Doctoral Dissertation

博士学位論文

有機分子触媒を用いる不斉マイケル付加反応及び環境調和型有機合成反応の開発

Development of Novel Organocatalysts for Asymmetric Michael Additions and Environment-Friendly Synthetic Reactions

令和 3 年 3 月

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茨城大学大学院理工学研究科
複雑系システム科学専攻

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Development of Novel Organocatalysts for Asymmetric Michael Additions and Environment-Friendly Synthetic Reactions

March 2021

Doctoral Program of the Department of Complex System Science, Graduate School of Science and Engineering, Ibaraki University

Wei Han

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Finally, I would like to thank my beloved family for their warm encouragement, great care, and confidence in me. You are always there for me.

Thesis Summary

Organic chemistry and organic synthesis play an important role in today's human society because they are efficient and essential in the process of drug discovery, medicinal chemistry, agrichemical industries, food, human-made materials, and so on. The asymmetric synthesis and the development of highly efficient green chemical transformations have made a great contribution to the affluent life of human society and the protection of the environment at the same time.

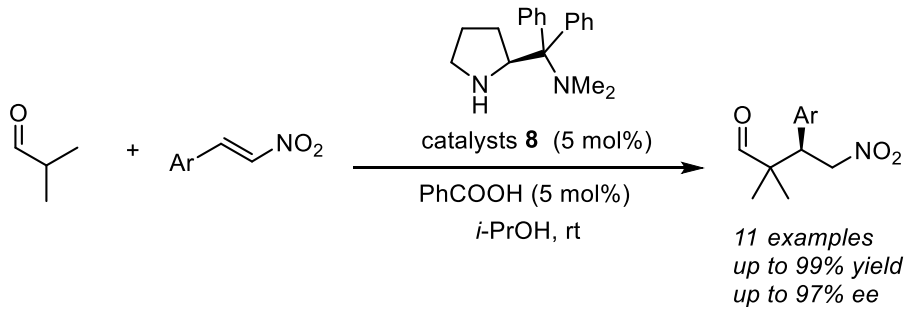
Particularly, many bioactive compounds including potential pharmaceuticals, are optically active and consist of two enantiomers that show different medicinal activities. Mostly, only one enantiomer can be used as a drug, the other enantiomer shows non-activity even toxicity. Thus, the development of asymmetric reactions for the stereoselective synthesis of the optically active organic compounds with desired absolute configuration is important and necessary. From the first proline-catalyzed asymmetric aldol reactions, many small molecular organocatalysts have been developed from natural amino acids for various asymmetric reactions such as Michael addition, Mannich, aldol, Diels-Alder, Friedel-Crafts reactions, α-, β- and γ-functionalization of carbonyl compounds, cyclization reactions, and so on. So far, organocatalysis is now one of the most important and efficient tools in organic synthesis. In comparison with metal catalysts, organocatalysts have advantages including usually nontoxic, inexpensive, non-sensitivity to moisture and oxygen, and environment friendly. On the other hand, Michael addition is one of the fundamental reactions which are widely used for the C–C bonds formation in organic synthesis. Moreover, this transformation is also atom-economic and an easy way to achieve high enantioselectivity. Therefore, I devote my interest to develop novel organocatalysts for asymmetric reactions.

Recently, the green chemical protocols for highly efficient organic synthesis have attracted much interest because sustainable development is more desirable in today's

society. The recyclable system for organic synthesis accords with the green chemical point of view. Molecular sieves (MS) are not merely known as a dehydrating agent but also are used as the promoter for many organic reactions due to their weak basicity. Moreover, molecular sieves are all inexpensive, commercially available, and recyclable. So far, many reactions proceeded smoothly when using MS as the promoter instead of transition-metal catalysts, strong organobase, heating, or other special reaction conditions. Thus, I also pay attention to the development of new synthetic reactions for constructing potentially useful compounds using recyclable molecular sieves under mild reaction conditions.

1. Asymmetric Michael addition of isobutyraldehyde to nitroolefins using an α,α-diphenyl-(*S*)-prolinol-derived chiral diamine catalyst

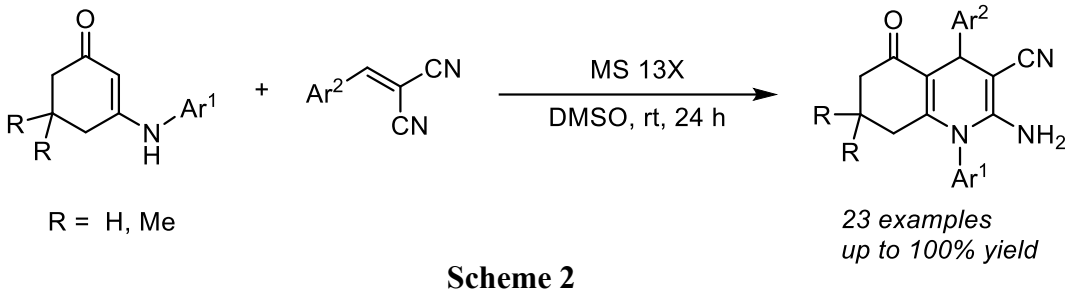
The asymmetric Michael addition of isobutyraldehyde to nitroolefins was achieved via the use of a chiral diamine catalyst derived from α,α-diphenyl-(*S*)-prolinol (**Scheme 1**). In this protocol, the Michael addition was successfully conducted with low catalyst and additive loadings of 5 mol%, respectively, due to the presence of the tertiary amine group in the chiral diamine catalyst. Moreover, various quaternary carbon-containing optically active γ–nitroaldehydes were obtained in good yields (up to 99%) and good to excellent enantioselectivity (up to 97% ee).



Scheme 1

2. Synthesis of *N*-aryl-4-arylhexahydroquinoline derivatives by reaction of cyclic enaminones with arylidenemalononitriles in DMSO

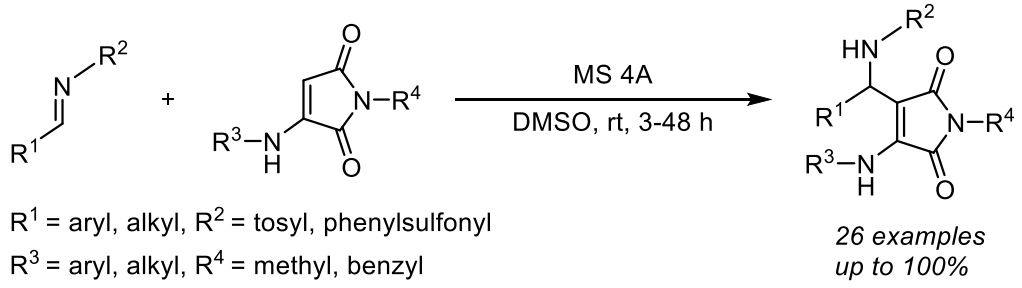
An efficient and environment-friendly cascade Michael–cyclization reaction of cyclic enaminones with arylidenemalononitriles was achieved in the presence of molecular sieves 13X in dimethyl sulfoxide (DMSO) (**Scheme 2**). Under these mild reaction conditions, various bioactive *N*-aryl-4-arylhexahydroquinoline derivatives were obtained in high yields without using a transition-metal catalyst, organobase, or reflux conditions.



Scheme 2

3. A novel and efficient Mannich-type reaction of α-aminomaleimides

In the presence of DMSO and MS 4A, the first Mannich-type reaction of α-aminomaleimides has been described (**Scheme 3**). Various valuable maleimide derivatives were constructed with high to excellent yields under mild reaction conditions. Moreover, this protocol accords with the green chemical point of view, because the molecular sieves are inexpensive, commercially available, and recyclable.



Scheme 3

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalyst
Cbz	carbobenzyloxy
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
ee	enantiomeric excess
eq.	equivalent
Et	ethyl
g	grams
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
***i*-Bu**	*iso*-butyl

***i*-Pr**	*iso*-propyl
IR	infrared
J	coupling constant
Me	methyl
Mes	mesitylene
MOM	methoxymethyl
MS	molecular sieves
Ms	methanelsulfonyl
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Ns	*para*-nitrobenzenesulfonyl
Ph	phenyl
Piv	pivaloyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Py	pyridine
quant.	quantitative
rac	racemic
rt	room temperature
***t*-Bu**	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	para-toluenesulfonyl
δ	chemical shift in parts per million

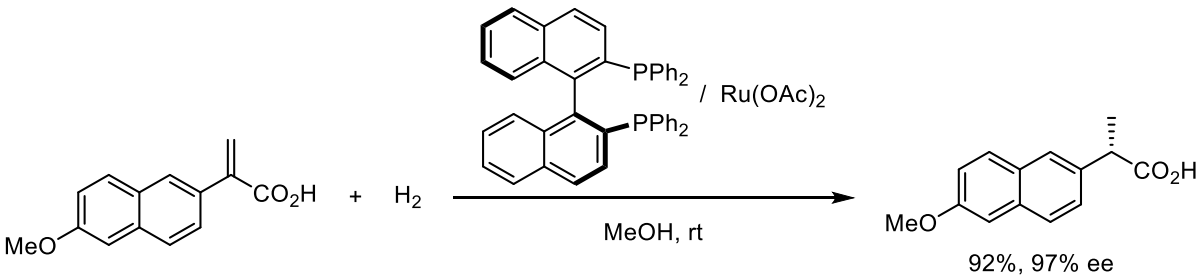
Chapter 1

Introduction

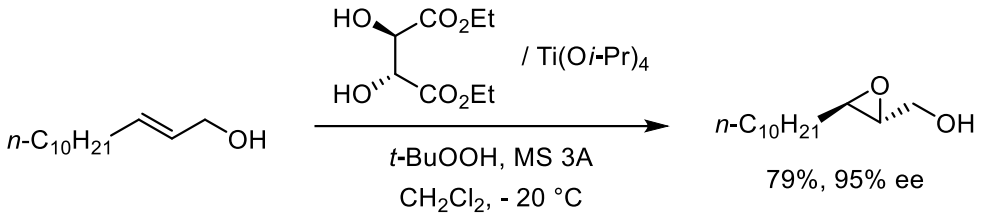
1.1 General introduction

Organic chemistry and organic synthesis contribute to modern society from familiar places in our life.[1] Thanks to the development of organic synthesis, hundreds of thousands of organic compounds with different properties can be efficiently prepared every year and many of them have been applied as pharmaceuticals, agrochemicals, food additives, new materials, polymer, dye, and so on. Because of the usefulness, many efforts have been done for the researches of organic synthesis and great achievements have also been made. As the result, since the beginning of this century, several organic chemists have won the Nobel Prize in Chemistry for their great contribution in organic synthesis, especially in the fields of transition-metal catalyzed asymmetric synthesis, olefin metathesis, and cross-coupling reactions.

In 2001, William Standish Knowles, Ryoji Noyori, and Karl Barry Sharpless won the Nobel Prize in Chemistry for their great works in chiral catalyzed hydrogenation (**Scheme 1.1**)[2] and oxidation reactions (**Scheme 1.2**)[3].

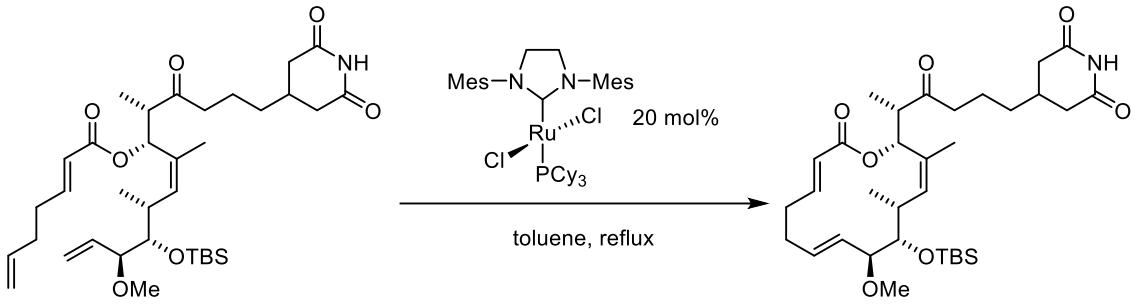


Scheme 1.1 Example of Noyori asymmetric hydrogenation of olefin



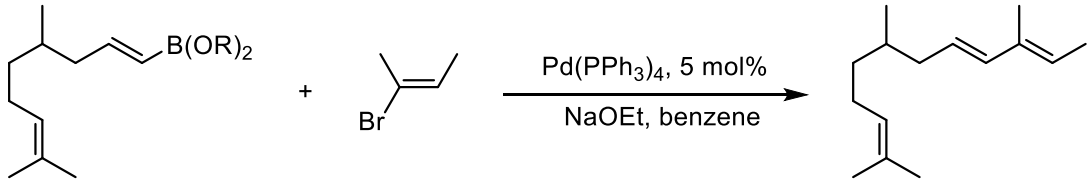
Scheme 1.2 Example of Sharpless asymmetric epoxidation

Grubbs together with Richard R. Schrock and Yves Chauvin received the 2005 Nobel Prize in Chemistry for their works in the field of olefin metathesis (**Scheme 1.3**)[4].



Scheme 1.3 Example of olefin metathesis catalyst used in total synthesis

In 2010, Richard Fred Heck, Ei-ichi Negishi, and Akira Suzuki won Nobel Prize in Chemistry for their contributions in palladium-catalyzed coupling reactions (**Scheme 1.4**)[5].



Scheme 1.4 Example of Suzuki coupling used in total synthesis

These great achievements promoted the advance of organometallic chemistry, biochemistry, medicinal chemistry, polymer chemistry, and so on. Moreover, from these Nobel prize level works, it is sure that further works in the fields of asymmetric synthesis and catalytic reactions are very important, necessary, and attractive.

1.2 Chirality and the importance of enantioselective synthesis

Chirality[6a] is a geometric property that means a molecule cannot be superposed on its mirror image by any combination of rotations and translations. A molecule owning the chirality property is a chiral molecule. A chiral molecule has two enantiomers, which have a relationship like about our right and left hands. Besides, two enantiomers are also mirroring images of each other (**Figure 1.1**).

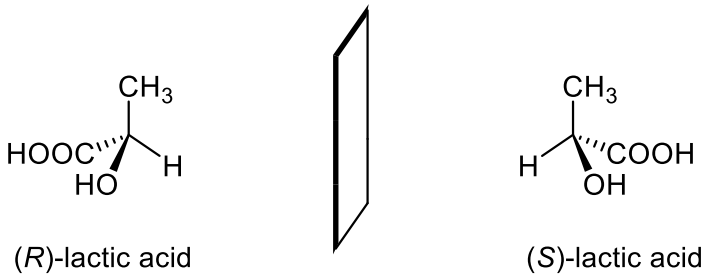


Figure 1.1 Enantiomers of lactic acid

Enantiomers have the same molecular formula, molecular weight, and exhibit the same physical properties such as melting point, boiling point, and solubility. However, in addition to exhibiting the opposite optical rotation, two enantiomers are non-identical to their mirror images. Thus, chiral molecules which also be called optically active compounds often exhibit different bioactivity (**Figure 1.2**).[6b]

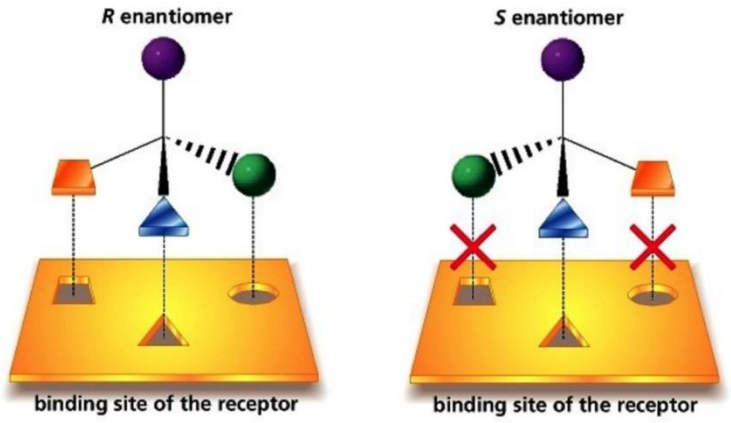


Figure 1.2 Image of the difference between two enantiomers

The most fundamental reason why the studies of chiral molecules and asymmetric synthesis are significant should be that many bioactive compounds including potential pharmaceuticals are optically active.[7] More importantly, two enantiomers of these bioactive molecules show different medicinal activities.[8] For example, (*R*)-thalidomide has analgesic effects and improves morning sickness and insomnia in pregnant women, whereas (*S*)-thalidomide has teratogenic effects (**Figure 1.3**).

Figure 1.3 Enantiomers of thalidomide

(*L*)-Dopa is a drug for treating Parkinson's disease, while (*D*)-dopa shows biologically inactive for people (**Figure 1.4**).

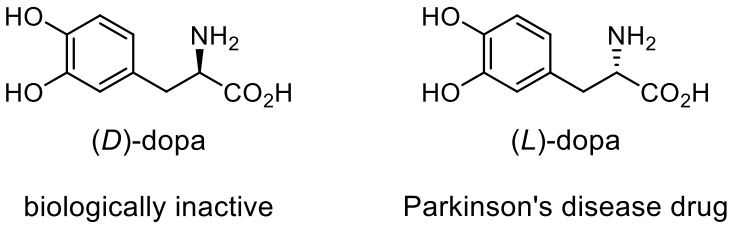
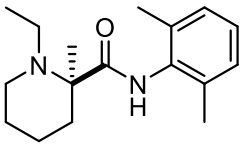


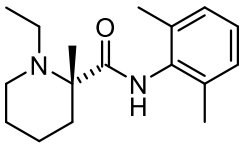
Figure 1.4 Enantiomers of dopa

(*R*)-Ropivacaine shows central nervous system toxicity such as cardiotoxicity and convulsions, whereas (*S*)-ropivacaine has a mild analgesic effect and is used as an analgesic after surgery (**Figure 1.5**).



(*R*)-ropivacaine

toxicity to nerves

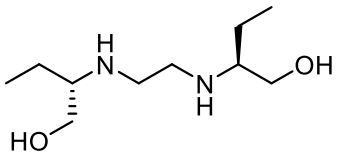


(*S*)-ropivacaine

analgesic effect

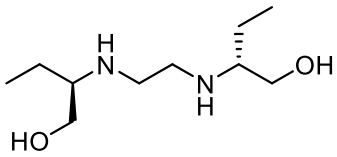
Figure 1.5 Enantiomers of ropivacaine

It was found that only the (*S*, *S*) -(+)- ethambutol can be used to treat tuberculosis, but the (*R*, *R*) -(–)-ethambutol causes blindness (**Figure 1.6**).



(*S*,*S*)-(+)-ethambutol

tuberculosis drug



(*R*,*R*)-(-)-ethambutol

causes blindness

Figure 1.6 Enantiomers of ethambutol

From the above examples, it has been unquestionable that the enantioselective synthesis of chiral bioactive molecules is especially essential and crucial for drug discovery.

Asymmetric synthesis has been a key process in modern chemistry. The development of efficient asymmetric synthetic systems for the preparation of enantiomerically pure molecules and building blocks continues to be of great interest to chemists around the world.

1.3 Organocatalysis, an efficient tool for asymmetric synthesis

Chiral catalysis for asymmetric synthesis is usually divided into three main parts: metal, enzyme, and organic catalysis. Especially, organocatalysis has been an efficient tool and powerful strategy for the constructing of optically active molecules in the past decades.[9]

Organocatalysis provides several advantages such as 1) metal-free catalysis thus consisting with green chemistry; 2) stable to water and oxygen thus easy to handle; 3) inexpensive thus low cost and non-toxicity; 4) recyclable; 5) small chiral molecules as catalysts thus atom-economy, and so on. Therefore, since the 1990s the development of organocatalysts using for asymmetric transformations has attracted much attention and is one of the most exciting research topics.

So far, various types and a remarkable number of organic catalysts have been developed. Almost all organic catalysts are synthesized using chiral amino acids,[10] chiral 1,2-diamines,[11] chiral diols,[12] and cinchona alkaloids[13] as the four main backbones (**Figure 1.7**).

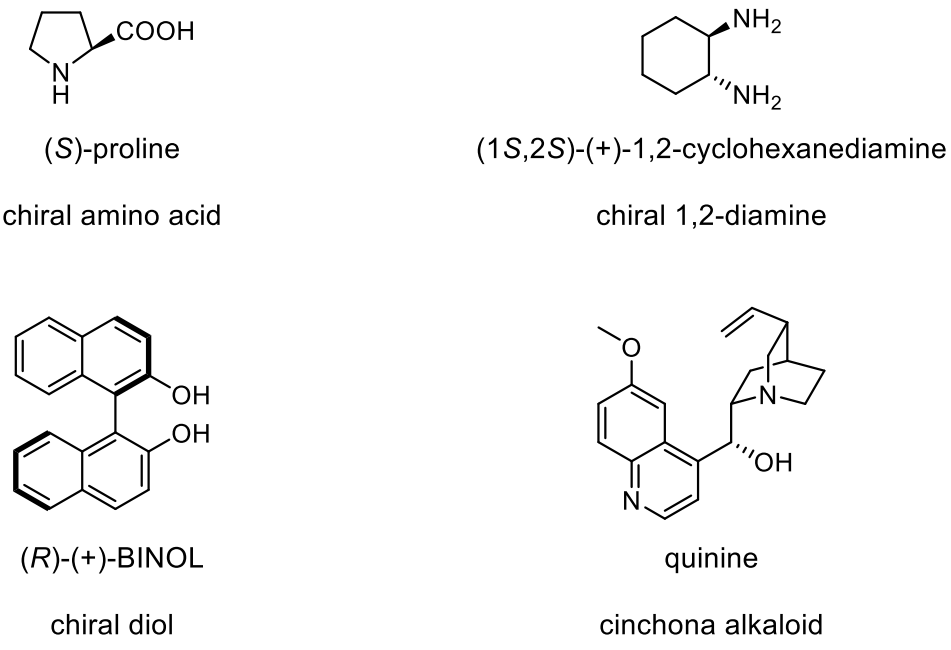
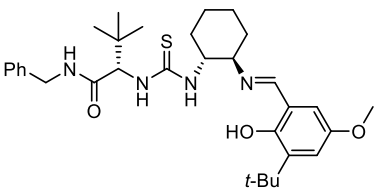


Figure 1.7 Four major representative backbones of organic catalysts

From the catalytic mechanism or activation mode, organocatalysts can be categorized mainly as Lewis acid type, Lewis base type, phase-transfer type, and bifunctional type *et al* (**Figure 1.8**).

