by filtration. The recovery efficacy was 99%. The recovered catalyst was used in the same reaction in another batch and the corresponding adduct **34** was obtained in 72% yield with 91% ee and 99% of the catalyst was recovered, which are comparable to those of the first trial. The the same reaction could be repeated up to four times without loss of reactivity or enantioselectivity. Although further trials have not been performed, based on the results obtained here it is considered to be possible to use the catalyst **20** more than four times. Here, an efficient asymmetric catalyst that can be readily recovered using only common solvent was established.

Scheme 2.4 Flowchart of recycle reaction.



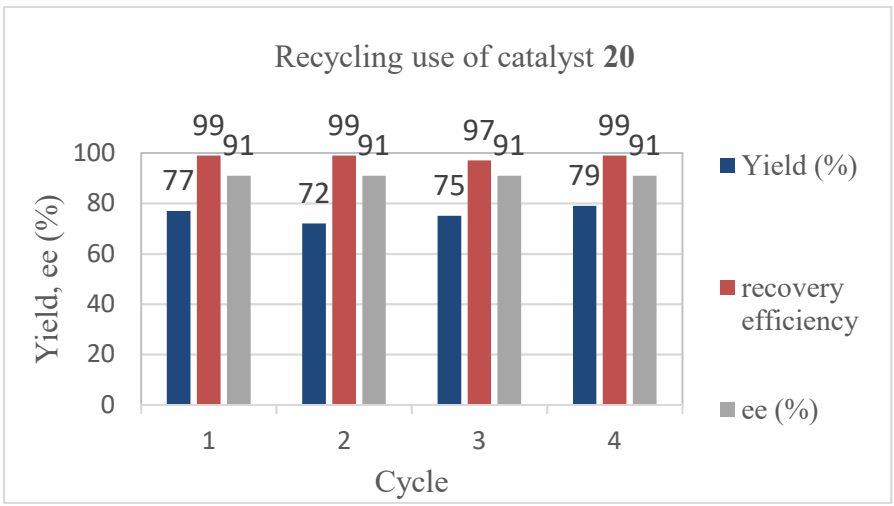
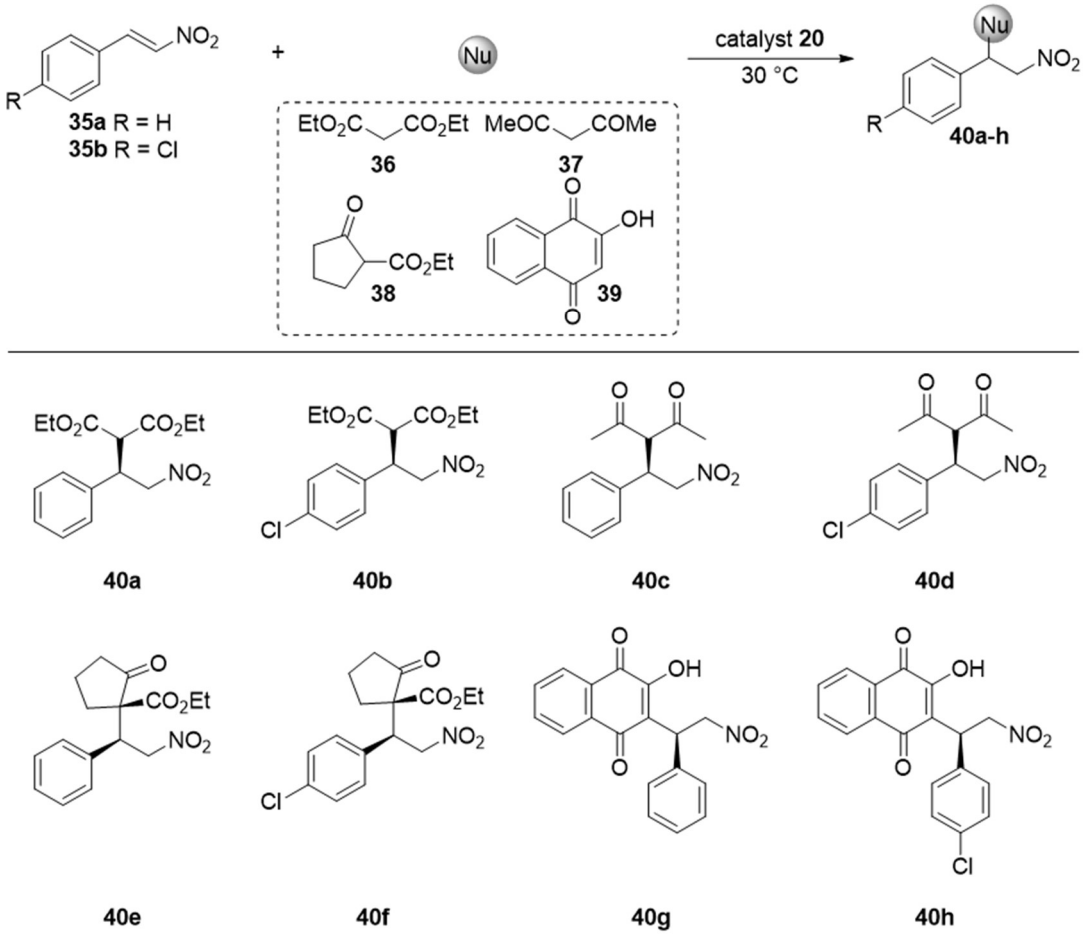


Figure 2.7 Recycling and reuse of the recyclable organocatalyst **20**.

2.5 Michael reaction of nitrostyrenes and several nucleophiles

Finally, the recyclable thiourea catalyst **20** was applied to another reaction, asymmetric Michael reaction of nitrostyrenes with several nucleophiles (Table 2). As a nucleophile, acyclic 1,3-dicarbonyl compounds such as diethyl malonate **36** or acetylacetone **37** could be introduced to the nitrostyrenes **35a**–**b** in the presence of 30 mol% of the catalyst **20** (entries 1–4). Good yields and enantioselectivities (71–95% ee) were obtained (entries 1–4). Among the products of those reactions, **35b** is an important intermediate for the synthesis of baclofen, activator of $GABA_B$ receptor.[25] The cyclic-type 1,3-dicarbonyl nucleophiles were also tested and it was found that 10 mol% of the catalyst was sufficient for the reaction progresses (entries 5–8). Reaction with cyclic-type nucleophiles **38** and **39** proceeded smoothly to generate desired products **40e-f** and **40g-h** with good enantioselectivity, respectively in high yields (78–93% ee). In general, chloro-nitrostyrene **35b** gave better enantioselectivity compared to **35a**.

Table 2. Michael reaction of nitrostyrenes and several nucleophiles.



Entry [a]	**35**	Solvent	Catalyst **20** (mol%)	Time (h)	Yield (%)[b]		Dr	Ee (%)[c]
1	**35a**	toluene	30	72	**40a**	81		90
2	**35b**	toluene	30	72	**40b**	80		93
3	**35a**	toluene	30	24	**40c**	98		74
4	**35b**	toluene	30	24	**40d**	97		90
5	**35a**	toluene	10	24	**40e**	95	9:1	78
6	**35b**	toluene	10	24	**40f**	88	9:1	80
7	**35a**	CH_2Cl_2	10	4	**40g**	95		91
8	**35b**	CH_2Cl_2	10	4	**40h**	90		93

[a] Reactions were carried out with **35** (1 eq.) and **36-39** (2 eq.) in solvent (0.1 M)

[b] Isolated yields.

[c] Determined by chiral HPLC analysis.

2.6 Conclusion

In summary, a novel recyclable asymmetric organocatalyst was developed by the introduction of a hydrophobic tag into the well-established asymmetric thiourea organocatalyst. This new catalyst **20** could be easily prepared and showed catalytic efficacy comparable to that of the parent thiourea catalyst. In addition, this catalyst can be easily recovered after being used in catalytic reactions by simple manipulations using common solvent, in contrast to the conventional fluorous-tagged catalyst, which requires expensive fluorinated reagents for recovery.

Conclusions

1. Development of a novel and simple protocol for the synthesis of α-imino carboxylic acid derivatives as versatile synthetic intermediates was achieved. This protocol features the use of manganese(IV) oxide which can oxidatively convert the N-protected amino acid derivatives to the corresponding α-imino derivatives in a heterogeneous fashion. Such heterogeneous reaction allows for both easy removal of the oxidant from the reaction mixture and extension to a following operationally easy asymmetric Mannich reaction.

2. Synthesis of a recyclable catalyst possessing a hydrophobic tag with practical application to asymmetric Michel addition was accomplished. Development of a recyclable catalyst could avoid problems associated with developed resin-bound type catalyst. Notably, the newly developed catalyst can perform catalytic reaction in homogeneous manner and allows for easy recycling of the used catalyst simply by addition of polar solvent into the reaction.

Experimental section

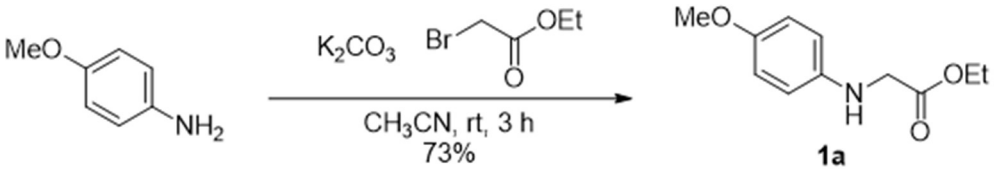
General Methods

All reactions were carried out under a positive pressure of argon. Analytical TLC was performed on Merck TLC silica gel $60F_{254}$ silica gel plates. Visualization was accomplished with molybdenum phosphate, *p*-anisaldehyde, Hannessian's cocktail or ninhydrin. For column chromatography, silica gel (KANTO KAGAKU N-60) was employed. NMR spectra were recorded using a Bruker AV400N at 400 MHz frequency or JEOL JNM-AL300 for ^{1}H, and JEOL JNM-AL300 at 75 MHz frequency for ^{13}C in the stated solvents using tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard (NMR descriptions: s, singlet; d, doublet; t, triplet; q, quartet; hept, heptet; m, multiplet; br, broad). Coupling constants, *J*, are reported in Hertz. For chiral HPLC analysis, a Chiralpak IA (DAICEL, 4.6×250 mm) or a Chiralpak IB-3 (DAICEL, 4.6×250 mm) or a Chiralpak IC-3 (DAICEL, 4.6×250 mm) or a Chiralcel OD-H (DAICEL,4.6×250 mm) were employed and eluting products were detected by UV at 254 nm. A solvent system consisting of HPLC grade of hexane and 2-propanol was used for HPLC analysis. Mass spectra were recorded on a Waters MICROMASS® LCT PREMIERTM (electrospray ionization-time-of-flight (ESI-TOF)). Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in g dL^{-1}). IR was measured using a JEOL FT-IR 6200. Melting point was determined on YANAGIMOTO micro melting point apparatus. Elemental combustion analyses were performed using a J-SCIENCE LAB JM10. Measurement of absorbance at 250 nm was performed using a DU-650 spectrophotometer. Unless otherwise noted, materials were purchased from Tokyo Chemical Industry Co., Ltd. (Japan), Aldrich Inc. (U.S.A.), Wako Pure Chemical Industries, Ltd. (Osaka, Japan), Nacalai Tesque Inc., Kanto Chemical Co., Inc. (Japan) commercial suppliers and were used as purchased. For manganese(IV) oxide, Wako manganese(IV) oxide, powder (order number 138-09675) was used. The substrates **1p**,[14] **r**[15] and catalyst **3** were prepared according to the literature procedure.