Furthermore, many classic and famous organocatalysts have been demonstrated successfully for various enantioselective reactions. Asymmetric aldol reactions,[14] Michael additions,[15] Diels-Alder reactions,[16] Mannich reactions,[17] Strecker reactions,[18] Morita-Baylis-Hillman reactions,[19] and so on have been achieved in perfect stereoselectivities efficiently. As a result, using wonderful organic catalysts, many kinds of useful chiral molecules can be artificially synthesized in the desired stereo structures.



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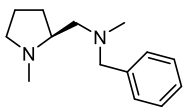

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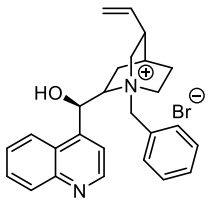

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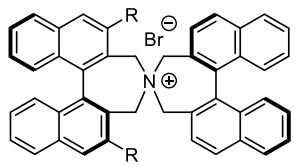

R= β -Naph

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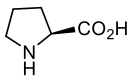

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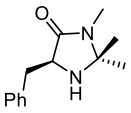

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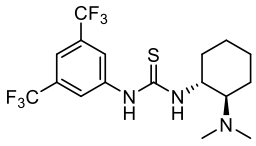

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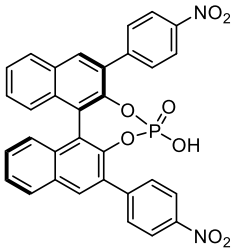

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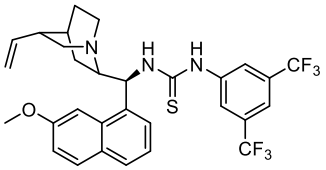

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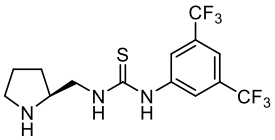

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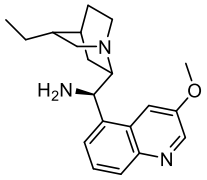

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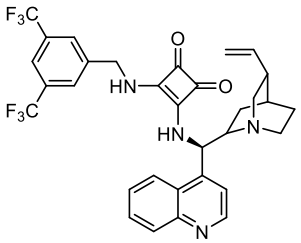

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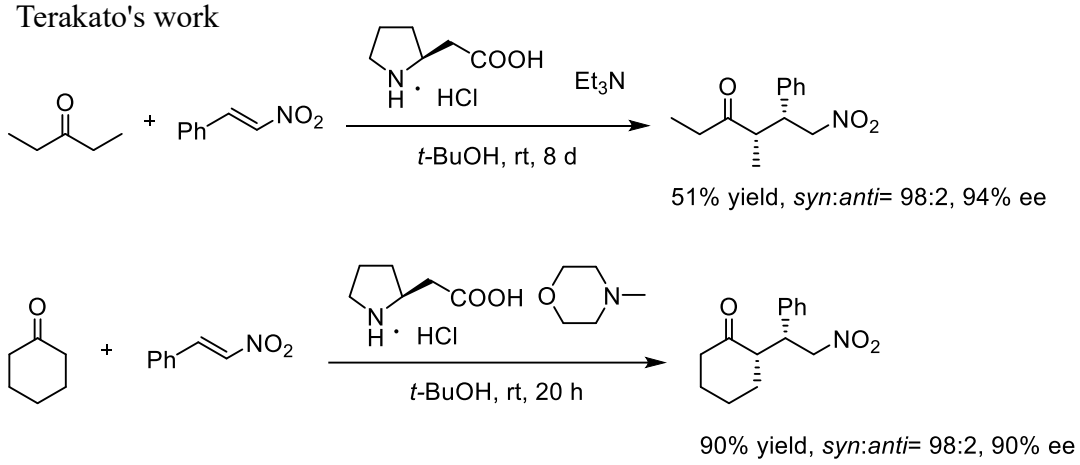
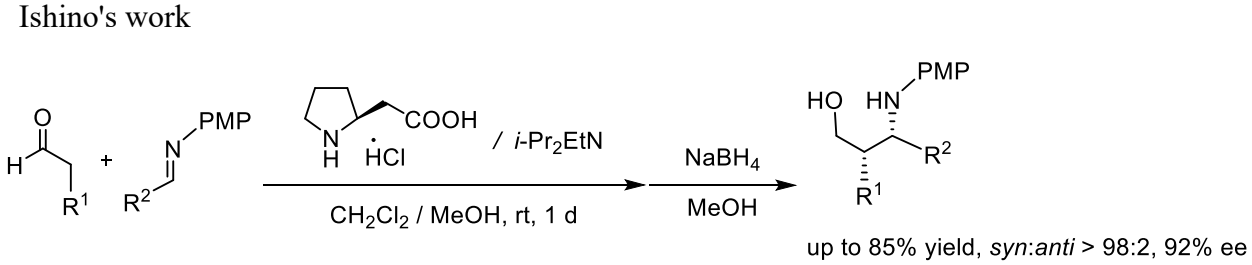
Figure 1.8 Examples of classic and successful organocatalysts

1.4 Previous results of asymmetric reactions in our group

On the other hand, our group also developed several novel organocatalysts for asymmetric reactions. In 2005 and 2006, our lab members Terakado and Ishino developed (*S*)-homoproline catalyzed asymmetric Michael addition (**Scheme 1.5**) and Mannich reaction (**Scheme 1.6**), respectively. The Michael adducts and Mannich products were obtained in high diastereoselectivity and high enantioselectivity over 90% ee. In 2015, Kawazoe reported novel symmetric urea-catalyzed asymmetric Michael addition of thiols to nitroolefins (**Scheme 1.7**).[20] Recently, our labmate Wang, developed two novel proline-based acridone bifunctional organocatalysts for the asymmetric Michael addition of cyclohexanone (**Scheme 1.8**).[21]

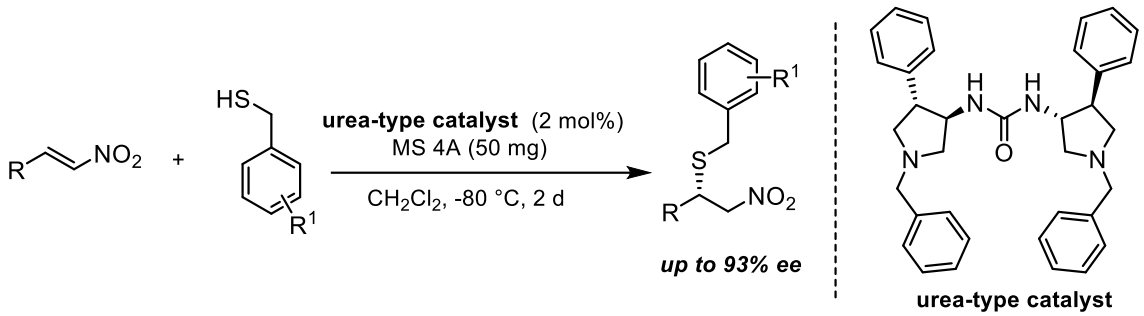


Scheme 1.5 (*S*)-Homoproline catalyzed asymmetric Michael addition



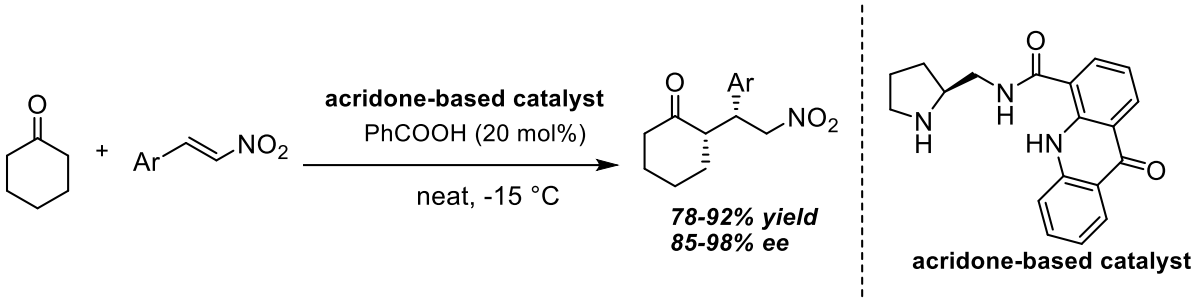
Scheme 1.6 (*S*)-Homoproline catalyzed asymmetric Mannich reaction

Kawazoe's work



Scheme 1.7 Symmetric urea-catalyzed asymmetric Michael addition

Wang's work



Scheme 1.8 Proline-based acridone catalyst for the asymmetric Michael addition

1.5 Molecular sieves, a recyclable system for green chemical organic synthesis

Green chemistry was defined by Paul Anastas and John Warner in 1998.[22] The 12 principles of green chemistry are also advocated for achieving energy conservation, waste reduction, renewable feedstocks, environment-friendly, and so on. In short, to commit to a sustainable society, chemists have also to develop green chemical protocols for efficient organic chemical syntheses. Among many advanced greener chemical processes and methods, molecular sieves (MS) as a recyclable system for organic synthesis match the green chemical point of view and contribute to environmental protection.

As well known, molecular sieves are not merely applied as a dehydrating agent but are also used as the promoter for many organic reactions due to their weak basicity. Moreover, molecular sieves are all inexpensive, commercially available, and recyclable (**Figure 1.9**). Nowadays, molecular sieves are receiving attention and play the roles of an additive, catalyst, co-catalyst, or catalyst support in organic reactions.[23]

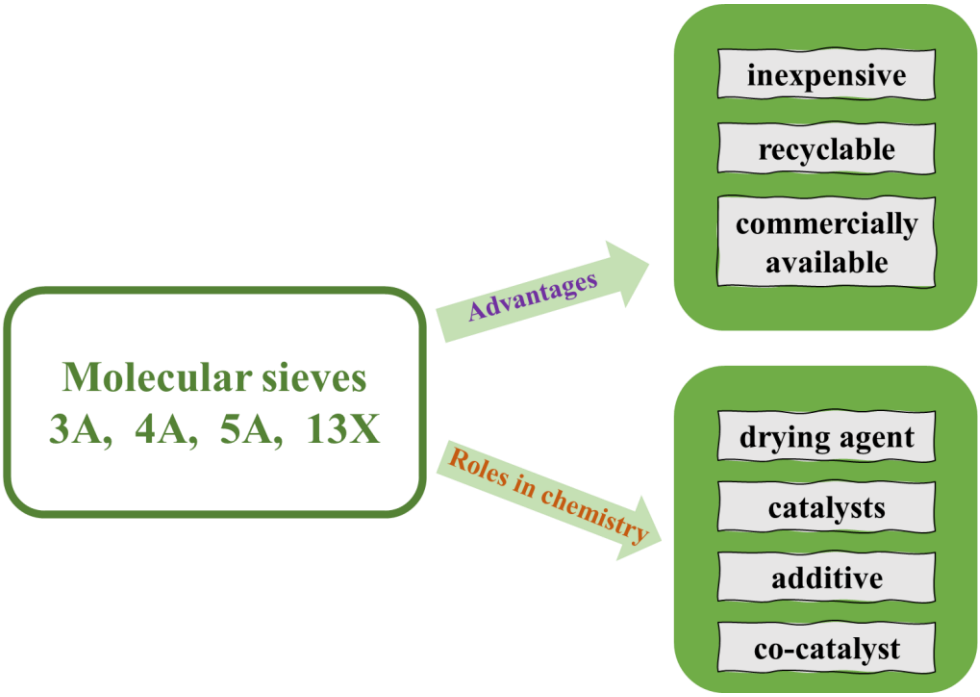


Figure 1.9 Molecular sieves in organic syntheses

1.6 Author's research direction and purpose

Based on the above backgrounds, during my Ph.D. research stage, I mainly focused on the research of (1) organocatlyzed asymmetric reactions and (2) the development of the green chemical protocols for highly efficient novel synthetic reactions.

In this article, the author described 1) a more efficient asymmetric Michael addition of isobutyraldehyde to nitroolefins, recyclable molecular sieves promoted 2) cascade Michael–cyclization, 3) Mannich reactions under mild reaction conditions. Besides, I hope these research results can make some contributions to the development of chiral building blocks and new useful compounds.

Chapter 2

Asymmetric Michael addition of isobutyraldehyde to nitroolefins using an α,α-diphenyl-(*S*)-prolinol-derived chiral diamine catalyst

2.1 Introduction

Michael addition is one of the most efficient and atom-economical reactions, which can construct not only new C-C bonds but also such as C-N, C-O, C-S, C-P bonds in synthetic chemistry.[15,24]

Michael addition of aldehydes to nitroolefins produced useful γ–nitroaldehydes which are precursors for γ–aminobutyric acid analogs, γ–hydroxyoximes, γ–hydroxynitrile, chiral cyclic amine (**Figure 2.1**). And many bioactive compounds exhibiting antidepressant, anticonvulsant, anxiolytic and others can be derived from these intermediates (**Figure 2.2**),[25] (**Figure 2.3**).[26] Thus, organocatalytic asymmetric Michael addition of aldehydes with nitroolefins to produce enantiomerically enriched γ–nitroaldehydes is important and desired.

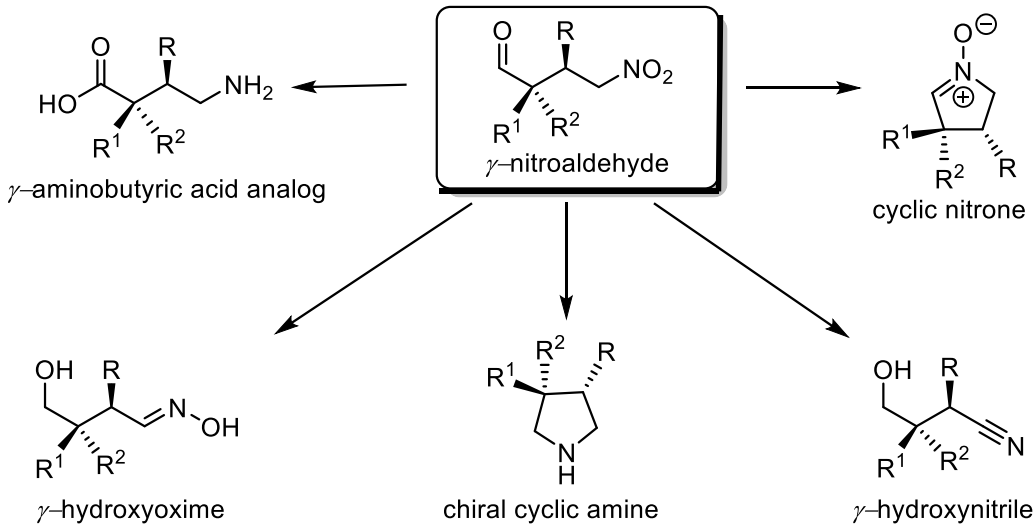


Figure 2.1 Utility of γ–nitroaldehydes

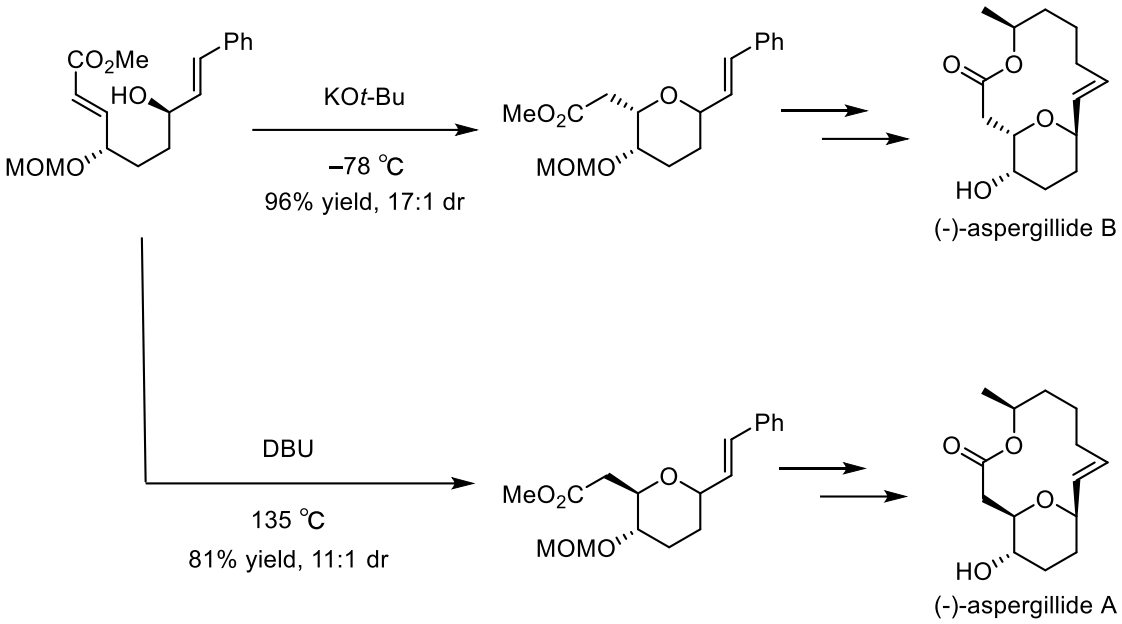


Figure 2.2 Total synthesis of aspergillide from Michael adduct

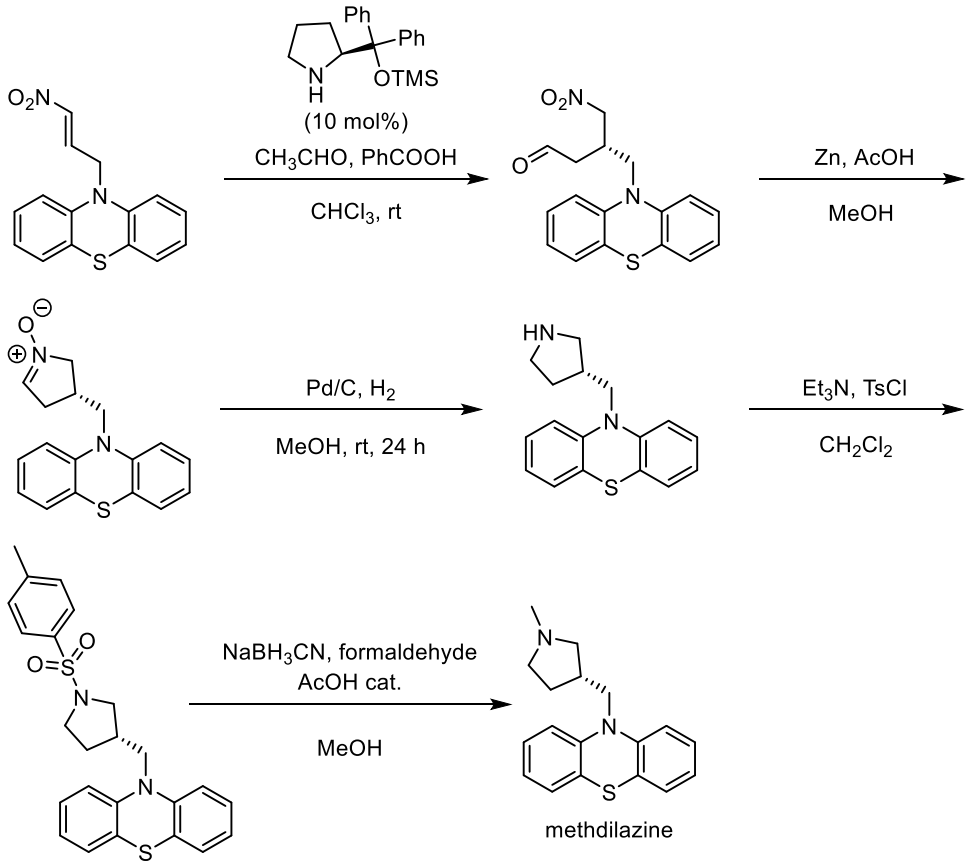
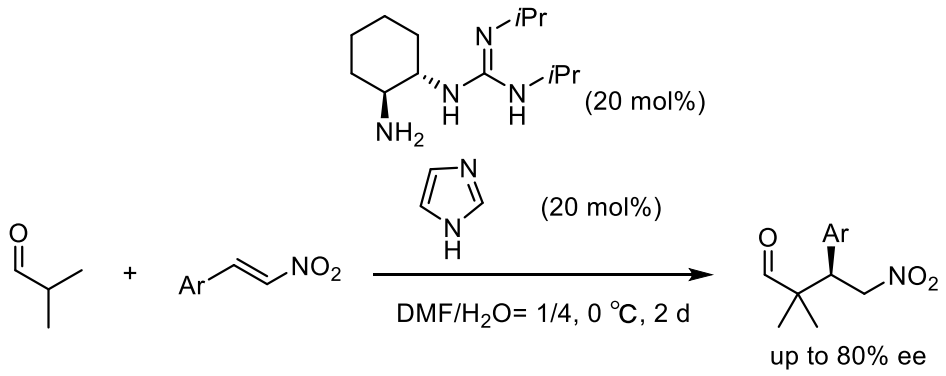


Figure 2.3 Total synthesis of methdilazine from Michael adduct

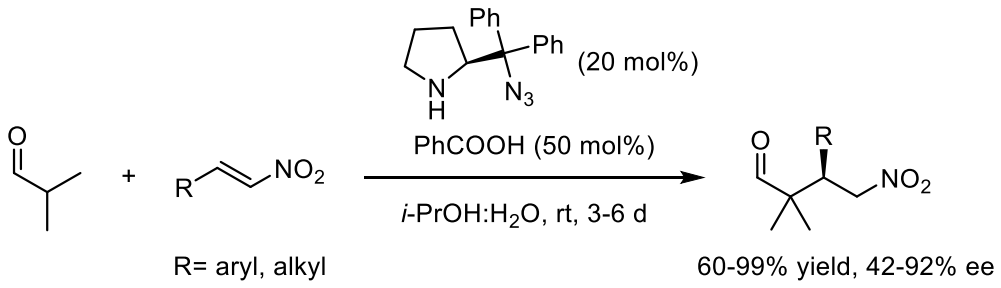
2.2 Limitation of the previous reports and author's strategy

So far, much effort has been devoted to the organocatalytic asymmetric conjugate addition of α,α-disubstituted aldehydes with nitroolefins.[27] However, only limited success has been achieved in this transformation. Problems like low chemical yield, moderate enantioselectivity (**Scheme 2.1**),[28] high catalyst loading, long reaction time, and so on have remained.

In 2016, Juaristi *et al*. reported an asymmetric Michael addition reaction of isobutyraldehyde and nitroalkene using an amine-azide catalyst derived from α,α-diphenyl-*L*-prolinol (**Scheme 2.2**).[29] However, 20 mol% of catalyst and 50 mol% of additives are required. Besides, there remains a challenge to be improved, which requires a long reaction time of 3 to 6 days.



Scheme 2.1 Previous reports of asymmetric Michael addition of isobutyraldehyde



Scheme 2.2 Previous reports of asymmetric Michael addition of isobutyraldehyde

Juaristi *et al*. showed that the amine-azide catalyst was the most suitable in the reports of **Scheme 2.2**, but instead of the azide moiety, catalysts such as primary amines, secondary amines, amides, and triazoles were also investigated (**Figure 2.4**). Of these eight catalysts, there are three chiral diamine catalysts, all of which are combinations of secondary or primary amines moieties on the right side of catalysts. However, these chiral diamine catalysts were unsuccessful. It is proposed that these chiral diamine catalysts lose their activity due to the generation of an aminal intermediate, via an intramolecular attack initiated by the catalyst's amide or the secondary amine moiety (**Scheme 2.3**).[30]

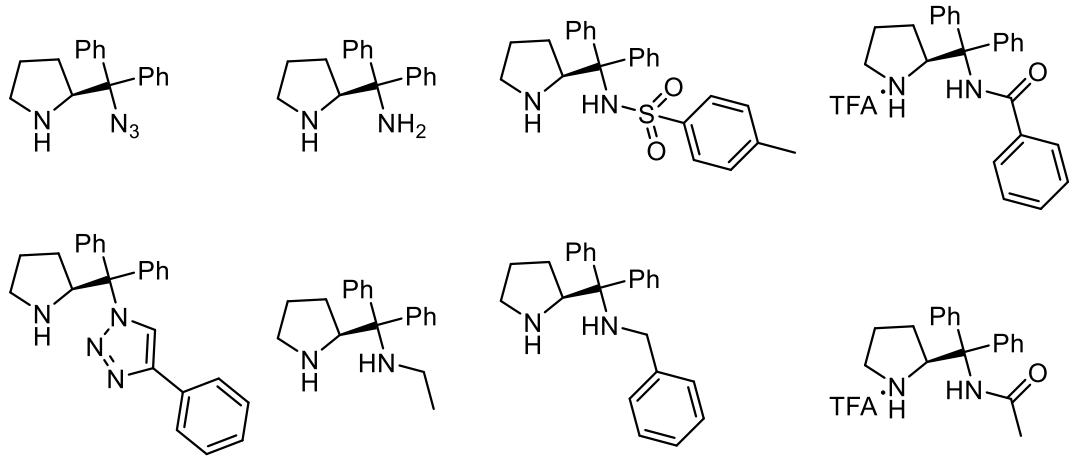
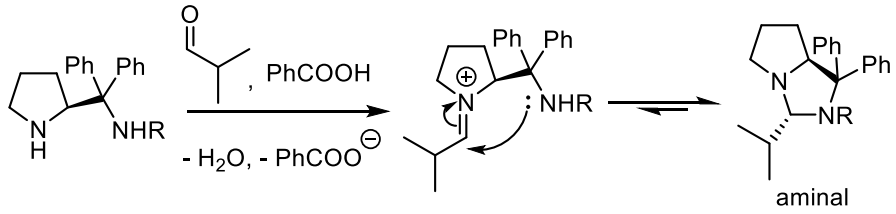


Figure 2.4 Catalysts synthesized by Juaristi's group



Scheme 2.3 The generation of aminal intermediate lose the catalyst activity

In this context, the author proposed that installing a tertiary amino group on the right side of the diamine catalyst **8** will circumvent the formation of the aminal and promote the proton transfer process, thereby accelerating the Michael reaction (**Figure 2.5**). As a result, a more efficient asymmetric Michael addition of α,α-disubstituted aldehydes to nitroolefins using a chiral diamine will be achieved.

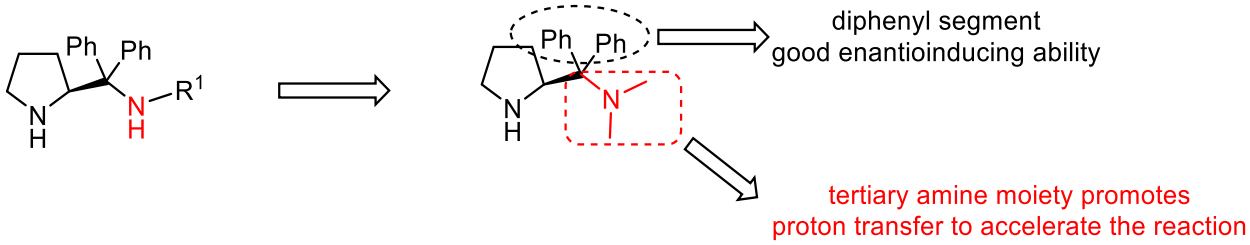
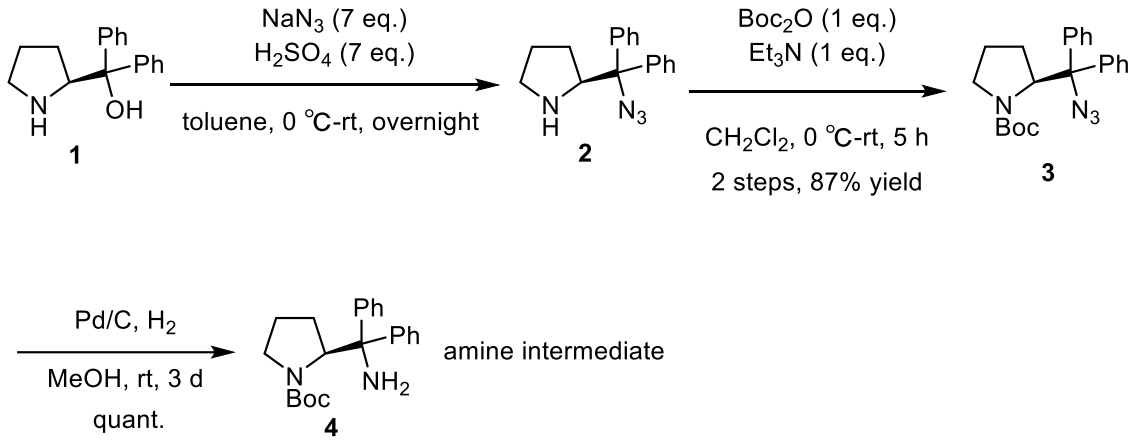


Figure 2.5 Author's strategy

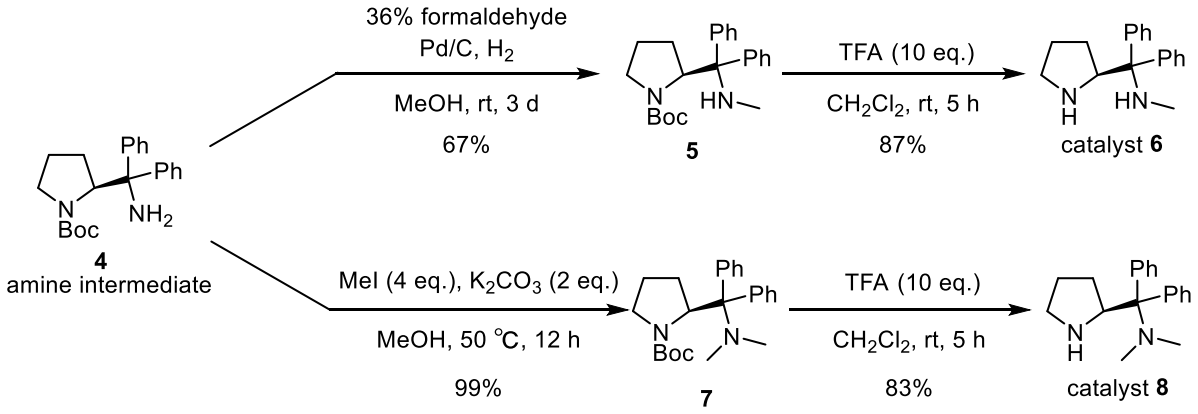
2.3 Synthesis of the chiral diamine catalysts

The synthesis of chiral amine intermediate **4** was carried out from *α*,*α*-diphenyl-*L*-prolinol by an improved synthetic route from literature (**Scheme 2.4**).[29]



Scheme 2.4 Synthesis of chiral amine intermediate

The chiral diamine catalysts **6** and **8** were synthesized from amine intermediate **4** in a short route (**Scheme 2.5**).[31]

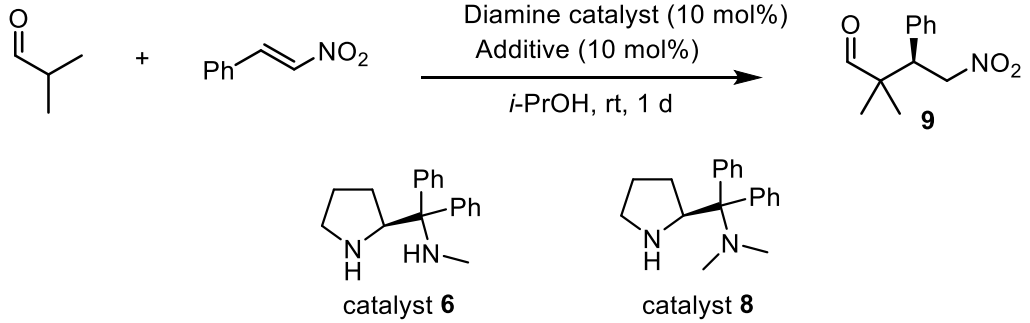


Scheme 2.5 Synthesis of diamine catalysts **6** and **8**

2.4 Chiral diamine catalyzed asymmetric Michael addition to nitroolefins

To demonstrate our hypothesis, we explored the catalytic activity of the chiral diamines **6** and **8** and acid additives' effect in the Michael addition of isobutyraldehyde to the nitroolefin (**Table 2.1**). When catalyst **6** was used, only trace amounts of the Michael adduct were observed even though the reaction was conducted over two days; in contrast, catalyst **8** provided the product with moderate yields of 45% and a high enantioselectivity value of 89% ee (Entries 1 and 2). Encouraged by these results, we then investigated the use of carboxylic acids such as salicylic acid, chloroacetic acid, and (-)-camphorsulfonic acid (Entries 3-5) as possible additives. However, since the best result of these series were obtained with benzoic acid (Entry 2), we decided to use diamine **8** as the catalyst and benzoic acid as the additive to screen other reaction conditions.

Table 2.1 Screening of catalysts and acid additives[a]

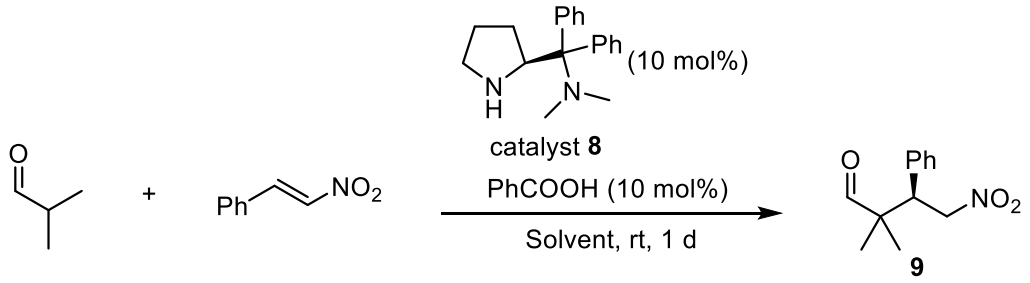


Entry	Catalyst	Additive	Yield[b] (%)	ee[c] (%)
1[d]	**6**	PhCOOH	trace	-
2	**8**	PhCOOH	45	89
3	**8**	salicylic acid	43	89
4	**8**	chloroacetic acid	21	90
5	**8**	(-)-CSA	N.R.	-

[a] Reaction conditions: isobutyraldehyde (0.2 mmol), nitroolefin (0.1 mmol), catalysts, and additives in *i*-PrOH (0.2 mL) at rt. N.R. = No reaction. [b]Isolated yield. [c]Determined by chiral HPLC. [d]2 days.

Subsequently, the effects of solvents were investigated (**Table 2.2**). Here, 4 equiv. of isobutyraldehyde was used instead of the usual 5 or 10 equiv. employed in previously reported studies. *i*-PrOH was found to be the most suitable solvent for this transformation, afforded the product with 91% yield and a high enantioselectivity value of, 93% ee (Entry 6). Although the reason is not unclear, we propose that alcohol solvents affect the nitro group of nitroolefin differently by H-bonding interactions leading to these results.

Table 2.2 Screening of solvents

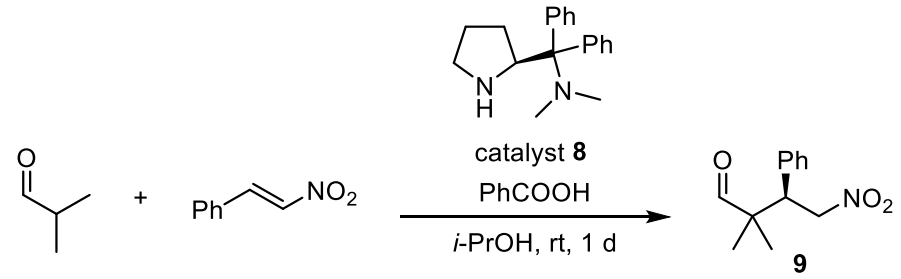


Entry	Solvent	Yield[b] (%)	ee[c] (%)
1[d]	neat	26	95
2	CH_2Cl_2	18	95
3	$CHCl_3$	21	94
4	toluene	trace	-
5	H_2O	N.R.	-
6	*i*-PrOH	91	93
7	MeOH	40	87
8	*t*-BuOH	N.R.	-
9	THF	N.R.	-
10	DMSO	30	77

[a] Reaction conditions: isobutyraldehyde (0.4 mmol), nitroolefin (0.1 mmol), catalyst **8**, and PhCOOH in the relevant solvent (0.2 mL) at rt. N.R. = No reaction. [b]Isolated yield. [c]Determined by chiral HPLC. [d]8 eq. of isobutyraldehyde was used.

The impact of catalyst and additive loadings on the Michael addition reaction was also investigated (**Table 2.3**). The ratio of catalyst **8** and PhCOOH only slightly affected the Michael addition of isobutyraldehyde to nitroolefin, as both the yield and the enantiomeric purity were obtained with almost the same degree (Entries 1-3). Fortunately, reducing the amount of catalyst and PhCOOH to 5 mol% respectively also resulted in success (Entries 1 and 4). More reducing the amount of PhCOOH lowed the yields (Entry 5). The acid additive affected the reaction rate but not the enantioselectivity (Entries 6 and 7). From the above results, the optimal reaction conditions were as follows: nitroolefins (0.1 mmol), 5 mol% each of catalyst **8** and PhCOOH, as well as 5 equiv. of aldehyde, in 0.2 mL *i*-PrOH at room temperature (Entry 6).

Table 2.3 Optimization of reaction conditions[a]

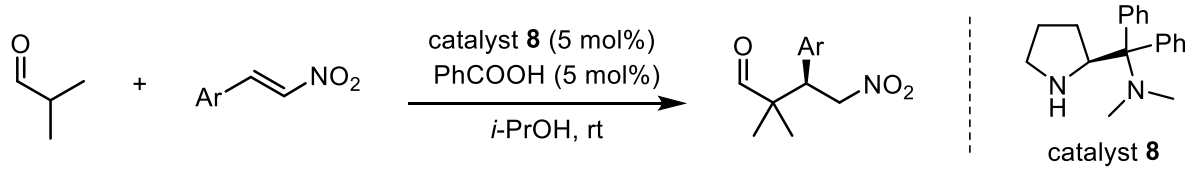


Entry	Aldehyde (equiv.)	**8** (mol%)	PhCOOH (mol%)	Yield[b] (%)	ee[c] (%)
1	4	10	10	91	93
2	4	10	5	97	92
3	4	5	10	94	92
4	4	5	5	94	92
5	4	5	3	70	95
6	5	5	5	96	93
7	5	5	-	39	92

[a] Reaction conditions: isobutyraldehyde, nitroolefin (0.1 mmol), catalyst **8**, and PhCOOH in *i*-PrOH (0.2 mL) at rt. [b]Isolated yield. [c]Determined by chiral HPLC.

With the optimized reaction conditions in hand, various nitroolefins using isobutyraldehyde as a Michael donor were explored (**Table 2.4**) and found that nitroolefins bearing an electron-withdrawing group, halogen atoms, 2-naphthyl group, and a heteroaryl ring were tolerated well (Entries 2, 4-6, and 10-11). The corresponding Michael adducts were provided in good to excellent yields with high enantioselectivity values. It should be noted that the groups substituted at the *ortho* position on the phenyl ring significantly lowered both the reactivity and the enantioselectivity of the nitroolefins (Entries 7 and 8 vs 5 and 6). Besides the electronic effect and *ortho*-substituted influence, it was theorized that reduced solubility in *i*-PrOH might lead to diminished chemical yields in some cases (Entries 5, 7, and 9).

Table 2.4 The screen of various nitroolefins[a]

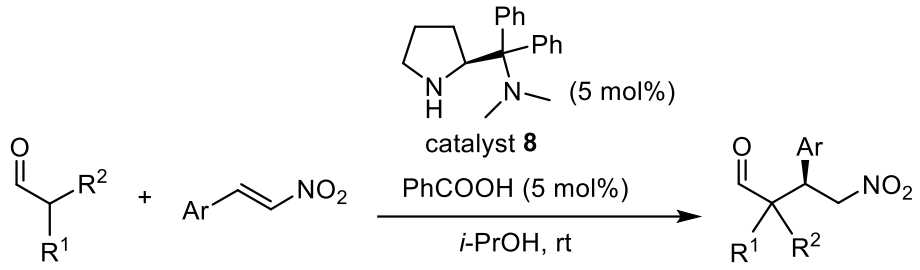


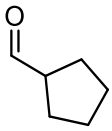
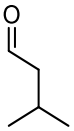
Entry	Ar	Time (d)	**Product**	Yield[b] (%)	ee[c] (%)
1	Ph	1	**9**	96	93
2	4-CNC_6H_4	1	**10**	78	97
3[d]	4-MeC_6H_4	3	**11**	39	90
4	4-ClC_6H_4	1	**12**	95	94
5[e]	4-BrC_6H_4	2	**13**	66	96
6	3-BrC_6H_4	1	**14**	99	96
7[f]	2-BrC_6H_4	4	**15**	26	74
8[f]	2-$MeOC_6H_4$	4	**16**	60	81
9[d]	2-naphthyl	3	**17**	33	91
10	2-furyl	1	**18**	97	91
11	2-thiophenyl	1	**19**	78	90

[a] Reaction conditions: aldehyde (0.5 mmol), nitroolefins (0.1 mmol), catalyst **8**, and PhCOOH in *i*-PrOH (0.2 mL) at rt. [b]Isolated yield. [c]Determined by chiral HPLC. [d]3 d. [e]2 d. [f]4 d.

Also, cyclopentanecarboxaldehyde (cyclic α-branched aldehyde) and 3-methylbutanal (an aliphatic β-branched aldehyde) were also examined as the Michael donors (**Table 2.5**). Cyclopentanecarboxaldehyde gives the corresponding Michael adduct **20** in 34% yield with 57% ee after 12 h. The Michael product of 3-methylbutanal **21** was obtained in 80% yield, *syn*/*anti* = 87/13 dr, and 98% ee for the *syn* diastereomer.

Table 2.5 The screen of various other aldehydes[a]



Entry	Aldehyde	Time	**Product**	Yield[b] (%)	Dr (*syn*/*anti*)	ee[c] (%)
1		12 h	**20**	34	-	57
2		1 d	**21**	80	87/13	98

[a] Reaction conditions: aldehydes (0.5 mmol), nitroolefin (0.1 mmol), catalyst **8**, and PhCOOH in *i*-PrOH (0.2 mL) at rt. [b]Isolated yield. [c]Determined by chiral HPLC.

2.5 The proposed reaction mechanism

A proposed reaction mechanism was shown in **Figure 2.6**. After the generation of iminium **A**, intramolecular proton transfer with benzoic acid produces enamine **B**. Next, hydrogen-bonded between the nitrogen atom of the protonated tertiary amine of **B** activated the nitroolefin. In the transition state, the conformation as shown by the Newman projection is less steric repulsion and stable, the *Si* surface attack causes intermediate **C**. Finally, intermediate **D** is hydrolyzed to regenerate catalyst **8** and benzoic acid, and the corresponding *γ*-nitroaldehyde is stereoselectively produced.

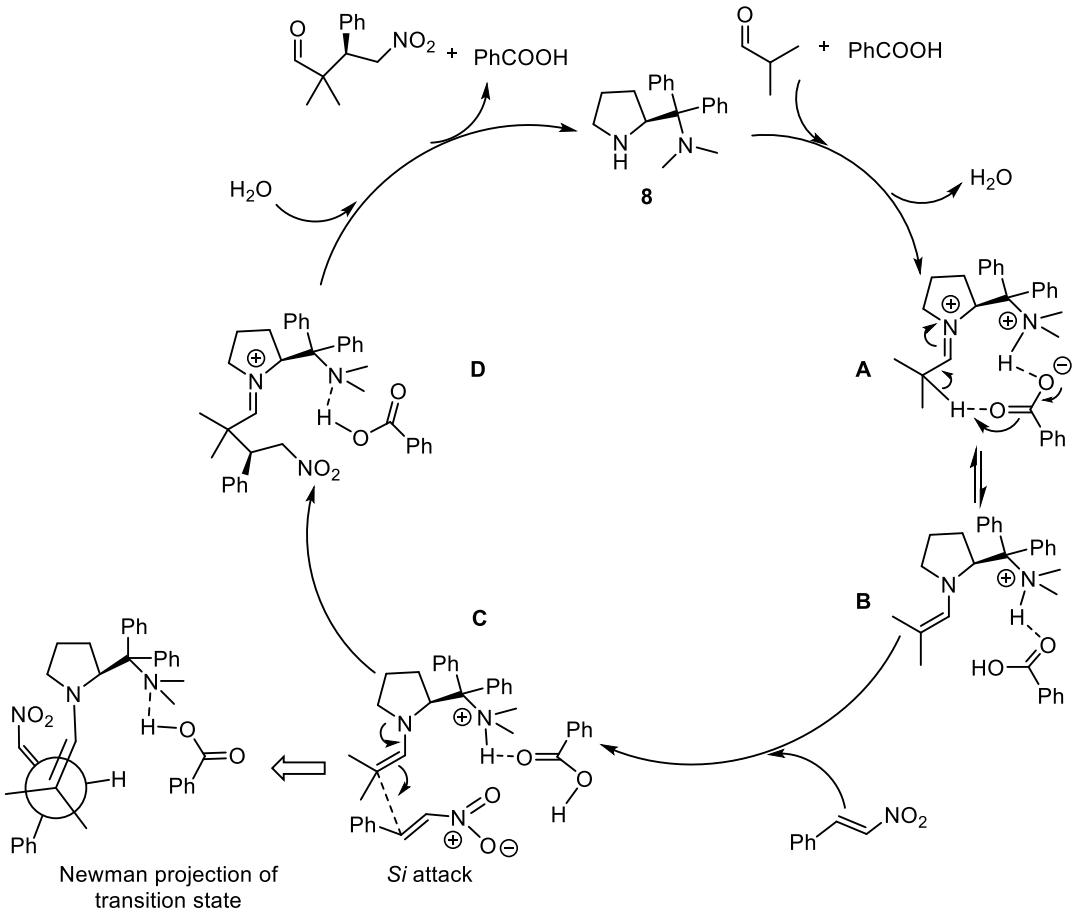


Figure 2.6 Proposed reaction mechanism

2.6 Conclusions

In conclusion, a more efficient method for the asymmetric Michael addition of isobutyraldehyde to nitroolefins was achieved via the use of a chiral diamine catalyst derived from α,α-diphenyl-(*S*)-prolinol. In our protocol, the Michael addition was successfully conducted with low catalyst and additive loadings of 5 mol%, respectively, due to the presence of the tertiary amine group in catalyst **8**. Moreover, various quaternary carbon-containing optically active γ–nitroaldehydes were obtained in good yields (up to 99%) and good to excellent enantioselectivity (up to 97% ee).