Supporting information-Chapter 1

Synthesis of the *N*-PMP Glycine Derivatives

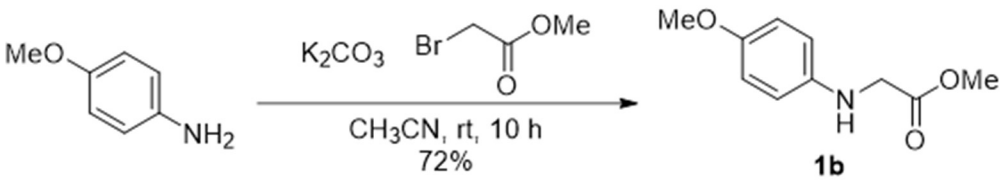
Ethyl (4-Methoxyphenyl)glycinate (1a)



To a solution of ethyl bromoacetate (1.11 mL, 10.0 mmol) in CH_3CN (25 mL) were added NaOAc (1.23 g, 15.0 mmol), NaI (1.65 g, 11.0 mmol) and *p*-anisidine (1.19 g, 9.66 mmol) at room temperature and stirred at the same temperature for 3 h. After that, the reaction mixture was extracted with EtOAc, washed with 5% $KHSO_4$ aq. and brine, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford **1a** (1.47 g, 73%) as a pale brown plate crystal.

mp 44–45°C (hexane–EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.29 (t, J = 7.0 Hz, 3H), 3.75 (s, 3H), 3.86 (s, 2H), 4.02 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 14.2, 46.8, 55.7, 61.2, 114.3, 114.9, 141.2, 152.6, 171.3; IR (neat) 826, 1443, 1518, 1732, 2992, 3385 cm^{-1}; MS (ESI^+) *m*/*z* 210 ($M+H^+$, 100); *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.94; H, 7.20; N, 6.77.

Methyl (4-methoxyphenyl)glycinate (1b)

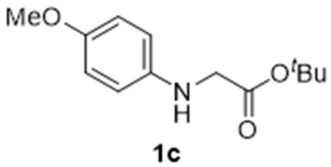


To a solution of *p*-anisidine (10.2 g, 82.8 mmol) in CH_3CN (100 mL) were added K_2CO_3 (12.3 g, 89.0 mmol) and methyl bromoacetate (8.25 mL, 89.0 mmol) at room temperature and stirred at the same temperature for 10 h. After that, the insolubilities were removed

by filtration. Then the resulting filtrate was evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 4/1 to 2/1) to afford
1b (11.7 g, 72%) as a pale brown plate crystal.

mp 44–45°C (hexane–EtOAc); H-NMR (400 MHz, $CDCl_3$); δ 1.29 (t, J = 7.0 Hz, 3H), 3.75 (s, 3H), 3.86 (s, 2H), 4.02 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 14.2, 46.8, 55.7, 61.2, 114.3, 114.9, 141.2, 152.6, 171.3; IR (neat) 826, 1443, 1518, 1732, 2992, 3385 cm^{-1}; MS (ESI^+) *m*/*z* 210 ($M+H^+$, 100); *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.94; H, 7.20; N, 6.77.

tert-Butyl (4-Methoxyphenyl)glycinate (1c)

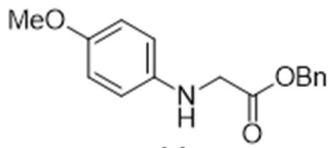


1c

A procedure similar to that described for the preparation of **1b** afforded **1c** in 92% yield as an yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$); δ 1.46 (s, 9H) 3.71 (s, 3H), 3.73 (s, 2H), 4.02 (s, 1H), 6.55 (d, J = 8.9 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 27.9, 47.3, 55.5, 81.5, 114.1, 114.7, 141.4, 152.3, 170.4; IR (neat) 1462, 1506, 1731, 2980, 3381 cm^{-1}; MS (ESI^+) *m*/*z* 238 ($M+H^+$, 100); high resolution (HR)-MS (ESI^+) *m*/*z* Calcd for $C_{13}H_{20}NO_3$ ($[M+H]^+$) 238.1438. Found 238.1444.

Benzyl (4-Methoxyphenyl)glycinate (1d)

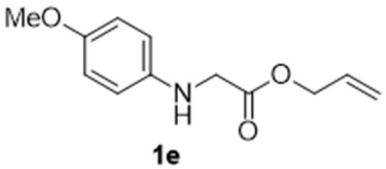


1d

A procedure similar to that described for the preparation of **1b** afforded **1d** in 92% yield as a white needle crystal.

mp 73–74°C (hexane–EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$); δ 3.73 (s, 3H) 3.91 (s, 2H), 4.04 (s, 1H), 5.19 (s, 2H), 6.57 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 7.31-7.38 (m, 5H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 46.9, 55.7, 66.9, 114.4, 114.9, 128.3, 128.4, 128.6, 135.3, 141.1, 152.7, 171.3; IR (KBr) 757, 797, 1451, 1464, 1518, 1728, 3388 cm^{-1}; MS (ESI$^+$) m/z 272 (M+H$^+$, 100); *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.72; H, 6.26; N, 5.07.

Allyl (4-Methoxyphenyl)glycinate (1e)

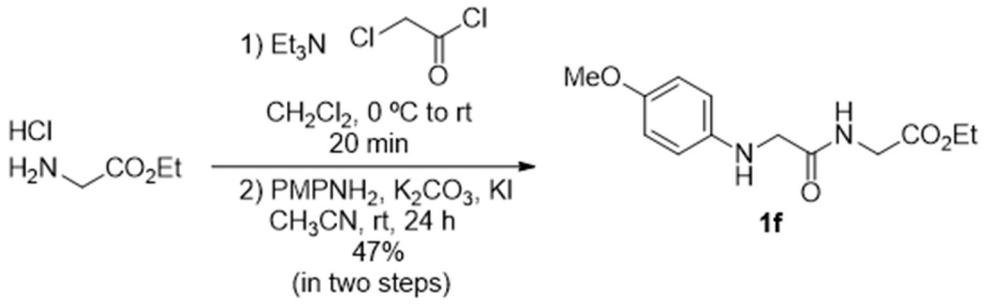


1e

A procedure similar to that described for the preparation of **1b** afforded **1e** in 92% yield as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$); δ 3.72 (s, 3H), 3.88 (s, 2H), 4.04 (s, 1H), 4.64 (ddd, J= 4.6, 1.5, 1.3 Hz, 2H), 5.24 (dt, J= 10.4, 1.3 Hz, 1H), 5.31 (dt, J= 17.2, 1.5 Hz, 1H), 5.90 (ddt, J= 17.2, 10.4, 4.6 Hz, 1H), 6.57 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 46.6, 55.6, 65.6, 114.2, 114.8, 118.7, 131.6, 141.1, 152.5, 171.0; IR (neat) 937, 987, 1444, 1516, 1744, 3031, 3389 cm^{-1}; MS (ESI$^+$) m/z 222 (M+H$^+$, 100); HRMS (ESI$^+$) m/z Calcd for $C_{12}H_{15}NNaO_3$ ([M+Na]$^+$) 244.0944. Found 244.0938.

Ethyl (4-Methoxyphenyl)glycylglycinate (1f)



1f

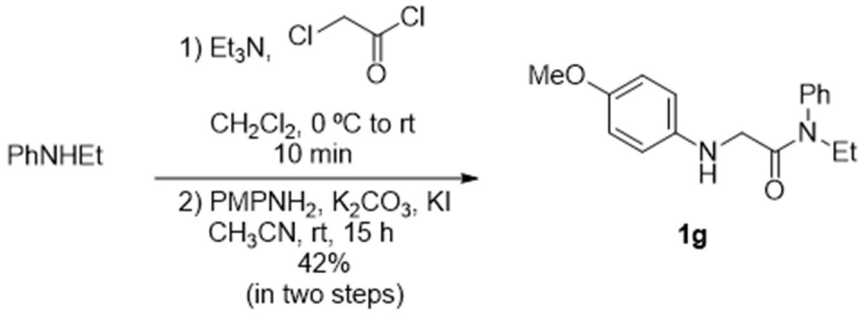
To a suspension of ethylglycinate hydrochloride (3.58 g, 25.6 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (10.7 mL, 76.9 mmol) and chloroacetyl chloride (3.05 mL, 38.4 mmol)

at 0 ºC and stirred at room temperature for 20 min. After that, sat. $NaHCO_3$ aq was added at 0 ºC and the reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated *in vacuo* to afford the chloroacetamide intermediate as a dark black solid. This intermediate was directly used for the next step without further purifications.

To a solution of chloroacetamide in CH_3CN (50 mL) were added *p*-anisidine (4.90 g, 39.8 mmol), K_2CO_3 (4.04 g, 29.2 mmol) and KI (4.25 g, 25.6 mmol) at room temperature and stirred at the same temperature for 24 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 1/1 to 1/2) to afford **1f** (3.21 g, 47% in two steps) as a pale brown powder.

^{1}H NMR (400 MHz, $CDCl_3$); δ 1.25 (t, *J* = 7.3 Hz, 3H), 3.74 (s, 3H), 3.78 (s, 2H), 4.04 (d, *J* = 5.5 Hz, 2H), 4.12 (s, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.31 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 14.0, 40.9, 49.5, 55.6, 61.4, 114.4, 114.9, 141.1, 153.1, 169.6, 171.3; IR (KBr); 1422, 1441, 1450, 1589, 1621, 1655, 2969, 3363 cm^{-1} ; MS (ESI^+) *m*/*z* 267 ($M + H^+$, 75), 289 ($M + Na^+$, 100); Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52; Found: C, 58.44; H, 6.81; N, 10.32.