Chapter 3

Synthesis of *N*-aryl-4-arylhexahydroquinoline derivatives by reaction of cyclic enaminones with arylidenemalononitriles in DMSO

3.1 Introduction

N-aryl-4-aryl-hexahydroquinoline derivatives exhibit a range of significant antitumor,[32] anticancer, cytotoxic,[33] antioxidant,[34] antiproliferative,[35] and antibacterial bioactivities[36] (**Figure 3.1**). Because of their great pharmaceutical value, the synthesis of *N*-aryl-4-aryl-hexahydroquinoline derivatives has attracted much attention.[37]

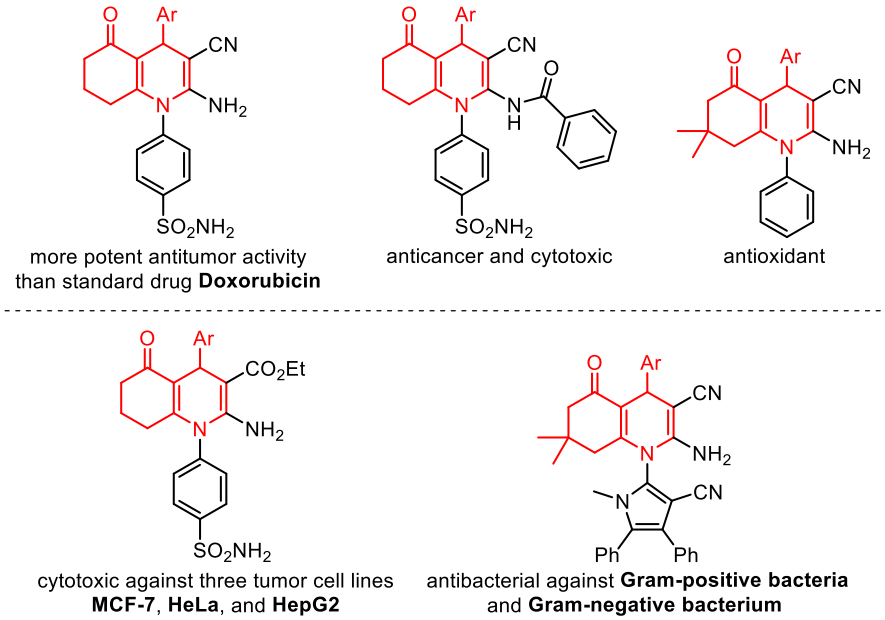


Figure 3.1 Selected bioactive *N*-aryl-4-aryl-hexahydroquinoline derivatives

3.2 Limitation of the previous reports

The reaction of cyclic enaminones with arylidenemalononitriles is an effective and straightforward process for the preparation of *N*-aryl-4-aryl-hexahydroquinoline derivatives. Although some examples of this type of reaction are reported,[32-37] catalysts such as oxido-vanadium (V) metal complexes,[37a] ZnO nanoparticles,[37b] chitosan,[37c]

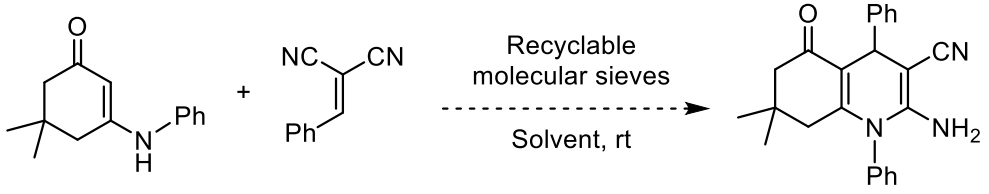
tetrabutylammonium fluoride (TBAF)[37d] or triethylbenzylammonium chloride (TEBAC)[37e] are usually needed in these reports. Among some other previous studies for the reaction of cyclic enaminones with arylidenemalononitriles, ultrasonic irradiation was used.[37b] Moreover, in most of the above examples, either a base or a reflux condition is necessary for this transformation. However, from the green chemical point of view, a simple and convenient procedure for constructing *N*-aryl-4-aryl-hexahydroquinoline derivatives under transition metal catalyst, organobase, and refluxing-free conditions is more desirable.

3.3 Author's strategy

Molecular sieves (MS) are not merely known as dehydrating agent, but also used as the promoter for many organic reactions due to their weekly basicity.[38] Moreover, MS are all cheap, commercially available, and recyclable.[38c,38f]

On the other hand, we have reported various reactions using the combination of dimethyl sulfoxide (DMSO) and molecular sieves.[39] For example, the double Michael addition of dithiols to acetylenic carbonyl compounds,[39g] aza-Henry reaction of *N*-tosylimines with nitroalkanes,[39i] and the ring-opening reaction of aziridines with amines[39j] are conducted smoothly using DMSO with MS 4A at room temperature without the necessity of transition metal catalyst or organobase.

Encouraged by such results, we report the cascade Michael-cyclization reaction of cyclic enaminones with arylidenemalononitriles, which yield useful *N*-aryl-4-aryl-hexahydroquinoline derivatives under mild reaction conditions using DMSO with MS 13X (**Scheme 3.1**).

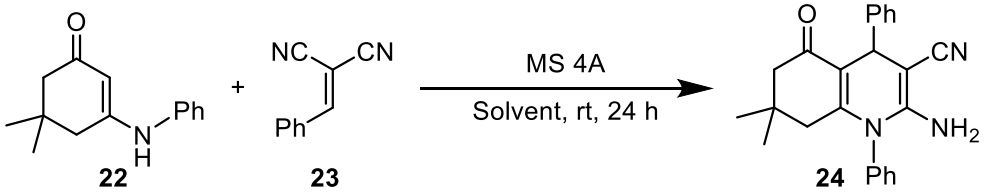


Scheme 3.1 Molecular sieves promote cascade reaction

3.4 Reaction of cyclic enaminones with arylidenemalononitriles in DMSO

Initially, author attempted the reaction of cyclic enaminone **22** (0.1 mmol) with benzylidenemalononitrile **23** (1.2 eq.) using MS 4A (100 mg) in various solvents (**Table 3.1**). Although the desired product **24** was obtained in only 35% yield, we found that DMSO was the most suitable solvent (Entry 1). Other aprotic and protic polar solvents such as MeCN, DMF, dimethylacetamide (DMA), *N*-methylpyrrolidone (NMP), THF, and MeOH were less effective for this reaction (Entries 2–7). Therefore, we decided to screen other reaction conditions in DMSO to improve the yield.

Table 3.1 Screening of solvents[a]

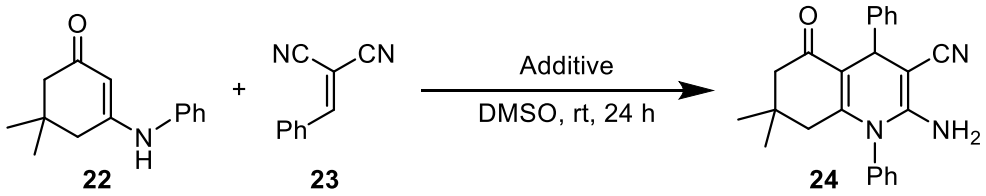


Entry	Solvent	Yield/%[b]
1	DMSO	35
2	MeCN	7
3	DMF	16
4	DMA	15
5	NMP	18
6	THF	trace
7	MeOH	5

[a]Reaction conditions: enaminone **22** (0.1 mmol) and benzylidenemalononitrile **23** (0.12 mmol) with the presence of MS 4A (100 mg) in solvent (1 mL). [b]Isolated yield by TLC.

Subsequently, various additives were explored for the cascade reaction in DMSO as summarized in **Table 3.2**. Without an additive, the desired product was obtained in trace amounts (Entry 1). The use of H_2O as an additive was also unsuccessful (Entry 2). In contrast, MS 3A promoted the reaction to afford product in similar yield to MS 4A (Entries 3 and 4). However, MS 5A was less effective for the reaction (Entry 5). MS 13X was more suitable than other molecular sieves, given the corresponding yield of 69% (Entry 5). Other dehydrating agents ($MgSO_4$, Na_2SO_4, and Drierite®) and activated alumina were also tested as additives in DMSO, which decreased the yields (Entries 7–10). Overall, MS 13X was determined to be the most suitable additive for this reaction.

Table 3.2 Screening of additives[a]

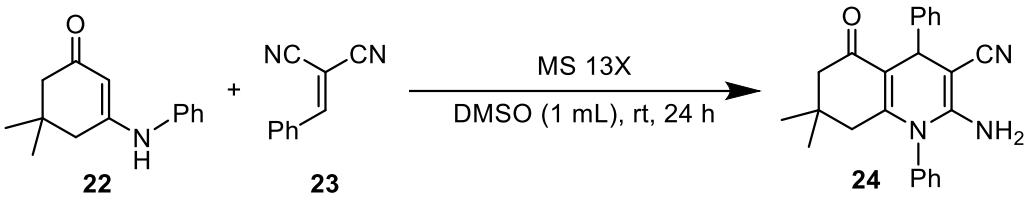


Entry	Additive	Yield/%[b]
1	none	trace
2	H_2O (100 μL)	4
3	MS 3A	37
4	MS 4A	35
5	MS 5A	9
6	MS 13X	69
7	$MgSO_4$	48
8	Na_2SO_4	8
9	Drierite®	11
10	activated alumina	19

[a]Reaction conditions: enaminone **22** (0.1 mmol), benzylidenemalononitrile **23** (0.12 mmol), and additives (100 mg) in DMSO (1 mL). [b]Isolated yield by TLC.

Next, the effects of reaction concentration and additive loading on the cascade reaction were screened (**Table 3.3**). By scaling the amount of MS 13X used with enaminone from 0.1–0.5 mmol in 1 mL DMSO, the yield was improved from 69% to 95% (Entries 1–6). Considering both purification and yield, we next conducted all reactions in 0.4 mmol scale of enaminone (Entries 7–10). Fortunately, decreasing the amount of MS 13X to 200 mg, almost no loss of yield was occurred (Entries 5–8). Further reducing the amount of MS 13X resulted in low yields (Entries 8–10). Thus, the optimal reaction conditions were determined to be enaminones (0.4 mmol) and arylidenemalononitriles (0.48 mmol) using MS 13X (200 mg) in DMSO (1 mL) at room temperature.

Table 3.3 Optimization of the reaction conditions[a]

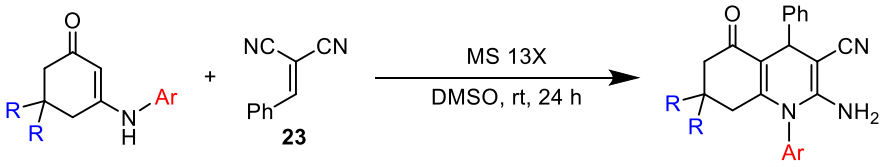


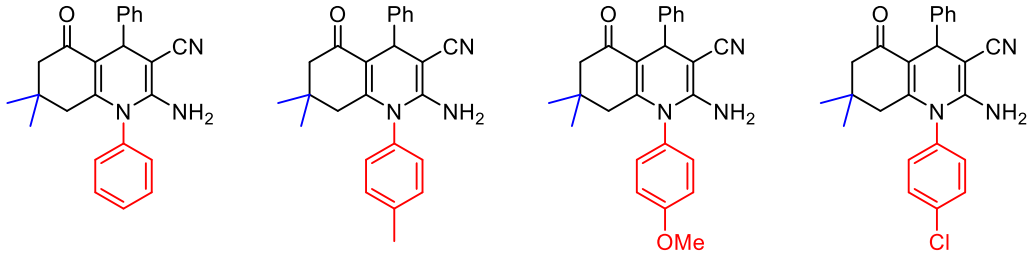
Entry	Enaminone **22** (mmol)	MS 13X (mg)	Yield/%
1[b]	0.1	100	69
2[b]	0.2	200	84
3[b]	0.3	300	89
4[c]	0.3	300	86
5[c]	0.4	400	94
6[c]	0.5	500	95
7[c]	0.4	300	93
8[c]	0.4	200	92
9[c]	0.4	150	88
10[c]	0.4	100	78

[a]Reaction conditions: enaminone **22**, benzylidenemalononitrile **23** (1.2 eq.), and MS 13X in DMSO (1 mL). [b]Isolated yield by TLC. [c]Product was purified by recrystallization and TLC.

With the optimized reaction conditions in hand, we next examined the cascade Michael-cyclization reaction of various enaminones with benzylidenemalononitrile **23** (**Table 3.4**). Enaminones bearing electron-donating and halogen-atom substituents at the *para*-position of a phenyl ring yielded the corresponding products (**25**–**28**) with good to excellent levels. However, with NO_2, when a strong electron-withdrawing group was substituted at the *para*-position of an aromatic ring, no reaction occurred. Enaminone, prepared from 1-naphthylamine and dimedone provided the corresponding product **30** in 90% yield (**3ga**). Furthermore, a 1,3-cyclohexanedione derived enaminone was also tolerated under the optimal reaction conditions, resulted in a 77% yield of the product **31**. However, enaminones derived from benzylamine, hexylamine (aliphatic amines), and an acyclic enaminone yielded poor results (products **32**, **33,** and **34**). Moreover, the gram-scale synthesis of product **24** was also achieved in 96% yield.

Table 3.4 Scope of enaminones[a,b]



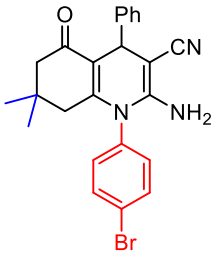


24, 92%, (96%)[c]

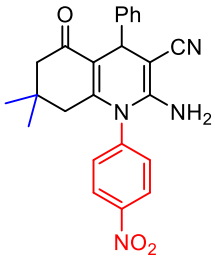
25,90%

26, 86%

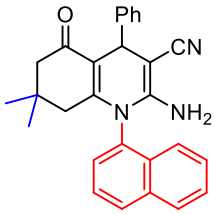
27, 100%



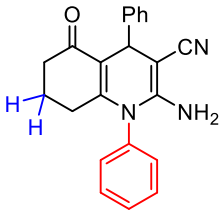
28, 99%



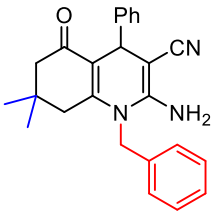
29, N.R.



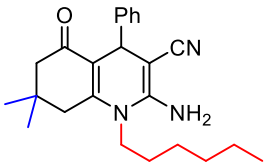
30, 90%



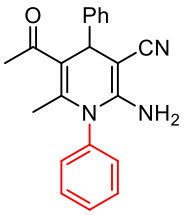
31, 77%



32, N.R.



33, N.R.



34, N.R.

[a]Reaction conditions: enaminone (0.4 mmol), **23** (0.48 mmol), and MS 13X (200 mg) in DMSO (1 mL) at rt.

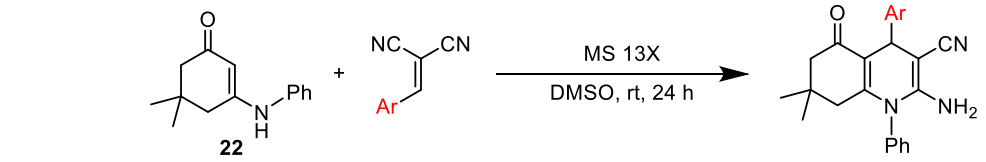
[b]All products were purified by recrystallization and TLC.

[c]Reaction was carried out using **22** (4.64 mmol, 1.0 g) and **23** (5.57 mmol) in DMSO (20 mL) in the presence of MS 13X (2.0 g) for 2 d.

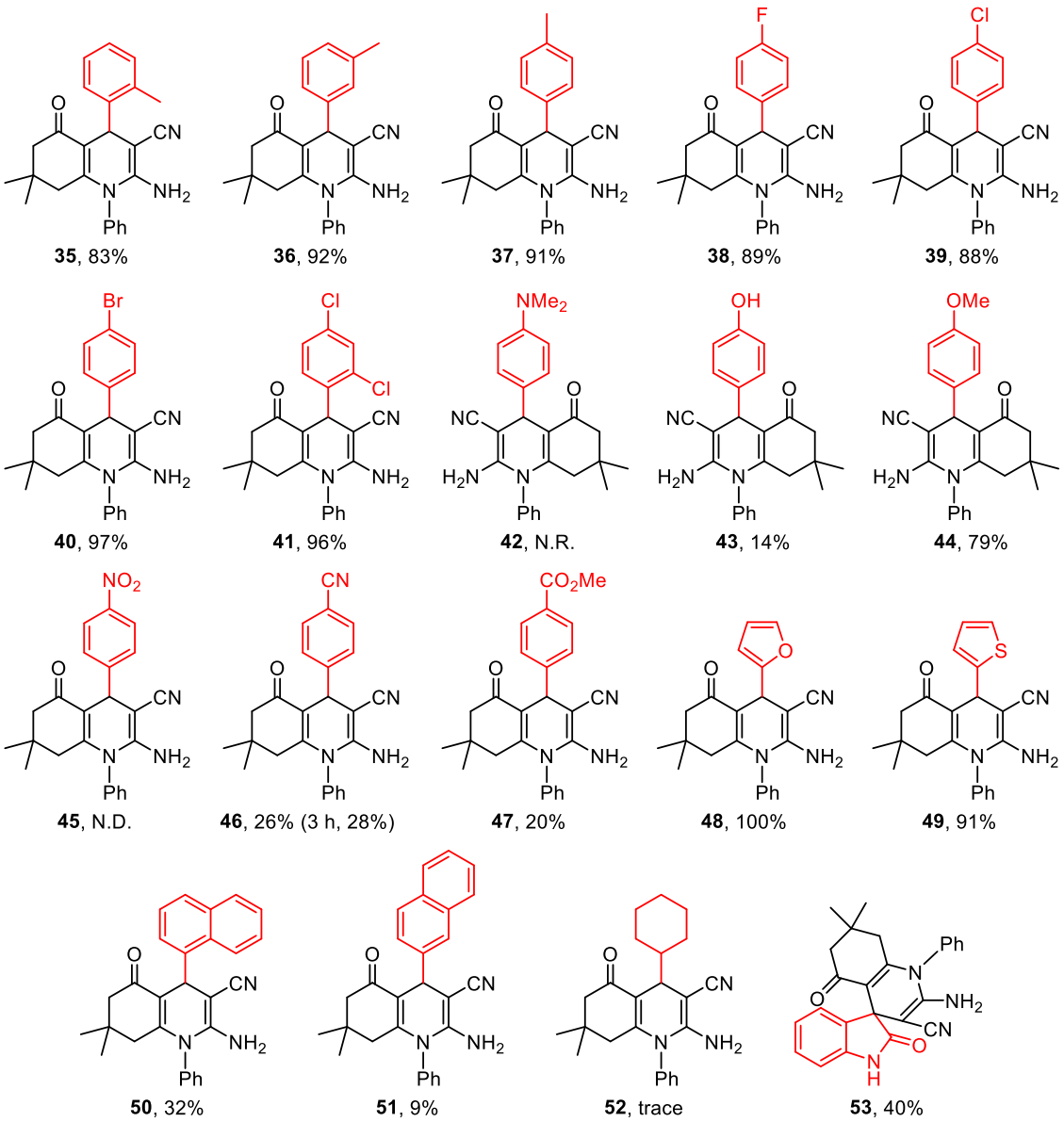
[d]N.R. = no reaction.

Author further evaluated the cascade Michael-cyclization reaction of various arylidenemalononitriles with enaminone **22** (**Table 3.5**). Arylidenemalononitriles containing a methyl group at the *ortho*-, *meta*-, and *para*-positions of the aromatic ring were tolerated, and all resulted in the high yields of the corresponding products **35**–**37**. Moreover, arylidenemalononitriles bearing various halogen-atom substituents (F, Cl, and Br) at the *para*-position and 2,4-dichloro substituents on the phenyl ring reacted smoothly with enaminone **22** to produce good to excellent yields (88%-97%) of the desired products **38**–**41**. Electron-donating groups such as dimethylamino and hydroxy substituted on the *para* position of phenyl ring drastically reduced the reactivity of the arylidenemalononitriles. Fortunately, when the 4-methoxyl group was substituted on the phenyl ring instead of a free hydroxyl group, the reaction proceeded smoothly, resulting in 79% yield of the product **44**. In contrast, the reactivity of the arylidenemalononitriles bearing electron-withdrawing groups (NO_2, CN, and CO_2Me) on the *para* position of phenyl ring was too high to cause the side reaction in these cases. An unidentified complex mixture was obtained instead of product **45**. Reacting *para*-cyanobenzylidenemalononitrile for either 24 or 3 h gave product **46** in nearly the same yield (26% or 28%, respectively). A low yield of **47** was also obtained (20%). Gratifyingly, arylidenemalononitriles bearing heteroaryl rings (2-furyl and 2-thienyl) gave the products **48**, **49** in quantitatively and 91% yield, respectively. Despite the low yields, naphthyl group containing products **50** and **51** were also isolated. Although cyclohexylmethylenemalononitrile was explored, product **52** was obtained only in trace amounts. Besides, isatylidenemalononitrile was examined producing a 40% yield of the corresponding product **53**.