_N_-Ethyl-2-((4-methoxyphenyl)amino)-N-phenylacetamide (1g)

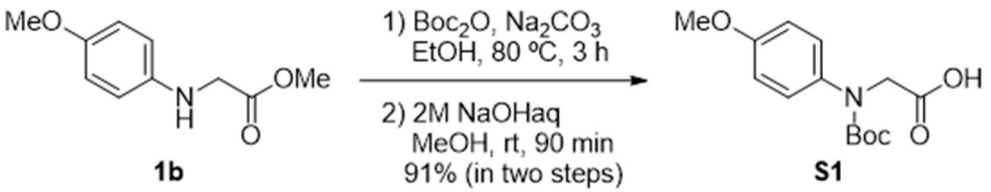


To a solution of *N*-ethylaniline (2.22 g, 18.3 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (2.80 mL, 20.1 mmol) and chloroacetyl chloride (1.60 mL, 20.1 mmol) at 0 ºC and stirred at room temperature for 10 min. After that, sat.$NaHCO_3$aq was added at 0 ºC and the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford the chloroacetamide intermediate as a pale yellow oil. This intermediate was directly used for the next step without further purifications.

To a solution of chloroacetamide in CH_3CN (50 mL) were added *p*-anisidine (3.43 g, 27.8 mmol), K_2CO_3 (2.85 g, 20.6 mmol) and KI (3.04 g, 18.3 mmol) at room temperature and stirred at the same temperature for 15 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 5/1 to 2/1) to afford **1g** (2.20 g, 42% in two steps) as a white needle crystal.

mp 118–119 ºC (hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.15 (t, *J* = 7.3 Hz, 3H), 3.47 (s, 2H), 3.71, (s, 3H), 3.80 (q, *J* = 7.3 Hz, 2H), 4.48 (s, 1H), 6.41 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 7.22-7.17 (m, 2H), 7.51-7.40 (m, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 12.9, 44.3, 47.1, 55.7, 114.1, 114.7, 128.2, 128.4, 129.9, 140.6, 141.7, 152.1, 169.0; IR (KBr) ; 1423, 1461, 1518, 1535, 1653, 2980, 3394 cm^{-1} ; MS (ESI$^+$) *m*/*z* 285 (M + H$^+$, 100); Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85; Found: C, 71.69; H, 7.13; N, 9.70.

***N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)glycine (S1)**

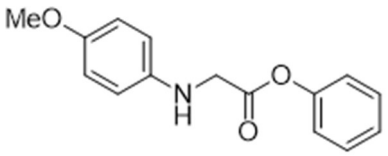


To a solution of **1b** (5.04 g, 25.8 mmol) in EtOH (100 mL) were added Na_2CO_3 (5.60 g, 52.8 mmol) and Boc_2O (11.5 g, 52.7 mmol) at room temperature and stirred at 80°C. After 2 h, Boc_2O (5.13 g, 23.5 mmol) was added at room temperature and stirred at 80°C for 1 h. Then the reaction mixture was cooled to 0°C, evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude Bocprotected product as yellow oil. This crude intermediate was directly used for the next transformation.

To a solution of crude Boc-protected intermediate in MeOH (25 mL) was added 2 M NaOH aq (25 mL) at room temperature and stirred at the same temperature for 90 min. Then the reaction mixture was evaporated *in vacuo*, washed with $CHCl_3$, acidified with 5% $KHSO_4$ aq, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford **S1** as a white powder.

^{1}H-NMR (300 MHz, DMSO-d_6, 40°C); δ 1.35 (s, 9H), 3.73 (s, 3H), 4.13 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 12.6 (s, 1H); ^{13}C-NMR (75.0 MHz, DMSO-d_6); δ: 27.7, 51.9, 55.1, 79.5, 113.6, 127.4, 135.55, 135.59, 153.8, 157.0; IR (KBr) 1415, 1513, 1668, 1769, 3142 cm^{-1}; MS (ESI^{+}) m/z 304 (M+Na^{+}, 100); *Anal.* Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.62; H, 6.75; N, 4.90.

Phenyl (4-methoxyphenyl)glycinate (1h)

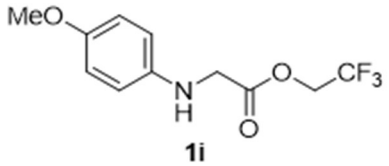


1h

To a solution of **S1** (519 mg, 1.84 mmol) in CH_2Cl_2 (9.2 mL) were added DMAP (22.4 mg, 0.18 mmol), PhOH (324 μL, 3.68 mmol) and EDC·HCl (936 mg, 5.23 mmol) at 0 ºC and stirred at room temperature. After 0.5 h, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude phenyl ester as colorless oil. This product was used for the next step without further purification.
To a solution of crude phenyl ester in CH_2Cl_2 (15.6 mL) was added TFA (1.56 mL) at 0 ºC and stirred at room temperature for 1 h. Then, the reaction mixture was cooled to 0 ºC, basified to pH 8 with sat.$NaHCO_3$aq, extracted with $CHCl_3$, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 3/1) to afford **1h** (284 mg, 60% over two steps) as a pale brown powder.

mp 118–119 ºC (hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.76 (s, 3H), 4.09 (s, 1H), 4.14 (s, 2H), 6.66 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 7.24 (dd, J = 7.5 Hz, 1H), 7.38 (dd, J = 7.5 Hz, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 170.1, 152.8, 150.3, 141.0, 129.5, 126.1, 121.3, 114.9, 114.5, 55.7, 47.0; IR (KBr) 821, 1441, 1517, 1749, 3403 cm^{-1}; MS (ESI^{+}) m/z 258 (M + H^{+}, 52), 280 (M + Na^{+}, 100); Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44; Found: C, 69.93; H, 5.85; N, 5.67.

2,2,2-trifluoroethyl (4-methoxyphenyl)glycinate (1i)



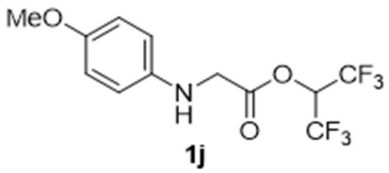
1i

To a solution of **S1** (1.00 g, 3.55 mmol) in CH_2Cl_2 (18 mL) were added DMAP (57.3 mg, 0.469 mmol), TFE (507 μL, 7.10 mmol) and EDC·HCl (936 mg, 5.23 mmol) at 0 ºC and stirred at room temperature. After 2 h, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude TFE ester as colorless oil. This product was used for the next step without further purification.

To a solution of crude TFE ester in CH_2Cl_2 (36 mL) was added TFA (3.55 mL) at 0 ºC and stirred at room temperature for 3 h. Then, the reaction mixture was cooled to 0 ºC, basified to pH 8 with sat.$NaHCO_3$aq, extracted with $CHCl_3$, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 3/1) to afford **1i** (763 mg, 82% over two steps) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$); δ 6.79 (dd, J = 8.8, 2.3 Hz, 2H), 6.58 (dd, J = 8.8, 2.3 Hz, 2H), 4.54 (q, J = 8.3 Hz, 2H), 4.00 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 170.1, 152.8, 140.7, 122.7 (q, J = 275.0 Hz), 114.8, 114.4, 60.5 (q, J = 36.5 Hz), 55.5, 46.2; IR (neat) 1423, 1445, 1517, 1766, 3393 cm^{-1}; MS (ESI$^+$) *m/z* 264 (M + H$^+$, 100), 286 (M + Na$^+$, 75); HRMS (ESI$^+$) *m/z* calcd for $C_{11}H_{13}F_3NO_3$ ([M + H]$^+$): 264.0842, found 264.0836

1,1,1,3,3,3-Hexafluoropropan-2-yl (4-methoxyphenyl)glycinate (1j)



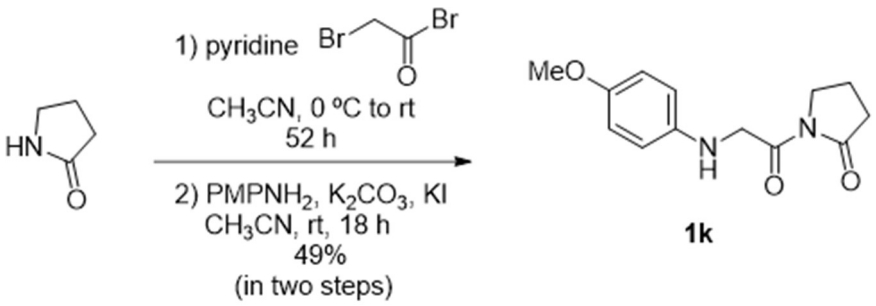
1j

To a solution of **S1** (1.01 g, 3.59 mmol) in CH_2Cl_2 (18 mL) were added DMAP (52.8 mg, 0.432 mmol), HFIP (745 μL, 7.18 mmol) and EDC·HCl (839 mg, 4.38 mmol) at 0 ºC and stirred at room temperature. After 90 min, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude HFIP ester as colorless oil. This product was used for the next step without further purification.

To a solution of crude HFIP ester in CH_2Cl_2 (36 mL) was added TFA (3.59 mL) at 0 ºC and stirred at room temperature for 3 h. Then, the reaction mixture was cooled to 0 ºC, basified to pH 8 with sat.$NaHCO_3$aq, extracted with $CHCl_3$, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 3/1) to afford **1j** (973.1 mg, 82% over two steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 3.75 (s, 3H), 4.13 (s, 2H), 5.80 (hept, *J* = 6.0 Hz, 1H), 6.58 (dd, *J* = 2.2, 9.0 Hz, 2H), 6.80 (dd, *J* = 2.2, 9.0 Hz, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 46.2, 55.7, 66.9 (hept, *J* = 34.6 Hz), 114.5, 115.0, 120.2 (q, *J* = 281.2 Hz), 140.1, 153.2, 168.9; IR (KBr) 1386, 1519, 1789, 3397 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{12}H_{12}F_6NO_3$ ([M + H]+): 332.0716, found 332.0717.