Table 3.5 Scope of various arylidenemalononitriles[a,b]



22



35, 83% | **36**, 92% | **37**, 91% | **38**, 89% | **39**, 88%

40, 97% | **41**, 96% | **42**, N.R. | **43**, 14% | **44**, 79%

45, N.D. | **46**, 26% (3 h, 28%) | **47**, 20% | **48**, 100% | **49**, 91%

50, 32% | **51**, 9% | **52**, trace | **53**, 40%

[a]Reaction conditions: **22** (0.4 mmol), arylidenemalononitriles (0.48 mmol), and MS 13X (200 mg) in DMSO (1 mL) at rt.

[b]All products were purified by recrystallization and TLC.

[c]N.R. = no reaction.

[d]N.D. = not determined.

3.5 Conclusions

In this chapter, the efficient and environment-friendly cascade Michael-cyclization reaction of cyclic enaminones with arylidenemalononitriles using the combination of MS 13X and DMSO has been described. In contrast to the conventional methods, this reaction was achieved for the first time without using transition metal catalyst, organobase, or heating conditions. Moreover, this protocol resulted in high yields (up to 100%) of various bioactive *N*-aryl-4-aryl-hexahydroquinoline derivatives.

Chapter 4

A novel Mannich reaction of α-aminomaleimides

4.1 Introduction

Maleimide analogs play important role in both medicinal chemistry, polymer materials, and organic synthetic chemistry (**Figure 4.1**).[40,41,42,43] The versatile maleimide motifs are widely present in many natural products and bioactive compounds[40] such as carpesiumaleimides,[44] oxaleimides,[45] polycitrin,[46] and himanimides.[47] Moreover, maleimide analogues exhibit significant biological activities including inhibition of ferroptosis and NETosis,[48] fungicidal activity,[49] anticancer activity,[50] inhibition of kinase,[51] as well as cell death-inhibitory activity.[52] Recently, many groups reported that maleimide derivatives can be applied as emission dyes[53] and organic fluorophores.[54,55,56] Because of their wide and significant uselessness, the synthesis of a new class of maleimide derivatives is desired and has attracted much attention.

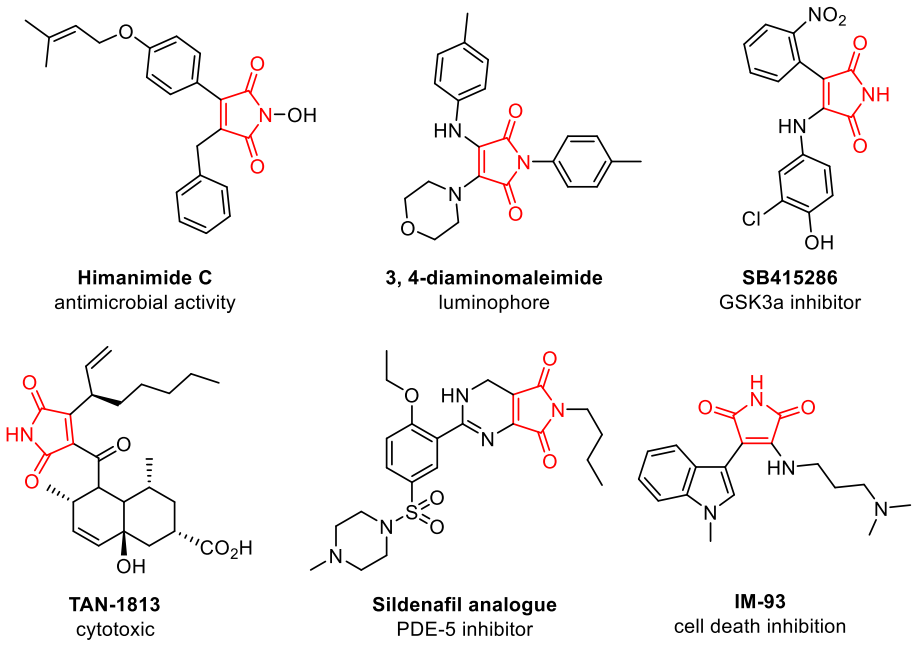


Figure 4.1 Examples of useful maleimide analogs

4.2 Recent studies about the reactions of α-aminomaleimides

a-Aminomaleimides, one kind of β-enamino imides is a useful synthetic building block for the constructing of nitrogen-containing heterocycles due to their similar structural character of β-enaminone and β-enamino ester.[57,58,59] Because of their important applications in organic synthesis, some reactions of this special β-enamino imide have been developed. For example, some groups respectively reported the synthesis of valuable heterocycles using *a*-aminomaleimide as the nucleophiles[60,61,62] (**Figure 4.2**). Despite the above advances, when comparing to other β-enaminone and β-enamino ester, the reactions of α-aminomaleimides are still few. Thus, the development of new reactions of α-aminomaleimides remains in high demand.

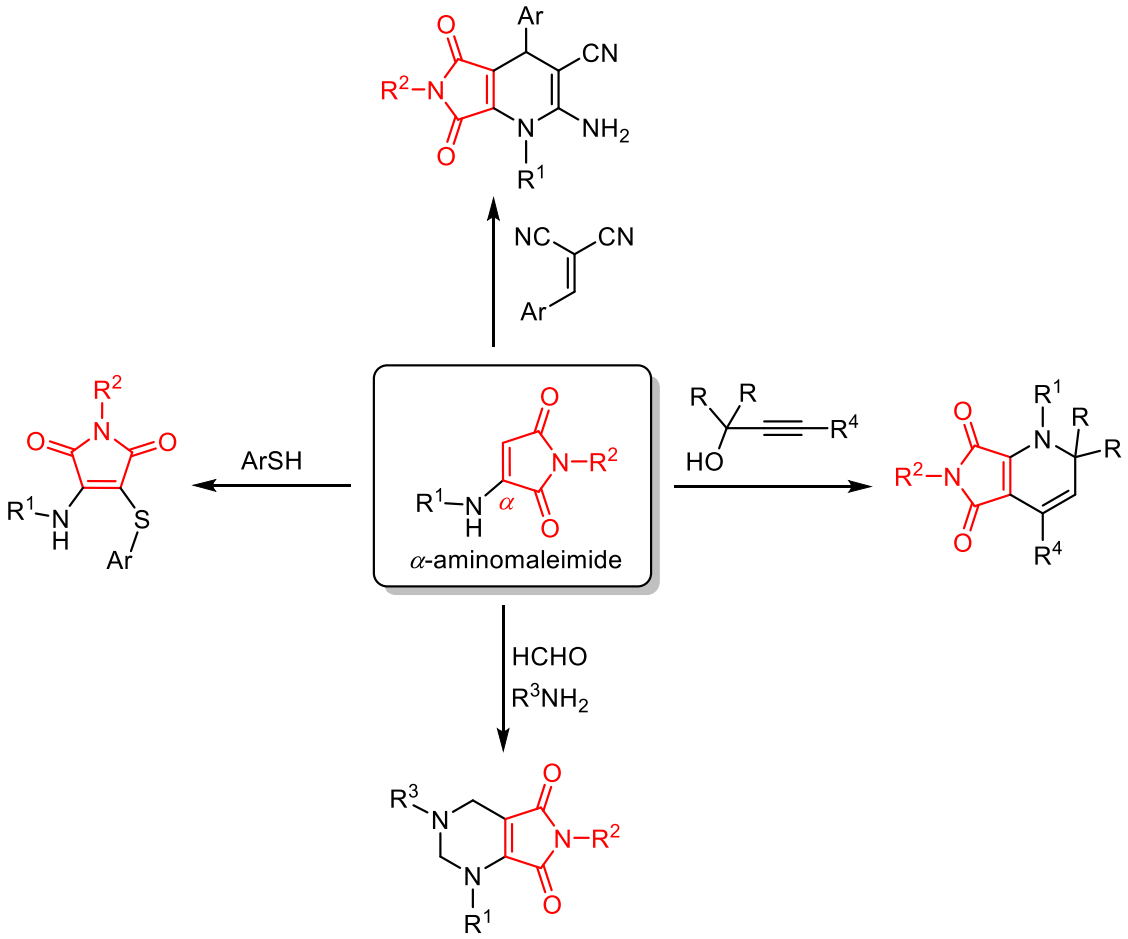
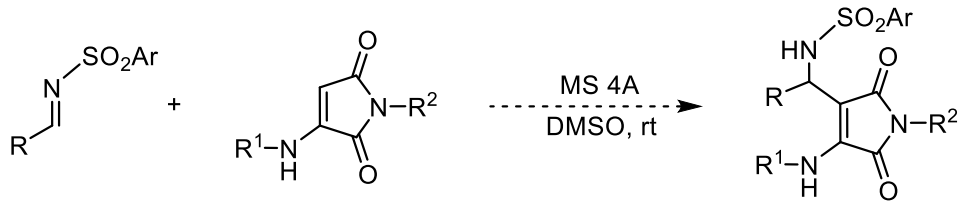


Figure 4.2 The synthesis of valuable heterocycles from α-aminomaleimide

4.3 A novel Mannich reaction of α-aminomaleimides in this study

The Mannich reaction is one of the fundamental and important reactions for the direct construction of nitrogen-containing natural products and bioactive compounds.[63,64,65] Many efforts also have been made to the research of this reaction.[66,67,68,69,70] For example, the Mannich reactions of 3-isothiocyanato oxindoles,[71] carbonyl compounds,[72,73,74,75] pyrrole,[76] indole,[77] and *et al*. have been reported. The Mannich reaction using α-aminomaleimide as a nucleophile is interesting and can install valuable maleimide-skeleton directly. To date, although only one related report about the multicomponent reaction of aldehydes, amines, and α-aminomaleimides[78] exists the Mannich reaction of α-aminomaleimides has not been reported yet. Therefore, the author also pays attention to this transformation.

Considering the advantages of molecular sieves from our previous works,[39] as a continuation of our interest in the synthesis of maleimide derivatives and the development of novel reactions, in this chapter author describe an MS 4A promoted novel Mannich reaction of α-aminomaleimides with *N*-sulfonyl imines in DMSO (**Scheme 4.1**).



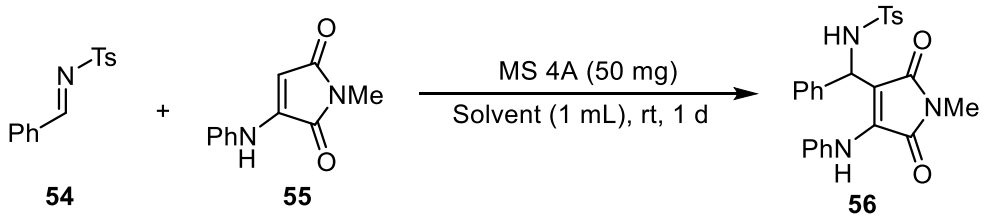
This work : The first Mannich reaction of *N*-arylsulfonyl imines and α-aminomaleimides

Scheme 4.1 Mannich reaction for the synthesis of new maleimide derivatives

4.4 Results and discussion

Initially, the reaction of *N*-tosylimine **54** and α-aminomaleimide **55** with MS 4A was examined in various solvents (**Table 4.1**). We found that DMSO was the most suitable solvent and gave the Mannich product **56** in 95% yield (Entry 1). THF, MeOH, DCM, and H_2O were ineffective (Entries 3−6). Using more less amount of 25 mg or without MS 4A, the reaction still occurred, but the yield was moderate (Entries 7 and 8). Decreasing the amount of imine, the yields also reduced (Entries 9 and 10). Overall, the optimal reaction conditions were determined as follows: imines **54** (0.13 mmol), α-aminomaleimide **55** (0.1 mmol), and MS 4A (50 mg) in DMSO (1 mL) at room temperature.

Table 4.1 Optimization of reaction conditions[a]



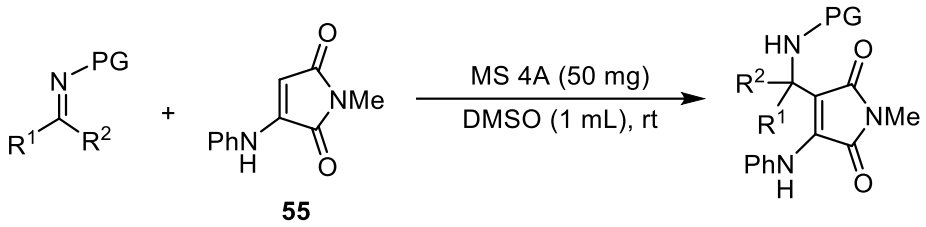
54 **55** **56**

Entry	Solvent	Yield[b] / %
1	DMSO	95
2	DMF	91
3	THF	0
4	MeOH	0
5	DCM	trace
6	H_2O	trace
7[c]	DMSO	83
8[d]	DMSO	75
9[e]	DMSO	86
10[f]	DMSO	89

[a]Reaction conditions: **54** (0.13 mmol), **55** (0.1 mmol), and MS 4A (50 mg) in DMSO (1 mL) at rt. [b]Isolated yield. [c]MS 4A 25 mg. [d]Without MS 4A. [e]imine 0.11 mmol. [f]imine 0.12 mmol.

With the optimized conditions in hand, we explored the substrate scope of the imines (**Table 4.2**). *N*-tosylimines bearing halogen-atoms or electron-donating groups at both *ortho*-, *meta*-, and *para*-positions were tolerated well, giving the corresponding products **57**−**65** in good to excellent yields (Entries 2−10) except the *ortho*-chloro substituted imine gave a poor yield, although extending the reaction time to 48 h (Entry 2). After comparing entries 2, 6, and 9, it seems that the electronic impact is greater than the substituent position. Satisfactory, *N*-tosylimines with electron-withdrawing groups on the *para*-position of the aryl ring exhibited higher reactivity and provided products **66**−**68** in high to excellent yields after a short time (within 4 h) (Entries 11−13). Naphthaldehydes derived *N*-tosylimines gave the Mannich products **69**−**70** in good yields (Entries 14−15). The yields were significantly decreased when using the heteroaryl aldehyde and aliphatic aldehyde derived imines as the substrates, but the products **71**−**72**were still obtained (Entries 16−17). Acetophenone derived *N*-tosylimine and *N*-*p*-methoxybenzyl imine was more challenging and unsuccessful (Entries 18−19). Fortunately, successful results of products **75**−**76**were also obtained using other *N*-sulfonyl imines such as *N*-nosylimine and *N*-phenylsulfonylimine (Entries 20−21).

Table 4.2 The substrate scope of imines[a]



Entry	R^1	R^2	PG	Time/h	**Product**	Yield[b] / %
1	Ph	H	Ts	24	**56**	95
2	2-ClC_6H_4	H	Ts	24	**57**	trace[c]
3	3-ClC_6H_4	H	Ts	24	**58**	91
4	4-ClC_6H_4	H	Ts	24	**59**	90
5	4-BrC_6H_4	H	Ts	24	**60**	93
6	2-MeC_6H_4	H	Ts	24	**61**	90
7	3-MeC_6H_4	H	Ts	24	**62**	100
8	4-MeC_6H_4	H	Ts	24	**63**	81
9	2-$PivOC_6H_4$	H	Ts	24	**64**	85
10	4-$MeOC_6H_4$	H	Ts	24	**65**	82
11	4-CNC_6H_4	H	Ts	3	**66**	93
12	4-$NO_2C_6H_4$	H	Ts	3	**67**	94
13	4-$MeO_2CC_6H_4$	H	Ts	4	**68**	97
14	1-naphthyl	H	Ts	24	**69**	91
15	2-naphthyl	H	Ts	24	**70**	85
16	2-furyl	H	Ts	48	**71**	36
17	Cy	H	Ts	48	**72**	25
18	Ph	Me	Ts	24	**73**	0
19	Ph	H	PMP	24	**74**	0
20	Ph	H	Ns	24	**75**	69
21	4-$NO_2C_6H_4$	H	$PhSO_2$	4	**76**	100

[a]Reaction conditions: imines (0.13 mmol), **55** (0.1 mmol), and MS 4A (50 mg) in DMSO (1 mL) at rt. [b]Isolated yield. [c]2 d.

Next, the Mannich reactions between *N*-tosylimine **54** and different α-aminomaleimides were conducted and the results were summarized in **Table 4.3**. α-Arylamino maleimides bearing chloro-atom and electron-donating groups on the phenyl ring reacted smoothly and gave the corresponding products **77**−**79** in high yields (Entries 1−3). Although we attempted to prepare the α-arylamino maleimides bearing electron-withdrawing groups from 4-nitroaniline, but it was unsuccessful due to the lower nucleophilicity. Luckily, α-aliphatic aminomaleimides were also tolerated and gave the products **80**−**81** in good yields (Entries 4−5). α-Aminomaleimide having benzyl group instead of methyl at the nitrogen atom of imide part gave the product **82** in quantitative yield (Entry 6). It is conceivable that the deprotection of benzyl group on the nitrogen atom of the imide part will give new intermediates that can be used for other transformations. Thus, the Mannich products also show additional potential value in organic synthesis.

Table 4.3 Mannich reaction of various α-aminomaleimides[a]

Entry	R^1	R^2	Time/h	**Product**	Yield[b] / %
1	4-ClC_6H_4	Me	24	**77**	92
2	4-MeC_6H_4	Me	7	**78**	99
3	4-$MeOC_6H_4$	Me	7	**79**	80
4	Me	Me	24	**80**	60
5	Bn	Me	24	**81**	72
6	Ph	Bn	7	**82**	100

[a]Reaction conditions: **54** (0.13 mmol), α-aminomaleimides (0.1 mmol), and MS 4A (50 mg) in DMSO (1 mL) at rt. [b]Isolated yield.

4.5 Fluorescence properties of the Mannich products

Moreover, some Mannich products were selected to test their optical properties under UV light (254 nm) and presented different fluorescence properties (**Figure 4.3**). Although a more detailed study about absorption spectra and emission spectra wasn't investigated, there's reason to believe that these new maleimide derivatives will attract great interest in the fields of application as organic fluorophores.

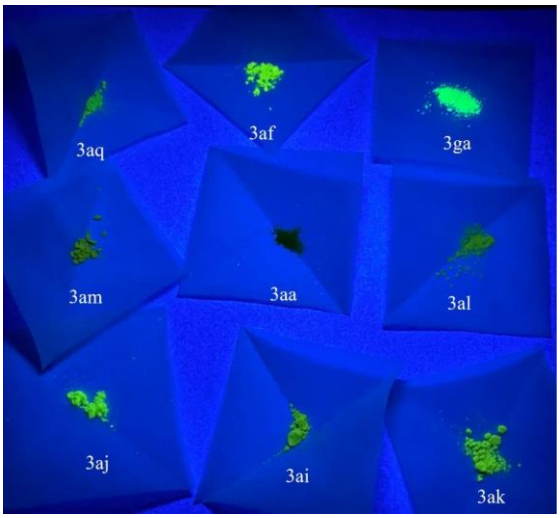


Figure 4.3 Optical properties of some products under UV light (254 nm)

4.6 Conclusions

In this chapter, the first Mannich reaction of α-aminomaleimides with *N*-arylsulfonyl imines under the influence of MS 4A in DMSO has been developed. The synthetic advantages of this protocol include: (1) using the recyclable molecular sieves as a promoter for organic synthesis accords with the green chemical point of view; (2) a wide range of substrates are tolerated well; (3) this method provides the Mannich products, new valuable maleimides derivatives bearing multi nitrogen-atom in good to excellent yields; (4) the reaction proceeded smoothly under mild reaction conditions. Also, the resulting products present the potential possibility to be applied as organic fluorophores.

5. Summary

In summary, the author mainly focused on the research of (1) organocatlyzed asymmetric reactions and (2) the development of the green chemical protocols for highly efficient novel synthetic reactions during his Ph.D. research program.

In chapter 2, the author described an efficient chiral diamine **8** catalyzed asymmetric Michael addition of isobutyraldehyde to nitroolefins. In this protocol, various enantiomerically enriched *γ*–nitroaldehydes were synthesized in moderate to high yield with excellent enantioselectivity (up to 99%, 90-97% ee) in the presence of just 5 mol% catalyst under mild reaction conditions.

In chapter 3, the reaction of cyclic enaminones with arylidenemalononitriles was achieved in the presence of molecular sieves 13X in dimethyl sulfoxide. Under these mild reaction conditions, various bioactive *N*-aryl-4-aryl-hexahydroquinoline derivatives were obtained in high yields without a base, a catalyst, or refluxing. Moreover, recyclable molecular sieves promoted cascade Michael–cyclization is consistent with the green chemical point of view.

In chapter 4, the author described a novel Mannich reaction of *a*-aminomaleimides with *N*-arylsulfonyl imines using molecular sieves 4A as the promoter in dimethyl sulfoxide. Valuable new maleimide derivatives were synthesized efficiently under mild reaction conditions. The products show different fluorescence properties under UV and have the potential possibility to be organic fluorophores.

The author hopes these research results can make some contributions to the development of novel reactions, chiral building blocks, and new useful compounds. By aiming to develop green chemical protocols using the recyclable system for organic synthesis, the author also hopes these results can make a meager contribution to the protection of the earth's environment.

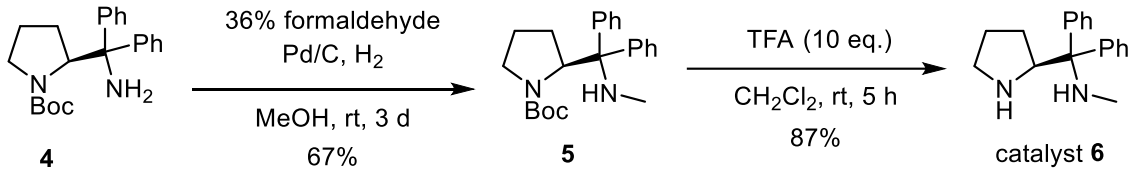
6. Experiments

6.1 General Information

^{1}H and ^{13}C NMR spectra were recorded in 500 MHz on a Bruker spectrometer. Chemical shifts are expressed in parts per million (δ-value) from TMS as an internal standard, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), and brs. (broad)], coupling constants in (Hz), integration, and assignment. IR spectra were recorded on a BRUKER TENSOR 27 spectrometer using KBr discs. Optical rotations were measured on a JASCO P-2300 polarimeter. The enantiomeric excess (ee) of the Michael products were determined by chiral HPLC analysis using 0.46 cm × 25 cm DAICEL CHIRALPAK OD-H or AD-H column. The melting point was measured by using a Mel-Temp® apparatus. HRMS data were obtained by ESI using JMS-700 MS tation. Chromatographic separations were performed on a silica gel column using Wakogel® C-200. Thin-layer chromatography was performed with Wakogel® B-5F. Molecular Sieves (MS) was powdered by a mortar and dried up with a heat gun before use. All commercial materials and solvents were used without further purification. Without other notes, all reactions were carried out under open-air conditions.