1-((4-Methoxyphenyl)glycyl)pyrrolidin-2-one (1k)

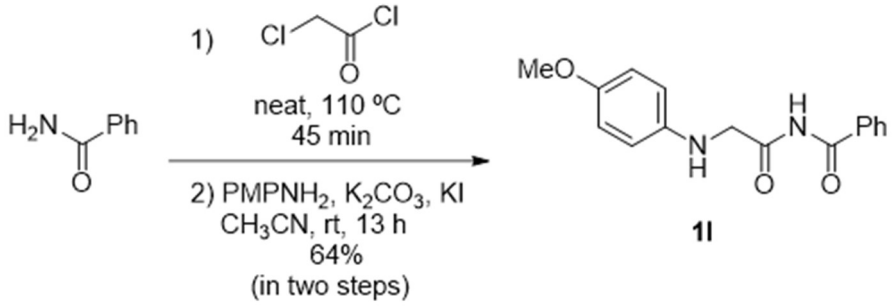


To a solution of pyrrolidin-2-one (630 mg, 7.40 mmol) in CH_3CN (20 mL) were added pyridine (1.19 mL, 14.8 mmol) and bromoacetyl bromide (1.29 mL, 14.8 mmol) at 0 ºC and stirred at room temperature for 52 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* to afford the bromoacetimide intermediate as a brown oil. This intermediate was directly used for the next step without further purifications.

To a solution of bromoacetimide in CH_3CN (20 mL) were added *p*-anisidine (1.12 g, 9.09 mmol), K_2CO_3 (1.54 g, 11.1 mmol) and KI (2.11 g, 12.7 mmol) at room temperature and stirred at the same temperature for 18 h. After that, the reaction mixture was extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to afford **1k** (900 mg, 49% in two steps) a yellow powder.

^{1}H NMR (300 MHz, CDCl3) δ: 2.11 (tt, *J* = 7.1, 8.1 Hz, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 3.74 (s, 3H), 3.86 (t, *J* = 7.1 Hz, 2H), 4.42 (s, 2H), 4.50 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 175.4, 171.6, 152.4, 141.4, 114.9, 114.4, 55.7, 50.1, 45.2, 33.2, 17.6; IR (KBr) 1420, 1515, 1690, 1727, 3385 cm^{-1}: MS (ESI$^+$) *m*/*z* 249 (M + H$^+$, 100); Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28; Found: C, 62.23; H, 6.47; N, 11.16.

_N_-((4-methoxyphenyl)glycyl)benzamide (1l)



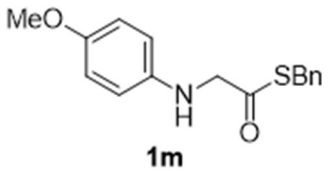
A mixture of benzamide (2.94 g, 24.3 mmol) and chloroacetyl chloride (2.32 mL, 29.1 mmol) was stirred at 110 ºC for 45 min. After that, the reaction mixture was evaporated *in vacuo* to remove the volatile by-products. The resulting residue was added Et_2O and the precipitate was crashed. Then, the supernatant was discarded. This process was repeated six times to afford the crude chloroacetimide. This intermediate was directly used for the next step without further purifications.

To a solution of chloroacetimide in CH_3CN (100 mL) were added *p*-anisidine (3.13 g, 25.4 mmol), K_2CO_3 (3.56 g, 25.8 mmol) and KI (3.24 g, 19.5 mmol) at room temperature and stirred at the same temperature for 13 h. After that, the reaction mixture was evaporated *in vacuo*, extracted with EtOAc, dried over Na_2SO_4, evaporated *in vacuo* and the resulting brown solid was purified by recrystallization from hexane and EtOAc to afford **1l** (4.45 g, 64% in two steps) as a yellow powder.

^{1}H NMR (300 MHz, $CDCl_3$); (300 MHz, CDCl3) δ: 3.76 (s, 3H), 4.36 (s, 1H), 4.40 (s, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.49 (dd, *J* = 7.4 Hz, 2H), 7.62 (dd, *J* = 7.4 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 9.13 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 173.2, 165.4, 152.8, 141.0, 133.3, 132.3, 128.9, 127.7, 115.0, 114.6, 55.7, 50.8; IR (KBr) 727, 1424, 1520, 1731, 3280, 3272 cm^{-1}; MS (ESI$^+$) *m*/*z* 285.3 (M + H$^+$, 100); Anal.

Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85; Found: C, 67.29; H, 5.64; N, 9.67.

_S_-Benzyl 2-((4-methoxyphenyl)amino)ethanethioate (1m)



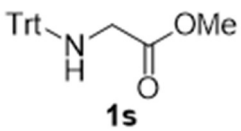
1m

To a solution of **S1** (1.00 g, 3.55 mmol) in CH_2Cl_2 (15 mL) were added BnSH (439 μL, 3.73 mmol) and EDC·HCl (842 mg, 4.39 mmol) at room temperature and stirred at the same temperature for 11 h. Then, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude thioester as an yellow oil. This product was used for the next step without further purification.

To a solution of crude thioester in CH_2Cl_2 (30 mL) was added TFA (3.00 mL) at room temperature and stirred at the same temperature for 2 h. Then, the reaction mixture was cooled to 0 ºC, basified to pH 8 with sat.$NaHCO_3$aq, extracted with $CHCl_3$, dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 4/1 to 3/1) to afford **1m** (525.8 mg, 52% over two steps) as a white powder.

^{1}H NMR (300 MHz, $CDCl_3$); δ 3.74 (s, 3H), 4.02 (s, 2H), 4.11 (s, 2H), 6.56 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 7.32-7.19 (m, 5H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 32.8, 55.0, 55.7, 114.1, 114.9, 127.3, 128.6, 128.8, 137.3, 140.7, 152.8, 200.6; IR (KBr) 823, 1436, 1459, 1515, 1682, 3399 cm^{-1}; MS (ESI$^+$) m/z 288 (M + H$^+$, 97), 310 (M + Na$^+$, 100); Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; Found: C, 66.57; H, 5.81; N, 4.81.

Methyl Tritylglycinate (1s)



1s

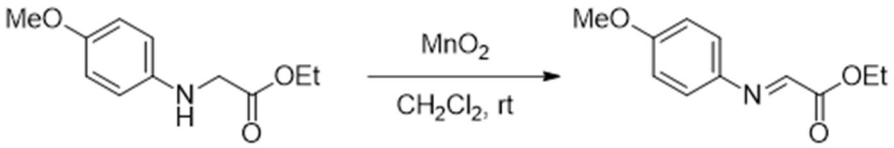
To a solution of methylglycinate hydrochloride (1.26 g, 10.0 mmol) in *N*,*N*-

dimethylformamide (DMF) (20 mL) were added Et_3N (3.50 mL, 25.1 mmol) and chlorotriphenylmethane (2.90 g, 10.4 mmol) at 0 °C. After stirring the resulting white suspension at room temperature for 19 h, the reaction was added H_2O, extracted with EtOAc/hexane (2/1), dried over Na_2SO_4, evaporated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford **1s** (2.74 g, 83%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$); δ 3.21 (s, 2H), 3.65 (s, 3H), 7.23–7.26 (m, 3H), 7.32–7.35 (m, 6H), 7.53–7.55 (m, 6H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 45.7, 51.7, 70.7, 126.5, 127.9, 128.6, 145.3, 172.6 cm^{-1}; IR (neat) 706, 1491, 1742, 3330 cm^{-1}; HRMS (ESI$^+$) *m*/*z* Calcd for $C_{22}H_{21}NO_2$ ([M+Na]$^+$) 354.1465. Found 354.1470.

MnO_2-mediated oxidation

Ethyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (2a)

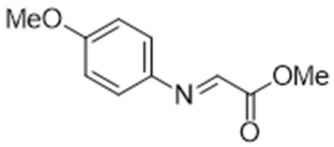


1a **2a**

To a solution of **1a** (209 mg, 1.00 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (740 mg, 20.0 mmol) at room temperature and stirred at room temperature for 1 h. Then, the reaction mixture was passed through Celite and the filtrate was evaporated *in vacuo* to afford the corresponding imine **2a** (193 mg, 93%) as a red oil.

^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.40 (t, J = 7.3 Hz, 3H), 3.84 (s, 3H), 4.42 (q, J = 7.3 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H), 7.94 (s, 1H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); δ 14.2, 55.5, 61.9, 114.5, 123.6, 141.3, 147.9, 160.5, 163.6; IR (neat) 1506, 1585, 1713, 1741, 2987 cm^{-1}; MS (ESI$^+$) *m*/*z* 208 (M+H$^+$, 13), 230 (M+Na$^+$, 100); HRMS (ESI$^+$) *m*/*z* Calcd for $C_{11}H_{14}NO_3$ ([M+H]$^+$) 208.0968. Found 208.0973.

Methyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (2b)

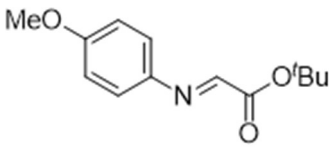


2b

The similar procedure described for the synthesis of **2a** afforded **2b** in 92% yield as a red oil.

^{1}H NMR (300 MHz, $CDCl_3$); δ: 3.84 (s, 3H), 3.95 (s, 3H), 6.94 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.95 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 164.1, 160.6, 147.3, 141.1, 123.6, 114.5, 55.5, 52.8; IR (neat) 1507, 1585, 1743 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{10}H_{12}NO_3$ ([M + H]$^+$): 194.0812, found 194.0814.

***tert*-butyl (*E*)-2-((4-methoxyphenyl)imino)acetate 2c**

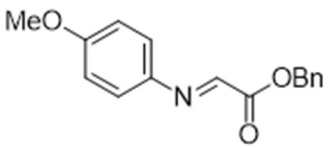


2c

The similar procedure described for the synthesis of **2a** afforded **2c** in 98% yield as a red oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 1.59 (s, 9H), 3.83 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.86 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 27.9, 55.4, 82.7, 114.3, 123.4, 136.4, 141.6, 149.4, 160.2,162.8; IR (neat) 1506, 1593, 1733, 2980 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{18}NO_3$ ([M + H]$^+$): 236.1281, found 236.1289.

Benzyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (2d)

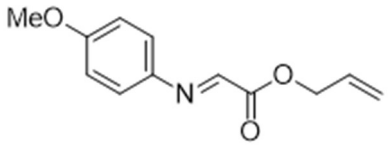


2d

The similar procedure described for the synthesis of **2a** afforded **2d** in 90% yield as a red oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 3.84 (s, 3H), 5.38 (s, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.42–7.34 (m, 5H), 7.48–7.44 (m, 2H), 7.97 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 55.5, 67.4, 114.5, 123.6, 128.5, 128.59, 128.62, 135.2, 141.3, 147.5, 160.6, 163.3; IR (neat) 836, 1459, 1510, 1585, 1741 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{16}H_{16}NO_3$ ([M + H]$^+$): 270.1125, found 270.1142.

Allyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (2e)

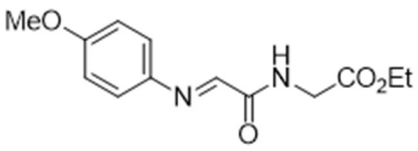


2e

The similar procedure described for the synthesis of **2a** afforded **2e** in 87% yield as a red oil.

^{1}H NMR (400 MHz, $CDCl_3$); δ 3.84 (s, 3H), 4.84 (ddd, *J* = 1.2, 1.2, 6.0 Hz, 2H), 5.32 (ddd, *J* = 1.2, 1.2, 10.3 Hz, 1H), 5.43 (ddd, *J* = 1.2, 1.2, 16.0 Hz, 1H), 6.03 (ddd, *J* = 6.0, 10.3, 16.0 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.97 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 55.4, 66.3, 114.5, 119.4, 123.6, 131.4, 136.5, 141.2, 147.4, 160.6, 163.2; IR (neat) 935, 990, 1463, 1506, 1585, 1743, 3367 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{12}H_{14}NO_3$ ([M + H]$^+$): 220.0968, found 220.0976

Ethyl (*E*)-(2-((4-methoxyphenyl)imino)acetyl)glycinate (2f)

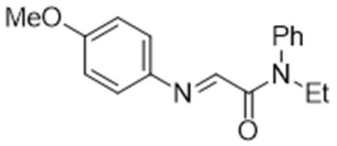


2f

The similar procedure described for the synthesis of **2a** afforded **2f** in 95% yield as a red solid.

^{1}H NMR (300 MHz, $CDCl_3$); δ 1.31 (t, J = 7.1 Hz, 3H), 4.18 (d, J = 5.5 Hz, 2H), 3.64 (s, 3H), 4.26 (q, J = 7.1 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.70 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 14.0, 40.9, 55.3, 61.4, 114.4, 123.4, 140.2, 149.4, 160.1, 163.8, 169.4; IR (neat) 1464, 1506, 1593, 1680, 1752, 2982, 3382 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{17}N_2O_4$ ([M + H]$^+$): 265.1183, found 265.1188

(E)-*N*-ethyl-2-((4-methoxyphenyl)imino)-*N*-phenylacetamide (2g)

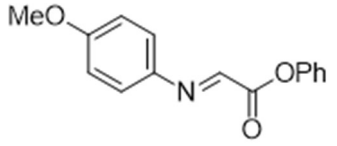


2g

The similar procedure described for the synthesis of **2a** afforded **2g** in 99% yield as a red solid.

^{1}H NMR (400 MHz, $CDCl_3$); δ 1.22 (t, J = 7.3 Hz, 3H), 3.77 (s, 3H), 3.95 (q, J = 7.3 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 7.3 Hz, 2H), 7.38 (dd, J = 7.3, 7.3 Hz, 1H), 7.44 (dd, J = 7.3, 7.3 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 12.7, 44.7, 55.3, 114.1, 122.8, 127.9, 128.2, 129.6, 136.4, 140.5, 142.5, 150.7, 159.1, 162.6; IR (neat) 835, 1458, 1498, 1593, 1662, 2979 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{17}H_{19}N_2O_2$ ([M + H]$^+$): 283.1441, found 283.1455

Phenyl (*E*)-2-((4-methoxyphenyl)imino)acetate (2h)



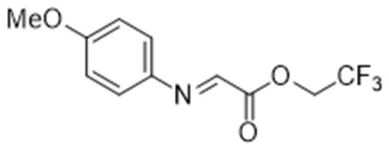
2h

The similar procedure described for the synthesis of **2a** afforded **2h** in 92% yield as a red solid.

^{1}H NMR (400 MHz, $CDCl_3$); δ 3.87 (s, 3H), 6.98 (d, J = 9.0 Hz, 2H), 7.31–7.23 (m, 3H), 7.46–7.40 (m, 4H), 8.14 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 55.5, 114.6, 121.4, 123.9, 126.2, 129.5, 141.0, 146.7, 150.5, 160.9, 162.0; IR (neat) 837, 1509, 1585, 1759

cm^{-1}; HRMS (ESI^+) *m*/*z* calcd for $C_{15}H_{14}NO_3$ ($[M + H]^+$): 256.0968, found 256.0963

2,2,2-Trifluoroethyl (*E*)-2-((4-Methoxyphenyl)imino)acetate (2i)

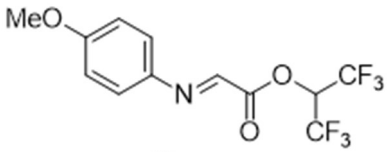


2i

The similar procedure described for the synthesis of **2a** afforded **2i** in 98% yield as a red solid.

^1H NMR (400 MHz, $CDCl_3$); δ 3.85 (s, 3H), 4.72 (q, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 55.5, 61.0 (q, *J* = 36.4 Hz), 114.6, 122.7 (q, *J* = 275.0 Hz), 124.0, 136.5, 140.7, 145.0, 161.1, 161.6; IR (neat) 1443, 1507, 1585, 1763 cm^{-1}; HRMS (ESI^+) *m*/*z* calcd for $C_{11}H_{11}F_3NO_3$ ($[M + H]^+$): 262.0686, found 262.0698

1,1,1,3,3,3-hexafluoropropan-2-yl (*E*)-2-((4-methoxyphenyl)imino)acetate (2j)

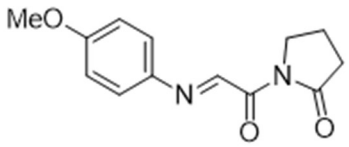


2j

The similar procedure described for the synthesis of **2a** afforded **2j** in 98% yield as a red solid.

^1H NMR (400 MHz, $CDCl_3$); δ 3.86 (s, 3H), 5.98 (hept, *J* = 6.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 8.07 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 55.5, 67.2 (hept, *J* = 35.2 Hz), 114.7, 120.3 (q, *J* = 280.0 Hz), 124.4, 140.4, 142.9, 159.9, 161.7; IR (neat) 1512, 1579, 1748 cm^{-1}; HRMS (ESI^+) *m*/*z* calcd for $C_{12}H_{10}F_6NO_3$ ($[M + H]^+$): 330.0559, found 330.0556

(*E*)-1-(2-((4-Methoxyphenyl)imino)acetyl)pyrrolidin-2-one (2k)

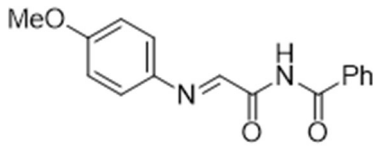


2k

The similar procedure described for the synthesis of **2a** afforded **2k** in 96% yield as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$); δ 2.18 (tt, *J* = 7.3, 8.3 Hz, 2H), 2.68 (t, *J* = 8.3 Hz, 2H), 3.97 (t, *J* = 7.3 Hz, 2H), 3.84 (s, 3H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 8.86 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 17.7, 32.9, 45.1, 55.4, 114.3, 123.6, 142.2, 150.6, 160.1, 163.7, 176.0; IR (neat) 1508, 1580, 1691, 1741 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{14}N_2NaO_3$ ([M + Na]$^+$): 269.0897, found 269.0892

(*E*)-*N*-(2-((4-methoxyphenyl)imino)acetyl)benzamide (2l)

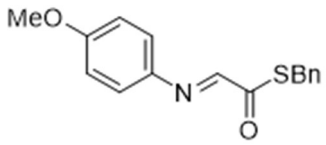


2l

The similar procedure described for the synthesis of **2a** afforded **2l** in 91% yield as a red solid.

^{1}H NMR (300 MHz, $CDCl_3$); δ 3.85 (s, 3H), 6.96 (dd, *J* = 2.0, 2.2 Hz 2H), 7.39 (dd, *J* = 2.0, 2.2 Hz, 2H), 7.60–7.63 (m, 1H), 7.92 (d, 1.5 Hz, 1H), 7.93 (br, 2H), 10.59 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 55.5, 114.7, 127.7, 128.9, 133.1, 138.8, 148.3, 161.2, 161.4, 164.3; IR (neat) 837, 1504, 1579, 1682, 1743, 3354 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{16}H_{15}N_2O_3$ ([M + H]$^+$): 283.1077, found 283.1085

_S_-Benzyl (_E_)-2-((4-Methoxyphenyl)imino)ethanethioate (2m)



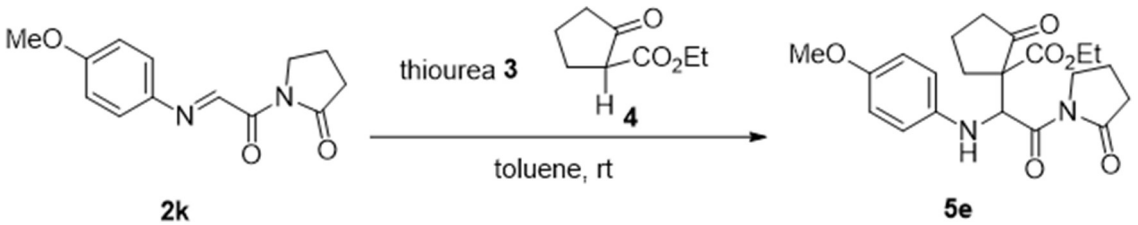
2m

The similar procedure described for the synthesis of **2a** afforded **2m** in quantitative yield as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$); δ 3.84 (s, 3H), 4.23 (s, 2H), 6.93 (d, J = 9.0 Hz, 2H), 7.38–7.22 (m, 7H), 8.02 (s, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 32.6, 55.5, 114.6, 124.1, 127.3, 128.6, 129.0, 137.2, 140.3, 151.0, 160.8, 191.9; IR (neat) 838, 1457, 1505, 1583, 1659 cm^{-1}; HRMS (ESI$^+$) m/z calcd for $C_{16}H_{16}NO_2S$ ([M + H]$^+$): 286.0896, found 286.0903

Asymmetric Mannich reaction of _α_-imino carboxylic acid derivatives

Ethyl 1-(1-((4-Methoxyphenyl)amino)-2-oxo-2-(2-oxopyrrolidin-1-yl)ethyl)-2-oxocyclopentane-1-carboxylate (5e)



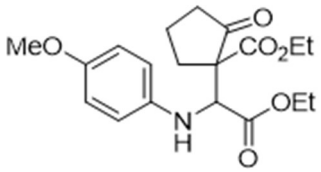
2k **5e**

A mixture of **2k** (18.4 mg, 0.0747 mmol), thiourea **3** (3.0 mg, 0.00726 mmol) and cyclopentanone-2-carboxylic acid ethyl ester **4** (21.6 μL, 0.149 mmol) in toluene (0.75 mL) was stirred at room temperature for 24 h. Then, the reaction mixture was directly purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to afford the desired Mannich adduct **5e** (23.1 mg, 77%, dr = 69 : 31) as a red oil.

HPLC [Chiralpak IA, hexane/2-propanol = 90/10, 1.0 mL/min, λ =254 nm, retention times: (major) 22.1 min (minor) 16.9 min, 90% ee]; $[\alpha]^{23}_D$ +9.2 (c = 0.94 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$); Mixture of diastereomers δ 1.24 (t, J = 9.5 Hz, 3H), 1.89–2.10 (m, 4H), 2.23–2.48 (m, 3H), 2.51–2.71 (m, 3H), 3.70–3.84 (m, 5H), 4.07–4.20 (m, 3H),

6.35 (s, 1H), 6.71–6.74 (m, 2H), 6.77–6.82 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 13.9, 17.0, 19.7, 31.5, 33.7, 38.3, 45.8, 55.7, 59.0, 61.9, 63.6, 114.7, 116.8, 140.1, 153.3, 170.0, 173.0, 175.5, 212.7; IR (neat) 1463, 1513, 1690, 1745, 2982, 3363 cm^{-1}; HRMS (ESI^+) *m*/*z* calcd for $C_{21}H_{27}N_2O_6$ ($[M + H]^+$): 403.1864, found 403.1862

Ethyl 1-(2-Ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclopentane-1-carboxylate (5a)

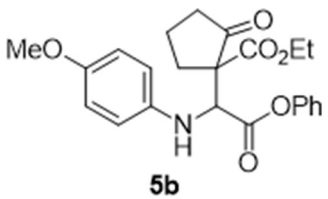


5a

A procedure similar to that described for the preparation of **5e** afforded **5a** in 25% yield as pale yellow oil. (dr=57 : 43).

HPLC [Chiralpak IC-3, hexane–2-propanol=95 : 5, 1.0 mL/min, λ =254 nm, retention times: (major) 63.6 min, (minor) 54.7 min, 84% ee and (major) 47.1 min, (minor) 35.4 min, 36% ee]; $[\alpha]^{20}_D$ +0.15 (*c* = 0.58 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$); (mixture of diastereomers, with signals corresponding to the one of them indicated by) δ 1.15–1.27 (m, 6H), 1.97–1.98 (m, 2H), 2.12–2.33 (m, 2H), 2.38–2.55 (m, 2H), 3.72 (s, 3H), 4.10–4.20 (m, 4H), 4.66–4.73 (m, 1H), 6.59–6.81 (m, 4H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) (mixture of diastereomers); δ 13.9, 14.0, 19.3, 19.8, 29.8, 30.9, 37.6, 38.7, 55.6, 61.1, 61.4, 61.7, 61.8, 62.5, 64.7, 114.5, 114.6, 115.9, 116.8, 140.8, 141.5, 153.2, 168.8, 169.4, 171.5, 171.6, 211.8, 212.3; IR (neat) 827, 1514, 1724, 2981, 3362 cm^{-1}; HRMS (ESI^+) *m*/*z* Calcd for $C_{19}H_{26}NO_6$ ($[M+H]^+$) 364.1755. Found 364.1743.

Ethyl 1-(1-((4-Methoxyphenyl)amino)-2-oxo-2-phenoxyethyl)-2-oxocyclopentane-1-carboxylate (5b)

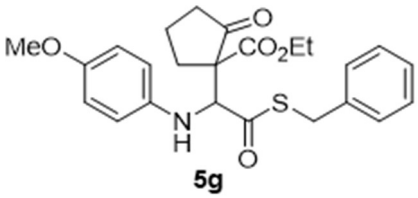


5b

A procedure similar to that described for the preparation of **5e** afforded **5b** in 31% yield as pale yellow oil. (dr=51 : 49).

HPLC [Chiralpak IB-3, hexane–2-propanol= 90 : 10, 1.0 mL/min, λ =254 nm, retention times: (major) 15.3 min, (minor) 11.6 min, 51% ee and (major) 13.6 min, (minor) 17.2 min, 7% ee]; $[\alpha]^{20}_{D}$ −11.1 (*c*=0.86 in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$); (mixture of diastereomers, with signals corresponding to the one of them indicated by) *δ*: 1.10–1.21 (m, 3H), 1.86–2.04 (m, 2H), 2.13–2.60 (m, 4H), 3.68 (s, 3H), 4.09–4.17 (m, 2H), 4.79 (s, 1H), 6.69–6.74 (m, 3H), 6.79–6.81 (m, 1H), 6.87–6.89 (m, 1H), 7.00–7.01 (m, 1H), 7.11–7.16 (m, 1H), 7.23–7.29 (m, 2H); ^{13}C-NMR (75.0 MHz, $CDCl_3$); (mixture of diastereomers) *δ*: 14.0, 19.4, 19.9, 30.2, 31.6, 37.5, 38.6, 55.6, 55.7, 61.4, 62.09, 62.12, 62.5, 62.6, 65.0, 114.7, 114.8, 116.2, 117.3, 121.2, 121.3, 126.1, 126.2, 129.4, 140.3, 150.2, 150.4, 153.7, 153.9, 169.1, 169.9, 170.3, 170.4, 212.3, 212.6; IR (neat) 825, 1463, 1514, 1724, 1753, 2980, 3368 cm^{-1}; HRMS (ESI^+) *m/z* Calcd for $C_{23}H_{26}NO_6$ ($[M+H]^+$) 412.1755. Found 412.1749.

Ethyl 1-(2-(Benzylthio)-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclopentane-1-carboxylate (5g)



5g

A procedure similar to that described for the preparation of **5e** afforded **5g** in 40% yield as pale yellow oil. (dr=51 : 49).

HPLC [Chiralpak IC-3, hexane/2-propanol = 97/3, 1.0 mL/min, λ = 254 nm, retention times: (major) 75.3 min, (minor) 85.5 min, 82% ee]; $[\alpha]^{23}_{D}$ −66.4 (*c* = 0.45 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); Mixture of diastereomers δ1.00 (t, *J* = 7.0 Hz, 3H × 1/2), 1.09 (t, *J* = 7.0 Hz, 3H × 1/2), 1.84–1.94 (m, 3H), 2.12–2.54 (m, 4H), 3.66 (s, 3H), 3.89–4.06 (m, 4H), 4.79 (s, 1H), 6.59–6.70 (m, 4H), 7.11–7.21 (m, 5H); ^{13}C NMR (75.0 MHz, $CDCl_3$); Mixture of diastereomers δ 13.7, 13.9 19.4, 19.8, 29.4, 30.4, 33.5, 33.8, 37.7, 38.7, 55.6, 55.6, 62.0, 62.1, 62.7, 65.0, 67.8, 67.9, 114.7, 114.8, 115.1, 115.7, 127.2, 127.3, 128.5, 128.8, 128.9, 136.9, 137.1, 139.8, 140.0, 153.2, 153.3, 168.3, 169.0, 200.0,

202.0, 210.6, 213.4; IR (neat) 824, 1460, 1514, 1679, 1724, 1752, 2980, 3382 cm^{-1}; HRMS (ESI^+) *m/z* calcd for $C_{24}H_{28}NO_5S$ ($[M + H]^+$): 442.1683, found 442.1676

Measurement of absorbance at 250 nm

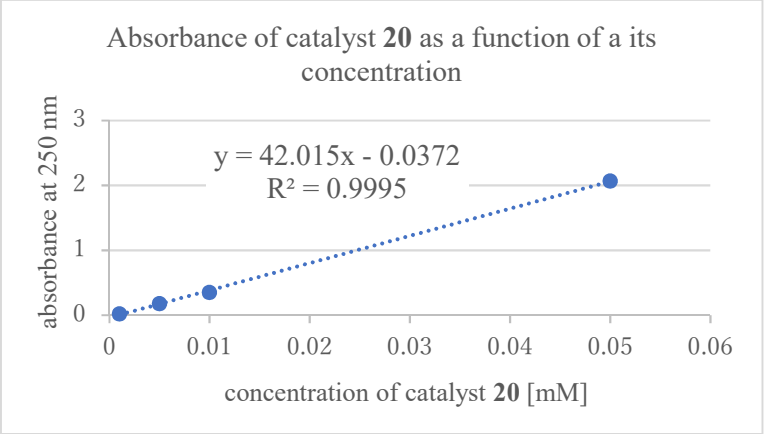


Figure S2.1 Plot of calibration curve

Absorbances of Solutions Saturated with catalyst **20** at 4 ℃

saturated solutions	Absorbance at 250 nm	catalyst **20** [mM]
$CHCl_3$	3.4	141.0
CH_2Cl_2	0.2	6.4
Toluene	0.04	1.5
THF	0.1	4.5
MeOH	N.D.	N.D.
MeCN	N.D.	N.D.

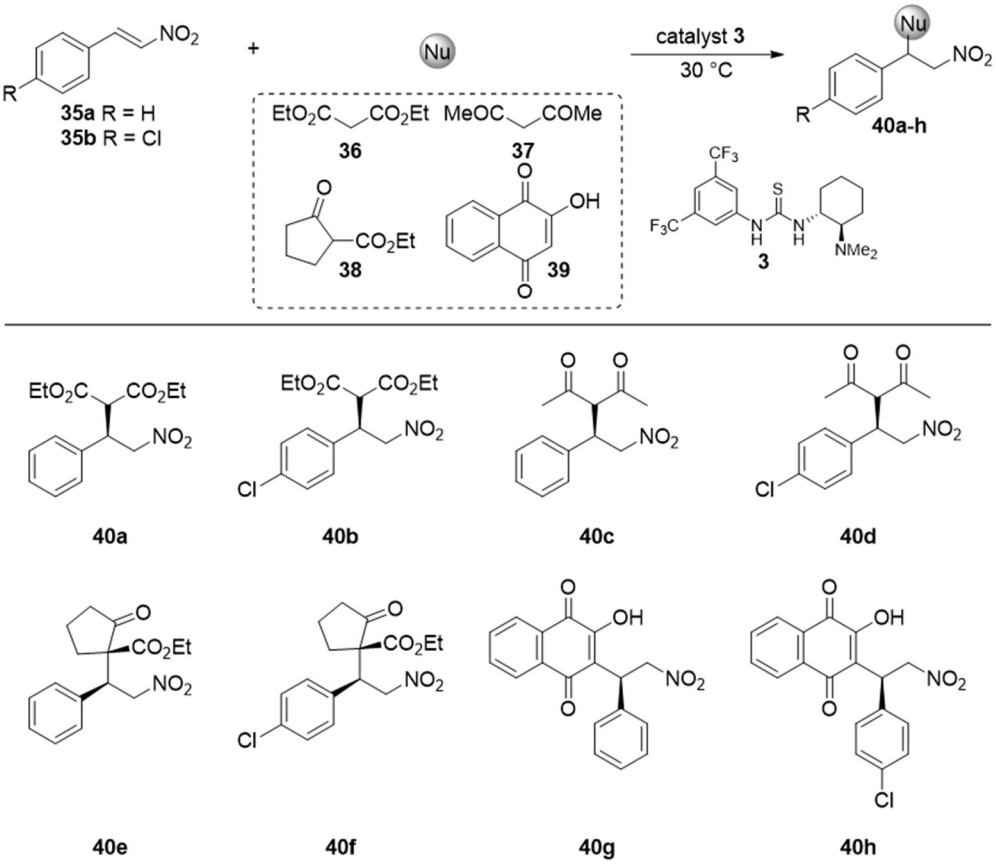
Absorbances of Solutions Saturated with catalyst **20** at 20 ℃

saturated solutions	Absorbance at 250 nm	catalyst **20** [mM]
$CHCl_3$	3.7	156.5
CH_2Cl_2	0.2	7.5
Toluene	0.04	1.7
THF	0.1	4.7
MeOH	N.D.	N.D.
MeCN	N.D.	N.D.