6.2 Experiments in chapter 2

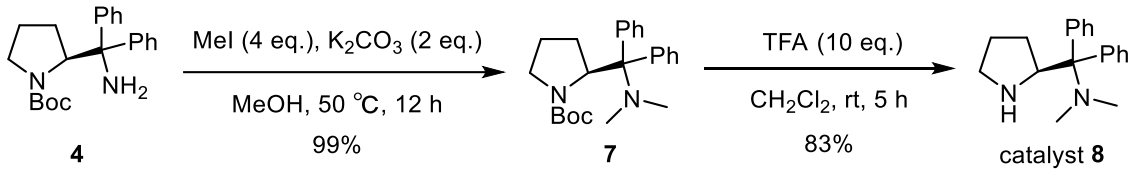
6.2.1 Synthesis of chiral diamine catalysts 6 and 8



Amine **4**[31c] (0.318 g, 0.902 mmol) and formaldehyde solution (36% in H_2O) (2.2 eq, 0.2 mL, 1.98 mmol) were dissolved in methanol and 10% Pd/C (0.032 g) was added. The mixture was stirred vigorously under the balloon of hydrogen at room temperature for 3 days. Then, the reaction mixture was filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column

chromatography on silica gel with hexane: EtOAc = 4: 1 as eluent to give the mono-methylated amine **5** (0.221 g, 0.603 mmol, 67%).

To a solution of amine **5** (0.221 g, 0.603 mmol) in CH_2Cl_2 (3 mL), trifluoroacetic acid (10 eq, 0.46 mL, 6.03 mmol) was added slowly. The mixture was stirred for 5 h and then quenched with aq NaOH (1 M, 10 mL). After extracted with CH_2Cl_2 (3x5 mL), the organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give diamine catalyst **6** as a colorless oil (0.138 g, 0.518 mmol, 87%).



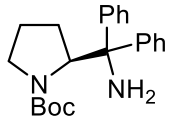
Amine **4**[31c] (0.35 g, 0.993 mmol) and K_2CO_3 (2 eq, 0.30 g, 1.99 mmol) were dissolved in methanol and iodomethane (4 eq, 0.3 mL, 3.97 mmol) was added. The mixture was heated at 50 °C for 12 h under argon. Then, the mixture was cooled to room temperature and filtered through a small pad of Celite. The precipitate was washed with EtOAc (5 mL). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel with hexane: EtOAc = 5: 1 as eluent to provide amine **7** (0.37 g, 0.971 mmol, 99%)

To a solution of amine **7** (0.370 g, 0.971 mmol,) in CH_2Cl_2 (4 mL), trifluoroacetic acid (10 eq, 0.74 mL, 9.71 mmol) was added slowly. The mixture was stirred for 5 h and then quenched with aq NaOH (1 M, 10 mL). After extracted with CH_2Cl_2 (3x5 mL), the organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give diamine catalyst **8** as a colorless oil (0.138 g, 0.518 mmol, 87%).

6.2.2 General procedure of asymmetric Michael reaction

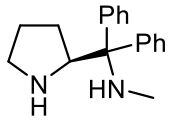
To a mixture of diamine catalysts (0.005 mmol, 5 mol%) and PhCOOH (0.005 mmol, 5 mol%) in *i*-PrOH (0.2 mL) was added isobutyraldehyde (0.5 mmol, 5 eq, 46 ul) at room temperature. Then, nitroolefins (0.0149 g, 0.1 mmol,) were added to the solution. The Michael products were purified by thin-layer chromatography with hexane: EtOAc = 3: 1. The absolute configuration of the Michael adducts was identified by comparing it to the literature.[28,29,79]

6.2.3 Analytical data of products in chapter 2



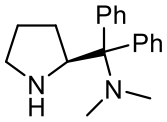
4

^{1}H NMR ($CDCl_3$, δ): 0.82-0.88 (1H, m), 1.37 (9H, s), 1.49-1.60 (1H, m), 1.84-1.89 (1H, m), 2.11-2.15 (1H, m), 2.91-3.01 (1H, brs), 3.36-3.49 (1H, brs), 4.96-5.05 (1H, m), 7.22-7.37 (10H, m). ^{13}C NMR ($CDCl_3$, δ): 22.9, 28.3, 28.9, 48.1, 64.9, 65.8, 79.5, 126.5, 126.7, 127.6, 127.8, 127.9, 128.4, 145.7, 148.0, 156.6. IR (neat, cm^{-1}): 3376, 3319, 3057, 2975, 1668, 1493, 1446, 1364, 1170, 762, 701. $[\alpha]_D$ -48.1 (c 0.15, $CHCl_3$).



catalyst **6**

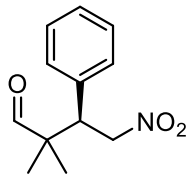
^{1}H NMR ($CDCl_3$, δ): 1.02-1.06 (1H, m), 1.47-1.61 (2H, m), 1.81-1.85 (1H, m), 1.98 (2H, brs), 2.09 (3H, s), 2.48-2.50 (1H, m), 2.74-2.76 (1H, m), 4.06 (1H, t, *J* = 7.5 Hz), 7.26-7.39 (10H, m). ^{13}C NMR ($CDCl_3$, δ): 25.6, 27.8, 29.8, 46.8, 62.7, 68.9, 126.7, 127.6, 129.2, 143.6. IR (KBr, cm^{-1}): 3343, 3297, 3020, 2963, 2901, 2860, 1681, 1491, 1445, 1130, 1010, 854, 760, 712, 700. $[\alpha]_D$ -37.3 (c 0.10, $CHCl_3$).



catalyst **8**

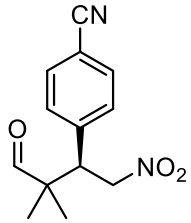
^{1}H NMR ($CDCl_3$, δ): 0.66-0.70 (1H, m), 1.41-1.44 (2H, m), 1.81-1.85 (1H, m), 2.06 (6H, s), 2.23-2.25 (1H, m), 2.59-2.62 (1H, m), 4.41 (1H, t, *J* = 7.5 Hz), 7.26-7.34 (10H, m). ^{13}C NMR ($CDCl_3$, δ): 25.3, 27.2, 39.6, 46.7, 59.6, 73.7, 126.7, 128.2, 130.6, 138.4. IR (neat, cm^{-1}): 3055, 2948, 2865, 2826, 2783, 1491, 1444, 1022, 889, 754, 705. $[\alpha]_D$ -23.7 (c 0.12, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-phenylbutanal, (*R*)-**9**



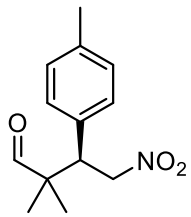
^{1}H NMR ($CDCl_3$, δ): 1.00 (3H, s), 1.13 (3H, s), 3.78 (1H, dd, *J* = 11.3, 4.2 Hz), 4.69 (1H, dd, *J* = 13.0, 4.2 Hz), 4.85 (1H, dd, *J* = 13.0, 11.3 Hz), 7.18-7.35 (5H, m), 9.53 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 19.0, 21.6, 48.2, 48.4, 76.2, 128.1, 128.7, 129.0, 135.3, 204.2. IR (neat, cm^{-1}): 2975, 1726, 1555, 1455, 1379, 882, 750, 705. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 14.4 min, t_R (minor) = 20.9 min, ee = 93%. $[\alpha]_D$ + 5.3 (c 0.20, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(4-cyanophenyl) butanal, (*R*)-**10**



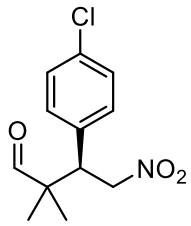
^{1}H NMR ($CDCl_3$, δ): 1.03 (3H, s), 1.14 (3H, s), 3.86 (1H, dd, *J* = 11.5, 4.0 Hz), 4.74 (1H, dd, *J* = 13.5, 4.0 Hz), 4.88 (1H, dd, *J* = 13.5, 11.5 Hz), 7.36 (2H, d, *J* = 8.3 Hz), 7.65 (2H, d, *J* = 8.3 Hz), 9.48 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 19.1, 21.9, 48.3, 60.3, 75.7, 112.2, 118.2, 130.0, 132.4, 141.3, 203.2. IR (neat, cm^{-1}): 2974, 2230, 1724, 1555, 1379, 850. HPLC: Chiralpak AD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 220 nm, t_R (major) = 13.7 min, t_R (minor) = 16.6 min, ee = 97%. $[\alpha]_D$ + 7.1 (c 0.20, $CHCl_3$)

(R)-2,2-Dimethyl-4-nitro-3-(4-methylphenyl) butanal, (*R*)-**11**



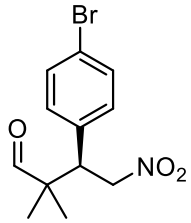
^{1}H NMR ($CDCl_3$, δ): 1.00 (3H, s), 1.12 (3H, s), 2.32 (3H, s), 3.74 (1H, dd, *J* = 11.4, 4.2 Hz), 4.66 (1H, dd, *J* = 13.0, 4.2 Hz), 4.82 (1H, dd, *J* = 13.0, 11.4 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 9.52 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 18.8, 21.0, 21.6, 48.2, 76.4, 128.9, 129.4, 132.1, 137.9, 204.4**.** IR (neat, cm^{-1}): 2974, 2719, 1725, 1555, 1516, 1436, 1379, 882, 825. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 11.4 min, t_R (minor) = 16.6 min, ee = 90%. $[\alpha]_D$ + 25.4 (c 0.50, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(4-chlorophenyl) butanal, (*R*)-**12**



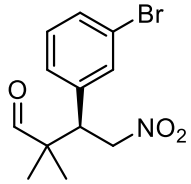
^{1}H NMR ($CDCl_3$, δ): 1.01 (3H, s), 1.12 (3H, s), 3.77 (1H, dd, *J* = 11.5, 4.2 Hz), 4.69 (1H, dd, *J* = 13.1, 4.2 Hz), 4.82 (1H, dd, *J* = 13.1, 11.5 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 7.31 (2H, d, *J* = 8.5 Hz), 9.50 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 18.9, 21.7, 47.8, 48.1, 76.1, 128.9, 130.4, 133.9, 134.2, 203.8. IR (neat, cm^{-1}): 2975, 2720, 1724, 1555, 1494, 1378, 1094, 882, 836. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 12.7 min, t_R (minor) = 20.7 min, ee = 94%. $[\alpha]_D$ + 3.3 (c 0.20, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(4-bromophenyl) butanal, (*R*)-**13**



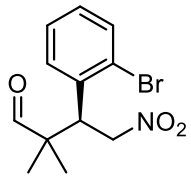
^{1}H NMR ($CDCl_3$, δ): 1.01 (3H, s), 1.12 (3H, s), 3.75 (1H, dd, *J* = 11.5, 4.1 Hz), 4.69 (1H, dd, *J* = 13.1, 4.1 Hz), 4.82 (1H, dd, *J* = 13.1, 11.5 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 7.46 (2H, d, *J* = 8.5 Hz), 9.50 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 18.9, 21.7, 47.9, 48.0, 76.0, 122.3, 130.7, 131.9, 134.5, 203.8. IR (neat, cm^{-1}): 2924, 2857,1727, 1555, 1485, 1379, 1008. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 15.7 min, t_R (minor) = 24.8 min, ee = 96%. $[\alpha]_D$ + 2.0 (c 0.19, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(3-bromophenyl) butanal, (*R*)-**14**



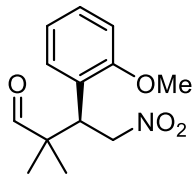
^{1}H NMR ($CDCl_3$, δ): 1.01 (3H, s), 1.13 (3H, s), 3.75 (1H, dd, *J* = 11.3, 4.0 Hz), 4.69 (1H, dd, *J* = 13.0, 4.0 Hz), 4.82 (1H, dd, *J* = 13.0, 11.3 Hz), 7.15 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz), 7.21 (1H, dd, *J* = 8.0, 8.0 Hz), 7.36 (1H, dd, *J* = 1.0, 1.0 Hz), 7.44 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz), 9.50 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 18.8, 21.8, 47.9, 48.2, 76.0, 122.8, 127.7, 130.2, 131.3, 132.1, 137.9, 203.7. IR (neat, cm^{-1}): 2974, 2877, 2812, 1726, 1555, 1476, 1433, 1380, 1378, 1077, 882, 778, 702. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 16.6 min, t_R (minor) = 22.9 min, ee = 96%. $[\alpha]_D$ + 3.9 (c 0.29, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(2-bromophenyl) butanal, (*R*)-**15**



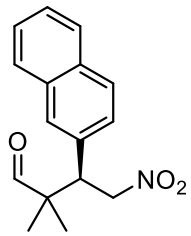
^{1}H NMR ($CDCl_3$, δ): 1.10 (3H, s), 1.17 (3H, s), 4.62 (1H, dd, *J* = 11.5, 4.0 Hz), 4.72 (1H, dd, *J* = 13.5, 4.0 Hz), 4.83 (1H, dd, *J* = 13.5, 11.5 Hz), 7.15 (1H, ddd, *J* = 9.0, 7.5, 1.5 Hz), 7.28 (1H, dd, *J* = 7.5, 1.5 Hz), 7.32 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.62 (1H, dd, *J* = 9.0, 1.2, Hz), 9.56 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 18.8, 21.0, 45.3, 49.1, 76.4, 127.1, 127.8, 128.3, 129.4, 133.9, 135.5, 203.7. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 11.6 min, t_R (minor) = 32.3 min, ee = 74%. The spectral analysis is consistent to the literature.[29]

(R)-2,2-Dimethyl-4-nitro-3-(2-methoxylphenyl) butanal, (*R*)-**16**



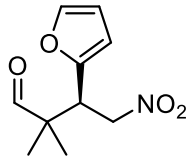
^{1}H NMR ($CDCl_3$, δ): 1.05 (3H, s), 1.10 (3H, s), 3.82 (3H, s), 4.22 (1H, dd, *J* = 13.0, 10.9 Hz), 4.72 (1H, dd, *J* = 13.0, 4.5 Hz), 4.90 (1H, dd, *J* = 13.0, 10.9 Hz), 6.88 (1H, d, *J* = 7.6, Hz), 6.93 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz), 7.13 (1H, dd, *J* = 7.6, 1.65 Hz), 7.27 (1H, ddd, *J* = 7.55, 7.55, 1.65 Hz), 9.51 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 19.9, 21.0, 48.3, 55.3, 75.8, 111.3, 120.7, 124.0, 129.2, 157.4, 204.1. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 9.4 min, t_R (minor) = 15.3 min, ee = 81%. The spectral analysis is consistent to the literature.[29]

(R)-2,2-Dimethyl-4-nitro-3-(2-naphthyl) butanal, (*R*)-**17**



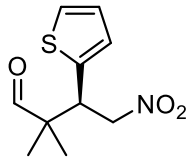
^{1}H NMR ($CDCl_3$, δ): 1.05 (3H, s), 1.18 (3H, s), 3.95 (1H, dd, *J* = 11.4, 4.0 Hz), 4.77 (1H, dd, *J* = 13.0, 4.0 Hz), 4.98 (1H, dd, *J* = 13.0, 11.4 Hz), 7.31 (1H, dd, *J* = 9.0, 2.0 Hz), 7.47-7.51 (2H, m), 7.66 (1H, d, *J* = 1.5 Hz), 7.80-7.83 (3H, m), 9.57 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 19.2, 21.9, 48.4, 48.7, 76.7, 126.4, 126.6, 127.6, 127.6, 127.9, 128.3, 128.5, 132.9, 133.1, 204.3. IR (KBr, cm^{-1}): 3429, 3053, 2969, 2929, 1723, 1554, 1440, 1380, 908, 873, 755. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 44.0 min, t_R (minor) = 26.5 min, ee = 91%. $[\alpha]_D$ – 1.8 (c 0.09, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(2-furyl) butanal, (*R*)-**18**



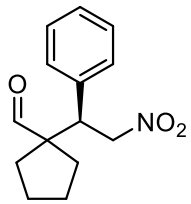
^{1}H NMR ($CDCl_3$, δ): 1.04 (3H, s), 1.17 (3H, s), 3.91 (1H dd, *J* = 11.0, 4.0 Hz), 4.59 (1H dd, *J* = 13.0, 4.0 Hz), 4.75 (1H dd, *J* = 13.0, 11.0 Hz), 6.21 (1H, d, *J* = 3.5 Hz), 6.31 (1H, dd, *J* = 3.5, 2.0 Hz), 7.37 (1H, dd, *J* = 2.0, 0.5 Hz), 9.52 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 19.0, 21.1, 42.2, 48.1, 74.9, 109.6, 110.5, 142.7, 149.7, 203.4. IR (neat, cm^{-1}): 2975, 1727, 1556, 1377, 1148, 1016, 914, 885, 739. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 9.4 min, t_R (minor) = 15.8 min, ee = 91%. $[\alpha]_D$ – 16.0 (c 0.20, $CHCl_3$).

(R)-2,2-Dimethyl-4-nitro-3-(2-thiophenyl) butanal, (*R*)-**19**



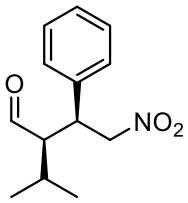
^{1}H NMR ($CDCl_3$, δ): 1.08 (3H, s), 1.21 (3H, s), 4.13 (1H, dd, *J* = 11.0, 4.0 Hz), 4.66 (1H, dd, *J* = 13.0, 8.5 Hz), 4.72 (1H, dd, *J* = 13.0, 11.0 Hz), 6.92 (1H, d, *J* = 3.5 Hz), 6.96 (1H, dd, *J* = 5.0, 3.5 Hz), 7.24 (1H, d, *J* = 5.0 Hz), 9.53 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 18.8, 21.5, 44.1, 48.3, 77.8, 125.5, 126.9, 127.8, 137.8, 203.6. IR (neat, cm^{-1}): 2974, 2721, 1724, 1554, 1467, 1379, 1248, 882, 707. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 12.8 min, t_R (minor) = 22.1 min, ee = 90%. $[\alpha]_D$ + 19.7 (c 0.10, $CHCl_3$).

(R)-1-(2-Nitro-1-phenylethyl) cyclopentanecarbaldehyde, **20**[79]



^{1}H NMR ($CDCl_3$, δ): 1.54-1.66 (6H, m), 1.86-1.89 (1H, m), 2.04-2.07 (1H, m), 3.69 (1H, dd, J = 11.5 and 3.5 Hz), 4.69 (1H, dd, J = 13.0 and 3.5 Hz), 4.96 (1H, dd, J = 13.0 and 11.5 Hz), 7.19-7.20 (2H, m), 7.27-7.31 (3H, m), 9.49 (1H, s). ^{13}C NMR ($CDCl_3$, δ): 24.6, 24.8, 31.5, 32.6, 49.3, 60.2, 77.3, 128.0, 128.8, 128.9, 136.3, 204.4. HPLC: Chiralpak OD-H column, hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, t_R (major) = 11.4 min, t_R (minor) = 16.3 min, ee = 57%.

(2R,3S)-2-Isopropyl-4-nitro-3-phenylbutanal, **21**[80]



^{1}H NMR ($CDCl_3$, δ): 0.88 (3H, d, J = 7.0 Hz), 1.09 (3H, d, J = 7.2 Hz), 1.72 (1H, m), 2.76 (1H, m), 3.91 (1H, m), 4.55-4.79 (2H, m), 7.15-7.20 (2H, m), 7.27-7.36 (3H, m), 9.92 (1H, d, J = 2.4 Hz). ^{13}C NMR ($CDCl_3$, δ): 16.9, 21.6, 27.9, 41.9, 59.0, 78.4, 127.9, 128.2, 129.1, 137.0, 204.3 (syn CHO), 204.4 (anti CHO). HPLC: Chiralpak AD-H column, hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, t_R (*syn*, major) = 8.6 min, t_R (*syn*, minor) = 10.0 min, ee = 98%, dr (*syn*/*anti*) = 87/13 (determined by ^{1}H NMR spectroscopy).

6.3 Experiments in chapter 3

6.3.1 Synthesis of starting materials

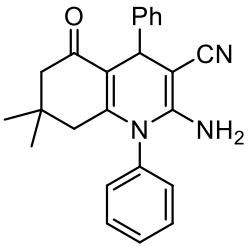
Enaminones and arylidenemalononitriles were synthesized according to the literature procedures.[81,82]

6.3.2 General procedures for the synthesis of starting materials *N*-aryl-4-aryl hexahydroquinoline derivatives

In a 30 mL two-necked, enaminone (86.1 mg, 0.4 mmol) and benzylidenemalononitrile (74.0 mg, 0.48 mmol), DMSO (1 mL) was added in the presence of MS 13X (200 mg) at room temperature. The reaction mixture was stirred for 24 h at room temperature, then quenched with phosphate buffer. After extracted with EtOAc and washed with brine, the organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was recrystallized from Hexane/EtOAc and filtered to give the main of the product. The filtrate was concentrated and purified by thin-layer chromatography (hexane-EtOAc, 3:1 to 1:1) on silica gel to afford the remained product. With the above operation, the total yield of *N*-aryl-4-aryl-hexahydroquinoline derivatives was calculated out.

6.3.3 Analytical data of products in chapter 3

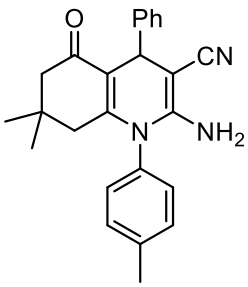
2-Amino-7,7-dimethyl-5-oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitril e, **24**[37d]



white solid; mp: 238-239 °C

^{1}H NMR ($CDCl_3$, δ): 0.84 (s, 3H), 0.96 (s, 3H), 1.79–1.82 (d, J = 17.45 Hz, 1H), 2.03–2.06 (d, J = 17.45 Hz, 1H), 2.13–2.22 (dd, *J* = 16.35, 14.22 Hz, 2H), 4.01 (s, 2H, NH_2), 4.76 (s, 1H), 7.18–7.59 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 27.02, 29.46, 32.40, 36.00, 41.71, 49.99, 63.68, 113.26, 120.84, 126.67, 127.13, 128.57, 129.78, 130.33, 130.62, 136.32, 145.56, 149.13, 150.09, 195.57. IR (KBr, cm^{-1}): 3461, 3333, 3220, 2957, 2179, 1655, 1620, 1571, 1490, 1415, 1373, 1258, 1176, 1145, 1041, 738, 697, 575.

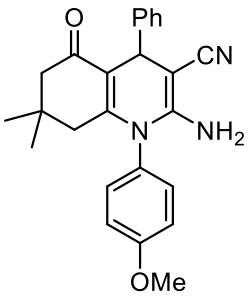
2-Amino-4-phenyl-7,7-dimethyl-5-oxo-1-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoli ne-3-carbonitrile, **25**



yellow solid; mp: 192-194 °C

^{1}H NMR ($CDCl_3$, δ): 0.84 (s, 3H), 0.96 (s, 3H), 1.81–1.84 (d, J = 17.55 Hz, 1H), 2.04–2.14 (d, J = 17.55 Hz, 1H), 2.12–2.21 (dd, *J* = 16.3, 14.5 Hz, 2H), 2.47 (s, 3H), 4.01 (s, 2H, NH_2), 4.75 (s, 1H), 7.16–7.20 (m, 3H), 7.29–7.37 (m, 6H). ^{13}C NMR ($CDCl_3$, δ): 21.30, 27.02, 29.46, 32.37, 35.98, 41.66, 49.98, 63.48, 113.14, 120.93, 126.63, 127.12, 128.54, 129.40, 133.49, 140.65, 145.64, 149.39, 150.24, 195.57. IR (KBr, cm^{-1}): 3564, 3462, 3336, 2956, 2925, 2179, 1653, 1570, 1509, 1452, 1414, 1373, 1257, 1177, 1144, 1043, 1017, 755, 699, 591, 560, 533. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{25}H_{25}N_3NaO$: 406.1890; found: 406.1881.

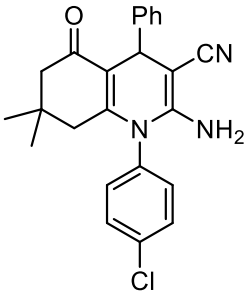
2-Amino-4-phenyl-7,7-dimethyl-5-oxo-1-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquino line-3-carbonitrile, **26**



orange solid; mp: 196-198 °C

^{1}H NMR ($CDCl_3$, δ): 0.84 (s, 3H), 0.96 (s, 3H), 1.82–1.85 (d, J = 17.45 Hz, 1H), 2.03–2.06 (d, J = 17.45 Hz, 1H), 2.11–2.21 (dd, *J* = 16.3, 15.2 Hz, 2H), 3.89 (s, 3H), 4.07 (s, 2H, NH_2), 4.74 (s, 1H), 7.04–7.05 (m,2H), 7.16–7.20 (m, 3H), 7.28–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): 14.21, 21.07, 27.03, 29.51, 32.34, 35.98, 41.69, 49.97, 55.70, 60.41, 113.15, 126.62, 127.12, 128.39, 128.54, 130.78, 145.68, 149.73, 150.52, 160.56, 195.61. IR (KBr, cm^{-1}): 3455, 3418, 3322, 3214, 2957, 2934, 2181, 1732, 1648, 1564, 1509, 1454, 1441, 1417, 1374, 1297, 1252, 1170, 1144, 1040, 1026, 762, 701, 565, 548. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{25}H_{25}N_3NaO_2$: 422.1839; found: 422.1860.

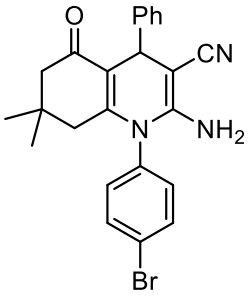
2-Amino-4-phenyl-7,7-dimethyl-5-oxo-1-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoli ne-3-carbonitrile, **27**[83]



white solid; mp: 249-250 °C

^{1}H NMR ($CDCl_3$, δ): 0.85 (s, 3H), 0.98 (s, 3H), 1.79–1.82 (d, J = 17.40 Hz, 1H), 2.03–2.06 (d, J = 17.40 Hz, 1H), 2.13–2.22 (dd, *J* = 16.3, 11.9 Hz, 2H), 3.97 (s, 2H, NH_2), 4.75 (s, 1H), 7.18–7.57 (m, 9H). ^{13}C NMR ($CDCl_3$, δ): 27.03, 29.47, 32.44, 35.96, 41.76, 49.92, 64.28, 113.56, 120.54, 126.76, 127.08, 128.61, 130.88, 131.12, 134.79, 136.56, 145.29, 148.64, 149.74, 195.47. IR (KBr, cm^{-1}): 3463, 3335, 2956, 2180, 1655, 1620, 1591, 1572, 1488, 1413, 1373, 1257, 1145, 1090, 1042, 1013, 757, 700, 581.

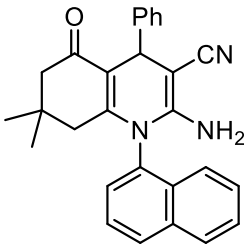
2-Amino-4-phenyl-7,7-dimethyl-5-oxo-1-(4-bromophenyl)-1,4,5,6,7,8-hexahydroquinoli ne-3-carbonitrile, **28**



white solid; mp: 240-242 °C

^{1}H NMR ($CDCl_3$, δ): 0.85 (s, 3H), 0.97 (s, 3H), 1.79–1.82 (d, J = 17.50 Hz, 1H), 2.02–2.05 (d, J = 17.50 Hz, 1H), 2.13–2.22 (dd, *J* = 16.5, 10.5 Hz, 2H), 3.97 (s, 2H, NH_2), 4.74 (s, 1H), 7.17–7.21 (m, 3H), 7.29–7.34 (m, 4H), 7.71–7.73 (d, J = 8.50 Hz, 2H). ^{13}C NMR ($CDCl_3$, δ): 27.03, 29.47, 32.45, 35.96, 41.76, 49.92, 64.31, 113.55, 120.52, 124.62, 126.76, 127.08, 128.61, 131.41, 133.89, 135.33, 145.27, 148.57, 149.66, 195.46. IR (KBr, cm^{-1}): 3463, 3333, 3221, 2955, 2180, 1655, 1644, 1621, 1571, 1486, 1413, 1373, 1255, 1145, 1069, 1041, 1011, 755, 700, 576. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{24}H_{22}BrN_3NaO$: 470.0838; found: 470.0837.

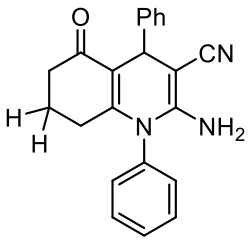
2-Amino-4-phenyl-7,7-dimethyl-5-oxo-1-(1-naphthalenyl)-1,4,5,6,7,8-hexahydroquinoli ne-3-carbonitrile, **30**[84]



white solid; mp: 264-266 °C

^{1}H NMR ($CDCl_3$, δ): (mixture of rotamers) 0.74 (0.87) (s, 2.5H), 0.79 (0.83) (s, 3.5H), 1.74–1.78 (1.91-1.95) (d, J = 17.30 Hz, 1H), 2.11–2.16 (2.17-2.24) (m, 2H), 3.93 (4.06) (s, 2H, NH_2), 4.85 (4.93) (s, 1H), 7.19–8.07 (m, 12H). ^{13}C NMR ($CDCl_3$, δ): (mixture of rotamers) 27.57 (26.37), 28.46 (29.71), 32.51 (32.04), 36.21 (35.91), 40.25 (41.31), 50.14 (50.01), 63.73 (63.09), 113.26 (113.07), 120.97 (120.88), 121.78 (121.65), 125.35, 126.71 (126.00), 127.25 (127.35), 127.73 (127.76), 128.04 (128.37), 128.58 (128.61), 128.61 (128.65), 129.13, 130.09 (130.97), 131.34 (131.44), 132.65 (132.15), 134.50 (134.67), 145.69 (145.42), 149.87 (149.92), 150.47 (150.27), 195.64 (195.79). IR (KBr, cm^{-1}): 3463, 3370, 2951, 2927, 2881, 2184, 1650, 1640, 1604, 1572, 1454, 1402, 1394, 1372, 1345, 1335, 1311, 1259, 1239, 1147, 1040, 809, 778, 756, 707, 699, 573.

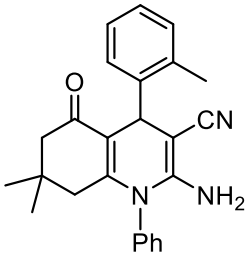
2-Amino-5-oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **31**[37a]



pale yellow solid; mp: 149-151 °C

^{1}H NMR ($CDCl_3$, δ): 1.73–2.04 (m, 3H), 2.14–2.40 (m, 3H), 4.00 (s, 2H, NH_2), 4.82 (s, 1H), 7.15–7.22 (m, 1H), 7.30–7.37 (m, 6H), 7.54–7.59 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 14.2, 20.98, 28.28, 35.66, 36.51, 60.41, 63.48, 114.22, 126.68, 127.10, 128.60, 129.77, 130.32, 136.30, 145.63, 150.10, 151.01, 195.73. IR (KBr, cm^{-1}): 3564, 3472, 3425, 3318, 3216, 2948, 2179, 1735, 1650, 1621, 1589, 1566, 1489, 1453, 1409, 1372, 1337, 1264, 1192, 1074, 1045, 1002, 746, 702, 637, 547.

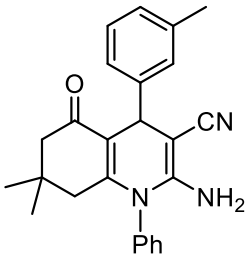
2-Amino-4-(2-methylphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **35**[85]



white solid; mp: 266-267 °C

^{1}H NMR ($CDCl_3$, δ): 0.88 (s, 3H), 0.96 (s, 3H), 1.83–1.87 (dd, J = 17.40 Hz, 0.8 Hz 1H), 2.04–2.19 (m, 3H), 2.66 (s, 3H), 3.92 (s, 2H, NH_2), 4.99 (s, 1H), 7.04–7.22 (m, 4H), 7.34–7.35 (m, 2H), 7.58–7.61 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 19.70, 27.12, 29.46, 31.87, 32.47, 41.72, 49.87, 64.36, 113.87, 120.91, 126.27, 126.45, 127.29, 129.86, 130.32, 130.50, 135.38, 136.34, 144.81, 149.31, 149.50, 195.62. IR (KBr, cm^{-1}): 3472, 3342, 2957, 2177, 1652, 1620, 1592, 1570, 1488, 1412, 1372, 1258, 1144, 1047, 744, 706, 575.

2-Amino-4-(3-methylphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **36**[85]

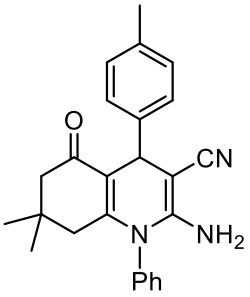


pale yellow solid; mp: 233-235 °C

^{1}H NMR ($CDCl_3$, δ): 0.85 (s, 3H), 0.96 (s, 3H), 1.79–1.83 (d, J = 17.40 Hz 1H), 2.03–2.06 (d, J = 17.40 Hz 1H), 2.13–2.22 (dd, J = 16.30, 4.9 Hz 2H), 2.34 (s, 3H), 4.02 (s, 2H, NH_2), 4.70 (s, 1H), 6.99–7.00 (d, J = 7.40 Hz 1H), 7.11–7.21 (m, 3H), 7.29–7.30 (m, 2H), 7.57–7.59 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 21.64, 27.04, 29.44, 32.41, 35.90, 41.69,

49.97, 63.83, 113.25, 120.90, 123.94, 127.47, 128.02, 128.46, 129.76, 130.29, 130.59, 136.35, 137.94, 145.50, 149.16, 150.00, 195.59. IR (KBr, cm^{-1}): 3461, 3328, 3218, 2970, 2957, 2903, 2868, 2177, 1647, 1620, 1594, 1568, 1490, 1449, 1416, 1372, 1315, 1296, 1260, 1235, 1178, 1167, 1144, 1124, 1070, 1024, 805, 765, 752, 697, 583, 572.

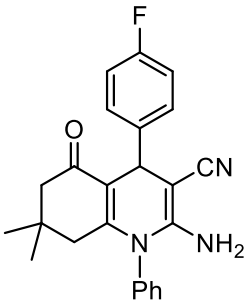
2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **37**[37a]



white solid; mp: 241-242 °C

^{1}H NMR ($CDCl_3$, δ): 0.85 (s, 3H), 0.95 (s, 3H), 1.78–1.82 (d, J = 17.40 Hz 1H), 2.02–2.05 (d, J = 17.40 Hz 1H), 2.12–2.22 (dd, J = 16.30, 7.95 Hz 2H), 2.30 (s, 3H), 3.98 (s, 2H, NH_2), 4.72 (s, 1H), 7.11–7.12 (d, J = 7.75 Hz 2H), 7.23–7.31 (m, 4H), 7.57–7.61 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 21.11, 27.11, 29.43, 32.42, 35.61, 41.70, 50.01, 63.97, 113.35, 120.86, 126.98, 129.30, 129.79, 130.29, 130.60, 136.12, 136.39, 142.69, 149.00, 149.91, 195.59. IR (KBr, cm^{-1}): 3458, 3333, 2952, 2178, 1653, 1619, 1593, 1571, 1491, 1412, 1384, 1371, 1257, 1179, 1169, 1144, 1124, 1039, 1017, 699, 575.

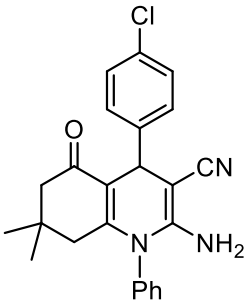
2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **38**[37d]



yellow solid; mp: 254-255 °C

^{1}H NMR ($CDCl_3$, δ): 0.82 (s, 3H), 0.95 (s, 3H), 1.78–1.81 (d, J = 17.30 Hz 1H), 2.02–2.05 (d, J = 17.30 Hz 1H), 2.12–2.22 (dd, J = 16.35, 8.90 Hz 2H), 4.02 (s, 2H, NH_2), 4.75 (s, 1H), 6.98–7.01 (m, 2H), 7.28–7.34 (m, 4H), 7.59–7.60 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 26.92, 29.43, 32.38, 35.44, 41.69, 49.94, 63.45, 113.19, 115.22, 115.39, 120.70, 128.66, 128.72, 129.72, 130.41, 136.16, 141.45, 149.07, 150.09, 195.58. IR (KBr, cm^{-1}): 3453, 3336, 2957, 2178, 1652, 1640, 1593, 1557, 1504, 1490, 1416, 1372, 1257, 1216, 1203, 1173, 1153, 1042, 850, 702, 574, 528.

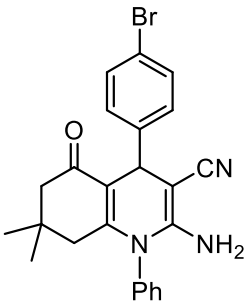
2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoli ne-3-carbonitrile, **39**[37d]



white solid; mp: 261-262 °C

^{1}H NMR ($CDCl_3$, δ): 0.82 (s, 3H), 0.95 (s, 3H), 1.77–1.81 (d, J = 17.50 Hz 1H), 2.02–2.05 (d, J = 17.50 Hz 1H), 2.12–2.22 (dd, J = 16.35, 8.90 Hz 2H), 4.06 (s, 2H, NH_2), 4.74 (s, 1H), 7.27–7.31 (m, 6H), 7.58–7.62 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 26.95, 29.44, 32.40, 35.64, 41.70, 49.93, 63.08, 112.93, 120.64, 128.60, 128.70, 129.72, 130.45, 130.71, 132.33, 136.11, 144.13, 149.26, 150.21, 195.55. IR (KBr, cm^{-1}): 3731, 3708, 3646, 3605, 3593, 3584, 3542, 3465, 3330, 2952, 2352, 2178, 1694, 1681, 1651, 1620, 1594, 1567, 1557, 1488, 1454, 1415, 1385, 1258, 1171, 1144, 1125, 1087, 1041, 1011, 858, 842, 698, 574, 517.

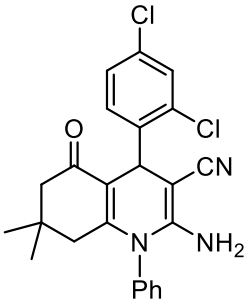
2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoli ne-3-carbonitrile, **40**[37a]



yellow solid; mp: 263-264 °C

^{1}H NMR ($CDCl_3$, δ): 0.82 (s, 3H), 0.95 (s, 3H), 1.77–1.81 (d, J = 17.35 Hz 1H), 2.02–2.05 (d, J = 17.35 Hz 1H), 2.12–2.22 (dd, J = 16.35, 8.90 Hz 2H), 4.05 (s, 2H, NH_2), 4.73 (s, 1H), 7.23–7.29 (m, 4H), 7.43–7.44 (m, 2H), 7.59–7.60 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 26.94, 29.42, 32.38, 35.70, 41.69, 49.90, 62.86, 112.81, 120.48, 120.66, 128.97, 129.69, 130.45, 130.70, 131.62, 136.05, 144.64, 149.33, 150.26, 195.57. IR (KBr, cm^{-1}): 3646, 3626, 3606, 3593, 3584, 3564, 3542, 3463, 3330, 3217, 2953, 2352, 2177, 1681, 1651, 1621, 1593, 1567, 1557, 1487, 1415, 1385, 1371, 1258, 1144, 1068, 1039, 1007, 839, 696, 574, 515.

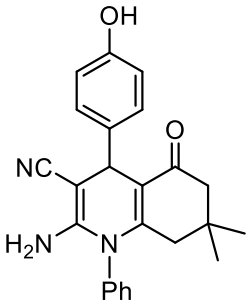
2-Amino-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **41**[86]



light orange solid; mp: 254-256 °C

^{1}H NMR ($CDCl_3$, δ): 0.89 (s, 3H), 0.95 (s, 3H), 1.77–1.81 (d, J = 17.65 Hz 1H), 2.02–2.05 (d, J = 17.65 Hz 1H), 2.08–2.19 (dd, J = 16.35, 18.25 Hz 2H), 4.01 (s, 2H, NH_2), 5.13 (s, 1H), 7.20–7.22 (dd, J = 8.30, 2.15 Hz 1H), 7.30–7.36 (m, 4H), 7.59–7.60 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 27.16, 29.36, 32.32, 35.49, 41.76, 49.75, 61.71, 110.97, 120.41, 127.24, 130.03, 130.49, 130.63, 131.69, 132.92, 133.79, 135.93, 140.73, 150.41, 195.48. IR (KBr, cm^{-1}): 3585, 3564, 3459, 3345, 2959, 2182, 1644, 1591, 1562, 1490, 1468, 1417, 1370, 1256, 1153, 1098, 1071, 1047, 1023, 1001, 858, 732, 703, 574.

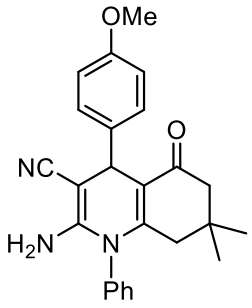
2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **43**[37d]



yellow solid; mp: 262-263 °C

^{1}H NMR (DMSO-d_6, δ): 0.74 (s, 3H), 0.88 (s, 3H), 1.67–1.70 (d, J = 17.45 Hz 1H), 1.99–2.02 (d, J = 17.45 Hz 1H), 2.17–2.21 (dd, J = 19.50, 3.70 Hz 2H), 4.37 (s, 1H), 5.24 (s, 2H, NH_2), 6.70–6.72 (d, J = 8.40 Hz 2H), 7.07–7.08 (d, J = 6.85 Hz 2H), 7.57–7.61 (m, 3H). ^{13}C NMR (DMSO-d_6, δ): 26.71, 29.57, 32.32, 35.84, 41.42, 49.86, 61.44, 112.74, 115.52, 122.12, 128.23, 130.16, 130.41, 130.65, 136.84, 137.54, 150.13, 151.42, 156.25, 195.33. IR (KBr, cm^{-1}): 3626, 3585, 3564, 3543, 3470, 3332, 2961, 2178, 1651, 1633, 1613, 1591, 1565, 1557, 1510, 1489, 1454, 1415, 1376, 1257, 1228, 1168, 1147, 1041, 852, 703, 576.

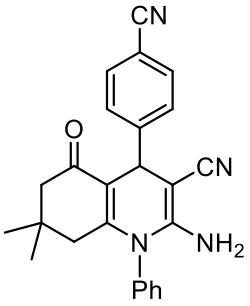
2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **44**[37d]



pale yellow solid; mp: 243-244 °C

^{1}H NMR ($CDCl_3$, δ): 0.83 (s, 3H), 0.95 (s, 3H), 1.78–1.81 (d, J = 17.45 Hz 1H), 2.01–2.05 (d, J = 17.45 Hz 1H), 2.12–2.22 (dd, J = 16.35, 13.70 Hz 2H), 3.78 (s, 3H), 3.98 (s, 2H, NH_2), 4.71 (s, 1H), 6.84–6.86 (d, J = 8.55 Hz 2H), 7.27–7.31 (m, 4H), 7.58–7.59 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 27.01, 29.45, 32.40, 35.23, 41.69, 50.01, 63.91, 113.48, 113.94, 120.93, 128.17, 129.78, 130.30, 130.60, 136.36, 138.06, 148.85, 149.94, 158.28, 195.68. IR (KBr, cm^{-1}): 3457, 3331, 2955, 2937, 2176, 1646, 1592, 1564, 1508, 1490, 1452, 1412, 1373, 1301, 1256, 1239, 1177, 1143, 1030, 850, 841, 705, 573.

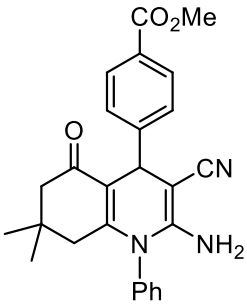
2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **46**



brown solid; mp: 263-264 °C

^{1}H NMR ($CDCl_3$, δ): 0.82 (s, 3H), 0.96 (s, 3H), 1.80–1.83 (d, J = 17.45 Hz 1H), 2.04–2.07 (d, J = 17.45 Hz 1H), 2.12–2.23 (dd, J = 16.35, 8.90 Hz 2H), 4.09 (s, 2H, NH_2), 4.82 (s, 1H), 7.29–7.31 (m, 2H), 7.46–7.48 (d, J = 8.25 Hz 2H), 7.61–7.63 (m, 5H). ^{13}C NMR ($CDCl_3$, δ): 26.96, 29.38, 32.42, 36.60, 41.74, 49.84, 62.26, 110.50, 112.20, 119.06, 120.32, 128.08, 129.66, 130.64, 132.55, 135.83, 149.78, 150.42, 150.75, 195.45. IR (KBr, cm^{-1}): 3626, 3606, 3593, 3584, 3564, 3469, 3340, 2958, 2224, 2196, 2177, 1650, 1615, 1594, 1565, 1492, 1463, 1416, 1373, 1258, 1143, 1042, 866, 845, 704, 576. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{25}H_{22}N_4NaO$: 417.1686; found: 417.1696.