Absorbances of Solutions Saturated with catalyst **20** at 30 ℃

saturated solutions	Absorbance at 250 nm	catalyst **20** [mM]
$CHCl_3$	4.2	176.5
CH_2Cl_2	0.7	30.9
Toluene	0.9	39.5
THF	0.8	32.4
MeOH	0.003	0.1
MeCN	0.002	0.1

Table S1. Evaluation of catalysts **3** in the Michael reactions



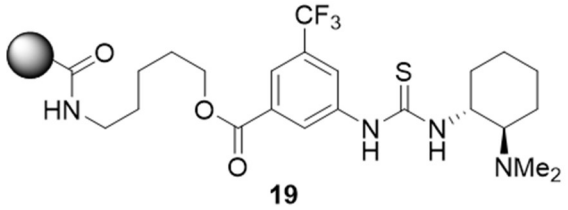
Entry [a]	35	Solvent	Time (h)	Yield (%)[b]		Dr	Ee (%)[c]
1	**35a**	toluene	24	**40a**	80		90
2	**35b**	toluene	24	**40b**	85		93
3	**35a**	toluene	24	**40c**	99		92
4	**35b**	toluene	24	**40d**	96		90
5	**35a**	toluene	24	**40e**	89	9:1	74
6	**35b**	toluene	24	**40f**	95	9:1	71
7	**35a**	CH_2Cl_2	4	**40g**	86		91
8	**35b**	CH_2Cl_2	4	**40h**	90		93

[a] Reactions were carried out with **35** (1 eq.) and **36**-**39** (2 eq.) in solvent (0.1 M) in the presence of **3** (10 mol%)

[b] Isolated yields.

[c] Determined by chiral HPLC analysis.

Resin-bound thiourea (19)

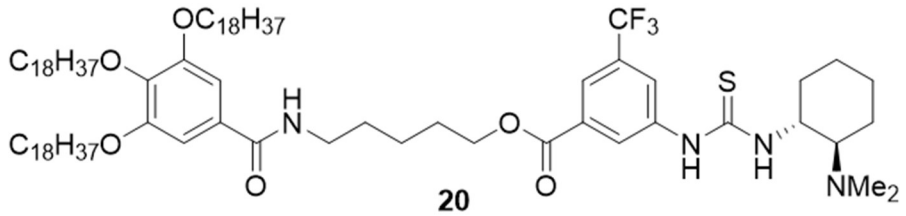


19

Yellow solid

IR (KBr) 1603, 1724, 1787, 2852, 2926, 3298 cm^{-1}

5-(3,4,5-tris(octadecyloxy)benzamido)pentyl 3-(3-((1R,2R)-2-(dimethylamino)cyclohexyl)thioureido)-5-(trifluoromethyl)benzoate (20)

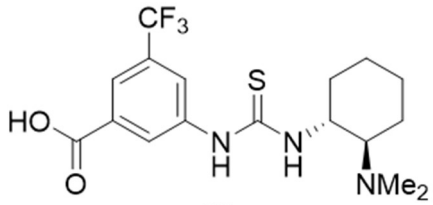


20

White powder

$[\alpha]^{20}_{D}$ −7.6 (*c* = 1.02 in $CHCl_3$) ^{1}H-NMR (400 MHz, $CDCl_3$); δ 0.88 (t, *J* = 10.2, 6.8 Hz, 9H), 1.20–1.37 (m, 90H), 1.40–1.50 (m, 8H), 1.67–1.90 (m, 14H), 2.31 (s, 6H), 3.47 (dd, *J* = 14.4, 6.2 Hz, 2H), 4.37 (t, *J* = 7.2 6.2 Hz, 2H), 6.13 (t, *J* = 7.2, 5.4 Hz, 1H), 6.95 (s, 1H), 7.97 (s, 1H), 8.04 (s, 1H), 8.12 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 23.8, 24.5, 24.7, 26.2, 28.4, 29.5, 29.6, 29.8, 29.9, 32.1, 40.1, 40.2, 65.6, 69.5, 73.6, 69.5, 73.6, 105.9, 121.7, 122.4, 125.3, 123.8, 127.2, 129.9, 131.4, 131.8, 132.0, 141.1, 153.2, 165.0, 167.7; IR (KBr) 1125, 1255, 1502, 1582, 1725, 2849, 2917, 3257 cm^{-1}; HRMS (ESI) m/z calcd for $C_{83}H_{145}F_3N_4O_6S$ [M+H] + 1384.0837, found 1384.0870.

3-(3-((1R,2R)-2-(dimethylamino)cyclohexyl)thioureido)-5-(trifluoromethyl)benzoic acid (29)

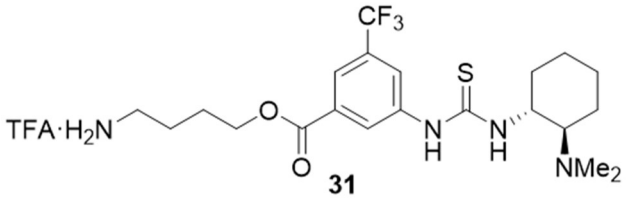


29

White powder

$[\alpha]^{20}_{D}$ +1.2 (*c* = 1.07 in $CHCl_3$) ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.34–1.57 (m, 4H), 1.79–1.89 (m, 1H), 1.94–2.04 (m, 1H), 2.09–2.17 (m, 1H), 2.24–2.34 (m, 1H), 3.74 (m, 1H), 4.86 (m, 1H), 7.75 (s, 1H), 8.25 (s, 1H), 8.34 (s, 1H), 8.61 (d, *J* = 8.76 Hz, 1H), 9.24 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6); δ 22.8, 23.6, 23.7, 31.7, 52.4, 66.2, 120.1, 122.0, 125.4, 126.3, 129.0, 129.4, 132.4, 141.3, 165.9, 180.5; IR (KBr) 1341, 1543, 1607, 1707, 2866, 2944, 3303 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{22}F_3N_3O_2S$ [M+H] +390.1385, found 390.1453.

4-aminobutyl 3-(3-((1R,2R)-2-(dimethylamino)cyclohexyl)thioureido)-5-(trifluoromethyl)benzoate (31)

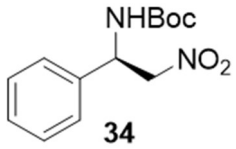


31

Colorless oil.

$[\alpha]^{20}_{D}$ +50.1 (*c* = 1.42 in MeOH); ^{1}H NMR (400 MHz, CD_3OD); δ 1.29–1.34 (m, 2H), 1.44 (br, 3H), 1.56–1.62 (m, 3H), 1.73–1.89 (m, 5H), 1.96 (br, 2H), 2.16–2.21 (m, 1H), 2.94 (s, 6H), 3.21 (q, *J* = 7.3 Hz, 2H), 4.40 (t, *J* = 6.3 Hz, 2H), 7.99 (s, 1H), 8.34 (s, 1H), 8.48 (s, 1H); ^{13}C-NMR (100 MHz, CD_3OD); 24.1, 25.1, 25.4, 28.2, 28.3, 29.2, 33.2, 40.7, 42.9, 47.9, 54.3, 66.3, 69.0, 117.3 (q, *J* = 287 Hz), 123.7, 124.5 (q, *J* = 205.8 Hz), 132.0 (q, *J* = 33.4 Hz), 142.4, 161.6 (q, *J* = 37.0 Hz), 166.3, 183.4; IR (KBr) 1260, 1776, 2870, 2949, 3252, 3570 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{33}F_3N_4O_2S$ [M+Na] + 474.2276, found 474.2166.

***tert*-Butyl (*R*)-2-nitro-1-phenylethylcarbamate (34)**[19b]



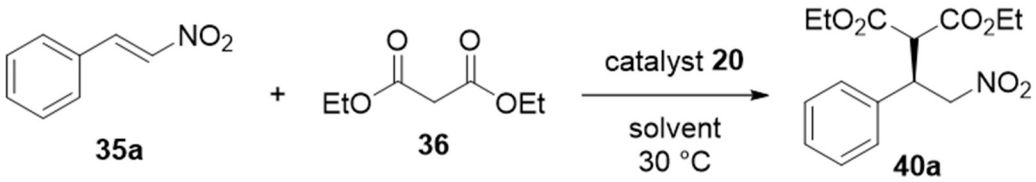
34

Yield 81% ; white solid.

HPLC [Chiralpak IC-3, hexane/2-propanol = 85/15, 1.0 mL/min, λ = 254 nm, retention times: (major) 10.0 min, (minor) 15.6 min, 91% ee]; $[\alpha]^{20}_{D}$ −21.1 (*c* = 1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.46 (s, 9H), 4.68–4.72 (m, 1 H), 4.85 (br s, 1H), 5.29 (br s, 1H), 5.37 (br s, 1 H), 7.35 (m, 5 H)

Michael reaction of nitrostyrenes and several nucleophiles.

Diethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate (40a)[25c]

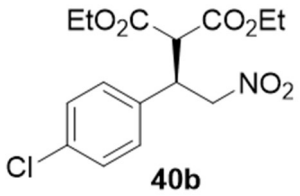


35a **36** **40a**

A mixture of **35** (14.9 mg, 0.1 mmol), catalyst **20** (41.5 mg, 0.03 mmol) and nucleophile **36** (30.2 μL, 0.2 mmol) in toluene (1.0 mL) was stirred at 30 °C for 72 h. Then, the reaction mixture was directly purified by silica gel column chromatography (hexane–EtOAc = 10/1 to 4/1) to afford the desired product **40a** (23.1 mg, 81%, 90% ee) as a colorless oil.

HPLC [Chiralpak IA, hexane/2-propanol = 90/10, 1.0 mL/min, λ = 254 nm, retention times: (major) 14.6 min, (minor) 31.7 min, 90% ee]; $[\alpha]^{20}_{D}$ −7.4 (*c* = 0.76 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.06 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 2.32 (d, *J* = 9.3 Hz, 1H), 4.01 (q, *J* = 7.3 Hz, 2H), 4.19–4.26 (m, 3H), 4.83–4.95 (m, 2H), 7.23–7.34 (m, 5H)

Ethyl (*S*)-2-carboethoxy-4-nitro-3-(4-chlorphenyl)butyrate (40b)[25c]

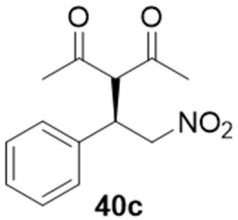


40b

A procedure similar to that described for the preparation of **40a** afforded **40b** in 80% yield as a colorless oil.

HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 1.0 mL/min, λ = 254 nm, retention times: (major) 18.3 min, (minor) 15.7 min, 93% ee]; $[\alpha]^{20}_{D}$ −7.5 (*c* = 1.47 in $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$); δ 1.09 (t, *J* = 9.3 Hz, 3H), 1.27 (t, *J* = 9.3 Hz, 3H), 3.78 (d, *J* = 12.2 Hz, 1H), 4.04 (q, *J* = 9.5 Hz, 2H), 4.18–4.25 (m, 3H), 4.83–4.92 (m, 2H), 7.19 (d, *J* = 11.0 Hz, 2H), 7.30 (d, *J* = 11.0 Hz, 2H)

(*R*)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione (40c)[26]

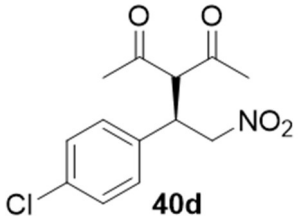


40c

A procedure similar to that described for the preparation of **40a** afforded **40c** in 98% yield as a white solid.

HPLC [Chiralpak IA, hexane/2-propanol = 95/5, 1.0 mL/min, λ = 210 nm, retention times: (major) 23.7 min, (minor) 17.5 min, 74% ee]; $[\alpha]^{20}_{D}$ −190.3 (*c* = 1.16 in $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$); δ 1.94 (s, 3H), 2.29 (s, 3H), 4.21–4.27 (m, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.59–4.68 (m, 2H), 7.17–7.19 (m, 2H), 7.29–7.35 (m, 3H)

(*R*)-3-(1-(4-chlorophenyl)-2-nitroethyl)pentane-2,4-dione[27]

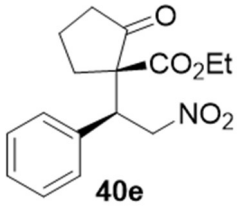


40d

A procedure similar to that described for the preparation of **40a** afforded **40d** in 97% yield as a white solid.

HPLC [Chiralpak IA, hexane/2-propanol = 90/10, 1.0 mL/min, λ = 210 nm, retention times: (major) 17.4 min, (minor) 36.9 min, 90% ee]; $[\alpha]^{20}_{D}$ −176.0 (*c* = 1.07 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.98 (s, 3H), 2.29 (s, 3H), 4.22–4.34 (m, 1H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.60–4.62 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H)

(*R*)-ethyl 1-((*S*)2-nitro-1-phenylethyl)-2-oxocyclopentane-1-carboxylate (40e)[28]

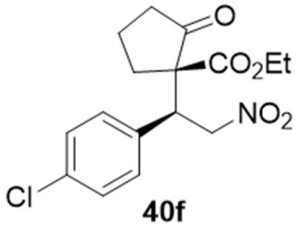


40e

A procedure similar to that described for the preparation of **40a** afforded **40e** in 95% yield as a colorless oil. (dr = 90 : 10)

HPLC [Chiralcel OD-H, hexane/2-propanol = 93/7, 1.0 mL/min, λ = 210 nm, retention times: (major) 21.3 min, (minor) 15.2 min, 78% ee]; $[\alpha]^{20}_{D}$ −22.4 (*c* = 0.45 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$); Mixture of diastereomers δ1.28 (t, *J* = 7.3 Hz, 3H), 1.81−2.05 (m, 4H), 2.32−2.41 (m, 2H), 4.07 (dd, *J* = 7.3, 3.8 Hz, 1H), 4.19−4.24 (m, 2H), 4.8−5.04 (m, 1H), 5.15−5.31, (m, 1H), 7.24−7.33 (m, 5H)

(*R*) -ethyl 1-((*S*)1-(4-chlorophenyl)-2-nitroethyl)-2-oxocyclopentane-1-carboxylate (40f)[20b,29]

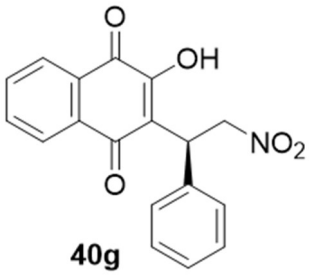


40f

A procedure similar to that described for the preparation of **40a** afforded **40f** in 88% yield as a colorless oil. (dr = 90 : 10)

HPLC [Chiralcel IC-3, hexane/2-propanol = 95/5, 1.0 mL/min, λ = 210 nm, retention times: (major) 24.9 min, (minor) 19.6 min, 80% ee]; $[\alpha]^{20}_{D}$ −25.5 (*c* = 1.12 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$); Mixture of diastereomers δ 1.24 (t, *J* = 5.8 Hz, 3H), 1.82−2.10 (m, 4H), 2.34−2.42 (m, 2H), 4.03 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.19 (q, 4.0 Hz, 1H), 4.22 (q, 4.0 Hz, 1H), 4.97 (dd, *J* = 10.8, 9.1 Hz, 1H), 5.15 (dd, *J* = 11.1, 3.0 Hz, 1H), 7.22 (d, *J* = 6.8 Hz, 2H), 7.28 (d, *J* = 6.8 Hz, 2H)

(*S*)-2-Hydroxy-3-(2-nitro-1-phenylethyl)naphthalene-1,4-dione (40g)[30]

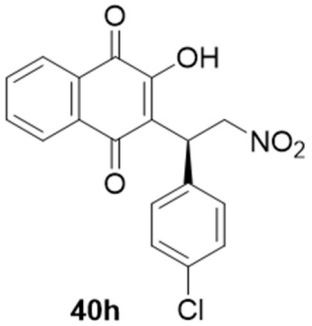


40g

A procedure similar to that described for the preparation of **40a** afforded **40g** in 95% yield as an orange solid.

HPLC [Chiralcel IA hexane (0.1% TFA)/DCM/EtOH = 90/5/5, 1.0 mL/min, λ = 254 nm, retention times: (major) 32.2 min, (minor) 41.7 min, 91% ee]; $[\alpha]^{20}_{D}$ +31.8 (*c* = 1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.15 (dd, *J* = 6.8, 13.3 Hz, 1H), 5.31 (dd, *J* = 6.8, 9.0 Hz, 1H), 5.48 (dd, *J* = 9.0, 13.3 Hz, 1H), 7.24−7.34 (m, 3H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.69 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.78 (dt, *J* = 1.3, 7.6 Hz, 1H), 8.07 (d, *J* = 6.5 Hz, 1H), 8.11 (d, *J* = 6.8 Hz, 1H)

(*S*)-2-(1-(4-Chlorophenyl)-2-nitroethyl)-3-hydroxynaphthalene-1,4-dione (40h)[30]



40h

A procedure similar to that described for the preparation of **40a** afforded **40h** in 90% yield as an orange solid.

HPLC [Chiralcel IA hexane (0.1% TFA)/DCM/EtOH = 90/5/5, 1.0 mL/min, λ = 254 nm, retention times: (major) 32.8 min, (minor) 38.7 min, 93% ee]; $[\alpha]^{20}_{D}$ +15.5 (*c* =1.03 in CH_3COOH); ^1H NMR (400 MHz, DMSO-d_6); δ 5.20 (t, *J* = 7.8, Hz, 1H), 5.33 (dd, *J* = 7.6, 13.8 Hz, 1H), 5.45 (dd, *J* = 8.3, 13.6 Hz, 1H), 7.36–7.43 (m, 4H), 7.78 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.84 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H)

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List of publications

This study was published in the following papers.

Chaptaer 1

A Convenient Method for Preparation of α-Imino Carboxylic Acid Derivatives and Application to the Asymmetric Synthesis of Unnatural α-Amino Acid Derivative

Tsubasa Inokuma, **Takahisa Jichu**, Kodai Nishida, Akira Shigenaga, Akira Otaka.

Chem. Pharm. Bull. **2017,** *65,* 573–581.

Chaptaer 2

Recyclable hydrophobic catalyst for thiourea mediated organocatalytic reactions

Takahisa Jichu, Tsubasa Inokuma, Keisuke Aihara, Taiki Kohiki, Kodai Nishida, Akira Shigenaga, Akira Otaka.

to be submitted.

Other publications

1. Direct photoinduced electron transfer from excited state of rhodamine B for carbon-radical generation
   Eito Yoshioka, Shigeru Kohtani, **Takahisa Jichu**, Takuya Fukazawa, Toyokazu Nagai, Yoshiji Takemoto, Hideto Miyabe.

   Synlett **2015**, *26*, 265–270.

2. Aqueous-Medium Carbon-Carbon Bond-Forming Radical Reactions Catalyzed by Excited Rhodamine B as a Metal-Free Organic Dye under Visible Light Irradiation
   Eito Yoshioka, Shigeru Kohtani, **Takahisa Jichu**, Takuya Fukazawa, Toyokazu Nagai, Akira Kawashima, Yoshiji Takemoto, Hideto Miyabe.

   J. Org. Chem. **2016**, *81*, 7217–7229.

3. Cysteine-Free Intramolecular Ligation of N-Sulfanylethylanilide Peptide Using 4-Mercaptobenzylphosphonic Acid: Synthesis of Cyclic Peptide Trichamide
   Keisuke Aihara, Tsubasa Inokuma, **Takahisa Jichu**, Zhenjian Lin, Feixue Fu, Kosuke Yamaoka, Akira Shigenaga, David Hutchins, Eric Schmidt, and Akira Otaka.

   Synlett **2017**, *28*, 1944–1949.