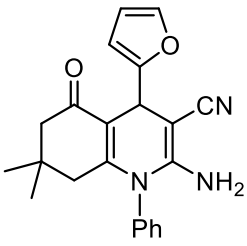
2-Amino-4-[4-(methoxycarbonyl)phenyl]-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexa hydroquinoline-3-carbonitrile, **47**



white solid; mp: 254-255 °C

^{1}H NMR ($CDCl_3$, δ): 0.81 (s, 3H), 0.96 (s, 3H), 1.79–1.82 (d, J = 17.60 Hz 1H), 2.04–2.07 (d, J = 17.60 Hz 1H), 2.12–2.22 (dd, J = 16.30, 18.45 Hz 2H), 3.89 (s, 3H), 4.06 (s, 2H, NH_2), 4.82 (s, 1H), 7.30–7.31 (m, 2H), 7.43–7.44 (d, J = 8.20 Hz 2H), 7.60–7.61 (m, 3H), 7.99–8.01 (d, J = 8.15 Hz 2H). ^{13}C NMR ($CDCl_3$, δ): 26.85, 29.47, 32.38, 36.18, 41.71, 49.89, 52.00, 112.70, 120.53, 127.20, 128.53, 129.71, 130.06, 130.48, 130.70, 136.05, 149.51, 150.33, 150.58, 167.07, 195.48. IR (KBr, cm^{-1}): 3469, 3329, 2956, 2182, 1721, 1656, 1621, 1609, 1592, 1570, 1488, 1434, 1415, 1373, 1307, 1284, 1258, 1147, 1109, 1044, 1019, 753, 702, 575. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3NaO_3$: 450.1788; found: 450.1802.

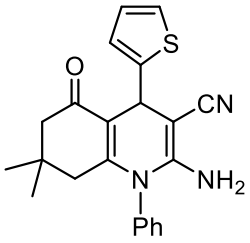
2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **48**



gray solid; mp: 222-223 °C

^{1}H NMR ($CDCl_3$, δ): 0.86 (s, 3H), 0.96 (s, 3H), 1.76–1.80 (d, J = 17.55 Hz 1H), 2.03–2.07 (d, J = 17.55 Hz 1H), 2.18–2.25 (dd, J = 16.35, 2.40 Hz 2H), 4.08 (s, 2H, NH_2), 4.89 (s, 1H), 6.16 (d, J = 3.10 Hz 1H), 6.28–6.29 (dd, J = 3.10, 1.90 Hz 1H), 7.30–7.31 (m, 3H), 7.56–7.58 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 26.63, 29.52, 29.60, 32.39, 41.62, 49.95, 60.56, 104.96, 110.44, 110.69, 120.68, 129.80, 130.30, 130.59, 136.40, 141.41, 150.15, 151.18, 156.66, 195.41. IR (KBr, cm^{-1}): 3408, 3327, 3211, 2956, 2176, 1650, 1617, 1593, 1571, 1492, 1409, 1382, 1370, 1276, 1259, 1145, 1036, 1013, 782, 725, 712, 693, 571. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{22}H_{21}N_3NaO_2$: 382.1526; found: 382.1548.

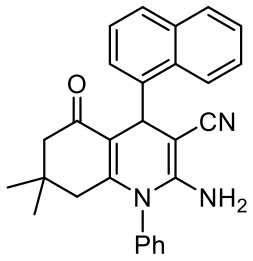
2-Amino-4-(thienyl-2-yl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **49**



brown solid; mp: 213-214 °C

^{1}H NMR ($CDCl_3$, δ): 0.86 (s, 3H), 0.96 (s, 3H), 1.74–1.78 (d, J = 17.40 Hz 1H), 2.04–2.07 (d, J = 17.40 Hz 1H), 2.18–2.26 (dd, J = 16.50, 4.40 Hz 2H), 4.07 (s, 2H, NH_2), 5.11 (s, 1H), 6.91–6.93 (dd, J = 3.50, 1.50 Hz 1H), 7.01–7.02 (d, J = 3.25 Hz 1H), 7.11–7.12 (dd, J = 3.50, 1.50 Hz 1H), 7.30–7.32 (m, 2H), 7.57–7.58 (m, 3H). ^{13}C NMR ($CDCl_3$, δ): 26.80, 29.61, 30.93, 32.36, 41.53, 49.93, 63.25, 113.37, 120.64, 123.52, 123.61, 127.15, 129.82, 130.37, 136.18, 149.12, 150.51, 150.61, 195.45. IR (KBr, cm^{-1}): 3457, 3361, 2947, 2867, 2182, 1648, 1628, 1607, 1593, 1564, 1492, 1402, 1378, 1359, 1315, 1287, 1258, 1240, 1142, 1038, 1023, 698, 666, 575. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{22}H_{21}N_3NaOS$: 398.1298; found: 398.1321.

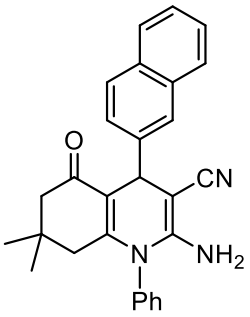
2-Amino-4-(1-naphthalenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **50**



yellow solid; mp: 247-249 °C

^{1}H NMR ($CDCl_3$, δ): 0.89 (s, 3H), 0.98 (s, 3H), 1.90–1.94 (d, J = 17.45 Hz 1H), 2.09–2.14 (dd, J = 12.05, 5.75 Hz 2H), 2.18–2.21 (d, J = 17.45 Hz 1H), 3.95 (s, 2H, NH_2), 5.61 (s, 1H), 7.38–7.49 (m, 5H), 7.58–7.64 (m, 4H), 7.71–7.73 (m, 1H), 7.81–7.83 (d, J = 8.40 Hz 1H), 8.60–8.62 (d, J = 8.95 Hz 1H). ^{13}C NMR ($CDCl_3$, δ): 26.25, 28.43, 31.38, 40.75, 48.82, 63.59, 112.57, 119.79, 122.87, 123.99, 124.30, 124.62, 125.10, 126.47, 127.47, 128.86, 129.34, 129.61, 130.06, 132.99, 135.30, 141.78, 148.45, 148.81, 194.51. IR (KBr, cm^{-1}): 3626, 3606, 3593, 3573, 3564, 3460, 3342, 2959, 2922, 2175, 1651, 1594, 1565, 1492, 1415, 1374, 1259, 1240, 1140, 1040, 794, 781, 708, 575, 550. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{28}H_{25}N_3NaO$: 442.1890; found: 442.1879.

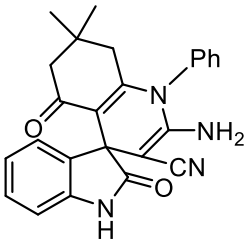
2-Amino-4-(2-naphthalenyl)-7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile, **51**



orange solid; mp: 172-173 °C

^{1}H NMR ($CDCl_3$, δ): 0.83 (s, 3H), 0.96 (s, 3H), 1.81–1.85 (d, J = 17.95 Hz 1H), 2.06–2.09 (d, J = 17.95 Hz 1H), 2.13–2.23 (dd, J = 16.35, 21.70 Hz 2H), 4.05 (s, 2H, NH_2), 4.95 (s, 1H), 7.33–7.62 (m, 8H), 7.78–7.84 (m, 4H). ^{13}C NMR ($CDCl_3$, δ): 26.93, 29.51, 32.38, 36.13, 41.75, 49.97, 63.43, 113.18, 120.83, 125.41, 125.65, 125.83, 127.53, 128.14, 128.44, 129.77, 130.37, 130.65, 132.56, 133.55, 136.30, 142.73, 149.25, 150.27, 195.62. IR (KBr, cm^{-1}): 3458, 3331, 3220, 2955, 2925, 2176, 1653, 1593, 1569, 1491, 1416, 1376, 1367, 1257, 1152, 1142, 1122, 1041, 704, 574. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{28}H_{25}N_3NaO$: 442.1890; found: 442.1881.

2'-Amino-1,2,5',6',7',8'-hexahydro-7',7'-dimethyl-2,5'-dioxo-1'-phenylspiro[3H-indole-3,4'(1'H)-quinoline]-3'-carbonitrile, **53**[87]



yellow solid; mp: 314-315 °C

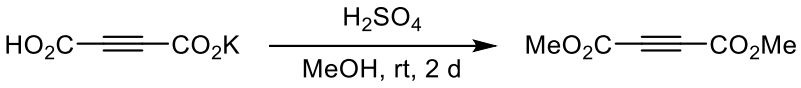
^{1}H NMR (DMSO-d_6, δ): 0.82 (s, 3H), 0.89 (s, 3H), 1.81–1.84 (d, J = 17.30 Hz 1H), 1.92–1.96 (d, J = 17.30 Hz 1H), 2.09–2.15 (dd, J = 14.40, 2.65 Hz 2H), 5.36 (s, 2H, NH_2), 6.77–6.78 (d, J = 7.60 Hz 1H), 6.91–6.94 (t, J = 7.40 Hz 1H), 7.12–7.15 (t, J = 7.40 Hz 1H), 7.17–7.19 (d, J = 7.60 Hz 1H), 7.49–7.64 (m, 5H). ^{13}C NMR (DMSO-d_6, δ): 27.09, 28.69, 32.58, 41.84, 48.98, 49.78, 61.40, 109.31, 110.86, 119.39, 121.87, 123.63, 128.15, 130.42, 130.78, 136.45, 137.13, 141.92, 151.57, 152.35, 179.94, 194.36. IR (KBr, cm^{-1}): 3467, 3333, 2957, 2196, 2187, 1712, 1689, 1641, 1620, 1592, 1555, 1489, 1470, 1416, 1362, 1336, 1315, 1260, 1222, 1195, 1176, 1152, 1052, 1017, 740, 723, 688, 647, 573.

6.4 Experiments in chapter 4

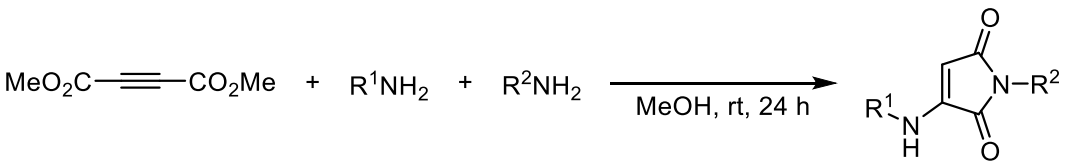
6.4.1 Synthesis of starting materials

Imines[88] and α-aminomaleimides[53] were synthesized according to the literature procedures.

6.4.2 Synthesis of α-aminomaleimides



Monopotassium acetylenedicarboxylate (3.04 g, 20.0 mmol) was dissolved in MeOH and cooled to 0 ºC in an ice bath. Then conc. H_2SO_4 (8 mL) was added slowly to the flask. After stirred at room temperature for 2 days, the liquid in the flask was dissolved in EtOAc and then washed with cold water, sat. $NaHCO_3$, and brine respectively for one time. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by Kugelrohr to give dimethyl acetylenedicarboxylate, DMAD (4.66 g, 16.4 mmol, 82%).



To a solution of DMAD (2.84 g, 20.0 mmol) in MeOH (20 mL), the corresponding amine R^1NH_2 (1.0 eq, 20.0 mmol) was added at 0 ºC and stirred for 30 min. Then another amine R^2NH_2 (1.0 eq, 20.0 mmol) was added and reacted at rt for 24 h. The solvent was removed under reduced pressure. The residue was recrystallized from EtOAc and hexane to afford the pure α-aminomaleimides.

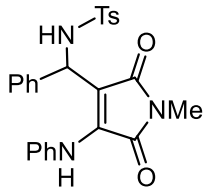
6.4.3 General procedures for the Mannich reaction of α-aminomaleimides

To a mixture of imines (0.13 mmol) and α-aminomaleimides (0.1 mmol) in DMSO (1.0

mL), MS 4A (50 mg) was added at room temperature. After the reaction was quenched with water, the organic phase was extracted with EtOAc (3x5 mL) and then dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding Mannich products.

6.4.4 Analytical data of products in chapter 4

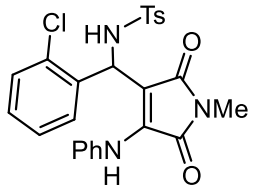
4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(phenyl) methyl)benzenesulfonamide, **56**



Yellow solid. mp: 203-205 °C.

^{1}H NMR ($CDCl_3$, δ): 2.40 (3H, s), 2.87 (3H, s), 5.21 (1H, d, *J* = 10.4 Hz), 6.15 (1H, d, *J* = 10.4 Hz), 6.88 (1H, brs), 6.96-6.98 (2H, m), 7.09-7.11 (2H, m), 7.18-7.21 (5H, m), 7.30-7.36 (3H, m), 7.57 (2H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.5, 52.1, 98.4, 124.3, 127.1, 127.2, 127.3, 127.6, 128.4, 129.0, 129.7, 136.3, 137.7, 138.2, 139.1, 143.1, 167.0, 173.0. IR (neat, cm^{-1}): 3425, 3296, 1693, 1635, 1452, 1336, 1162, 1004, 697, 569, 459. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{25}H_{23}N_3O_4SNa$: 484.1301; found: 484.1330.

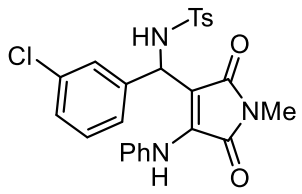
N-((2-chlorophenyl)(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)m ethyl)-4-methylbenzenesulfonamide, **57**



Yellow solid.

^{1}H NMR ($CDCl_3$, δ): 2.37 (3H, s), 2.86 (3H, s), 5.13 (1H, d, *J* = 10.3 Hz), 6.20 (1H, d, *J* = 10.3 Hz), 6.76 (1H, brs), 6.82 (1H, d, *J* = 7.6 Hz), 6.94 (1H, s), 7.07-7.17 (6H, m), 7.33-7.39 (3H, m), 7.52 (2H, d, *J* = 8.2 Hz). HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{25}H_{22}ClN_3O_4SNa$: 518.0912; found: 518.0941. Although this product was obtained by ^{1}H NMR, because of the trace yield, it's difficult to do other spectra measurements.

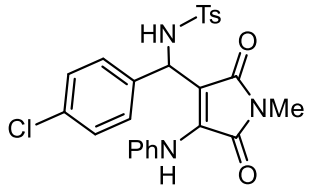
N-((3-chlorophenyl)(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide, **58**



Yellow solid. mp: 203-205 °C.

^{1}H NMR ($CDCl_3$, δ): 2.37 (3H, s), 2.85 (3H, s), 5.13 (1H, d, *J* = 10.3 Hz), 6.20 (1H, d, *J* = 10.3 Hz), 6.76 (1H, brs), 6.82 (1H, d, *J* = 7.6 Hz), 6.94 (1H, s), 7.07-7.17 (6H, m), 7.31-7.38 (3H, m), 7.52 (2H, d, *J* = 8.2 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.6, 51.7, 97.6, 124.7, 125.2, 127.1, 127.3, 127.6, 127.8, 129.1, 129.7, 129.8, 134.2, 136.2, 137.5, 139.3, 140.4, 143.3, 166.8, 172.9. IR (neat, cm^{-1}): 3304, 3286, 1701, 1650, 1595, 1531, 1450, 1161, 761, 668, 577, 557. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{25}H_{22}ClN_3O_4SNa$: 518.0912; found: 518.0904.

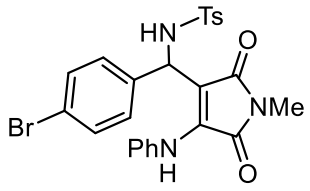
N-((4-chlorophenyl)(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide, **59**



Yellow solid. mp: 216-218 °C.

^{1}H NMR ($CDCl_3$, δ): 2.38 (3H, s), 2.84 (3H, s), 5.13 (1H, d, *J* = 10.4 Hz), 6.13 (1H, d, *J* = 10.4 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 6.89 (1H, brs), 7.07 (2H, d, *J* = 7.1 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.17 (2H, d, *J* = 8.1 Hz), 7.29-7.36 (3H, m), 7.52 (2H, d, *J* = 8.2 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.6, 51.5, 97.7, 124.4, 127.1, 127.5, 128.5, 128.6, 129.1, 129.7, 133.6, 136.2, 136.8, 137.5, 139.3, 143.3, 166.8, 173.0. IR (neat, cm^{-1}): 3304, 3284, 1699, 1651, 1594, 1533, 1448, 1347, 1162, 1071, 758, 666, 570. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{25}H_{22}ClN_3O_4SNa$: 518.0912; found: 518.0893.

N-((4-bromophenyl)(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide, **60**

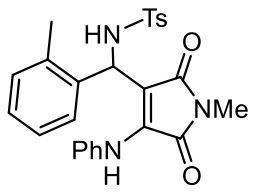


Yellow solid. mp: 211-213 °C.

^{1}H NMR ($CDCl_3$, δ): 2.38 (3H, s), 2.85 (3H, s), 5.11 (1H, d, *J* = 10.4 Hz), 6.14 (1H, d, *J* = 10.4 Hz), 6.79 (2H, d, *J* = 8.4 Hz),

6.90 (1H, brs), 7.06-7.08 (2H, m), 7.17 (2H, d, J = 8.0 Hz), 7.26-7.36 (5H, m), 7.52 (2H, d, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.6, 51.6, 97.6, 121.7, 124.4, 127.1, 127.5, 128.8, 129.1, 129.8, 131.5, 136.2, 137.4, 137.5, 139.3, 143.3, 166.8, 172.9. IR (neat, cm^{-1}): 3304, 3284, 3035, 1650, 1594, 1532, 1487, 1429, 1322, 1107, 1026, 757, 698, 671, 571. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{25}H_{22}BrN_3O_4SNa$: 562.0406; found: 562.0403.

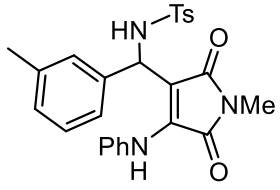
4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(o-tolyl) methyl)benzenesulfonamide, **61**



Yellow solid. mp: 202-204 °C.

^{1}H NMR ($CDCl_3$, δ): 1.91 (3H, s), 2.39 (3H, s), 2.75 (3H, s), 5.11 (1H, d, J = 10.6 Hz), 5.78 (1H, d, J = 10.6 Hz), 6.80 (1H, brs), 6.86 (2H, d, J = 7.6 Hz), 7.07-7.22 (9H, m), 7.60 (2H, d, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, δ): 18.8, 21.4, 23.3, 50.4, 98.1, 123.3, 125.8, 126.8, 126.9, 127.5, 128.4, 128.8, 129.7, 130.7, 135.0, 136.6, 137.5, 138.2, 139.7, 143.2, 166.6, 173.3. IR (neat, cm^{-1}): 3301, 3252, 3059, 1763, 1700, 1647, 1595, 1532, 1449, 1330, 1163, 1038, 754, 696, 573. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_4SNa$: 498.1458; found: 498.1455.

4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(m-tolyl) methyl)benzenesulfonamide, **62**

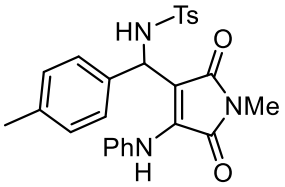


Yellow solid. mp: 193-195 °C.

^{1}H NMR ($CDCl_3$, δ): 2.20 (3H, s), 2.37 (3H, s), 2.84 (3H, s), 5.17 (1H, d, J = 10.4 Hz), 6.16 (1H, d, J = 10.4 Hz), 6.66 (1H, s), 6.72 (1H, d, J = 7.7 Hz), 6.86 (1H, brs), 6.97 (1H, d, J = 7.6 Hz), 7.03-7.09 (3H, m), 7.16 (1H, d, J = 8.0 Hz), 7.27-7.35 (3H, m), 7.54 (2H, d, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.3, 21.4, 23.5, 52.1, 98.6, 124.0, 124.3, 127.1, 127.2, 127.8, 128.3, 128.3, 129.0, 129.6, 136.4, 137.7, 138.1, 138.1, 138.9, 143.0, 167.1, 173.0. IR (neat, cm^{-1}): 3299, 3237, 3125, 1765, 1700, 1647, 1595, 1532, 1449, 1346, 1163, 753, 695, 553, 544, 528. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_4SNa$: 498.1458; found:

498.1476.

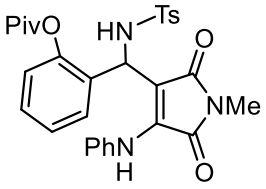
4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(p-tolyl) methyl)benzenesulfonamide, **63**



Yellow solid. mp: 203-205 °C.

^{1}H NMR ($CDCl_3$, δ): 2.27 (3H, s), 2.37 (3H, s), 2.83 (3H, s), 5.15 (1H, d, *J* = 10.4 Hz), 6.09 (1H, d, *J* = 10.4 Hz), 6.84 (2H, d, *J* = 8.1 Hz), 6.86 (1H, brs), 6.98 (2H, d, *J* = 8.0 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 7.16 (2H, d, *J* = 8.0 Hz), 7.27-7.33 (3H, m), 7.54 (2H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.0, 21.4, 23.5, 51.9, 98.6, 124.2, 127.0, 127.2, 129.0, 129.1, 129.7, 135.1, 136.4, 137.4, 137.7, 138.9, 143.1, 167.1, 173.0. IR (neat, cm^{-1}): 3296, 3235, 1700, 1647, 1511, 1421, 1164, 754, 693, 571. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_4SNa$: 498.1458; found: 498.1453.

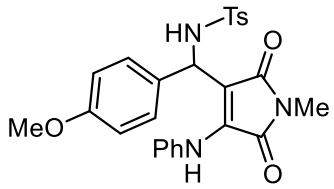
2-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)((4-methylphenyl)s ulfonamido)methyl)phenyl pivalate, **64**



Yellow solid. mp: 210-212 °C.

^{1}H NMR ($CDCl_3$, δ): 1.25 (9H, s), 2.39 (3H, s), 2.67 (3H, s), 5.35 (1H, d, *J* = 10.1 Hz), 5.70 (1H, d, *J* = 10.1 Hz), 6.87-6.89 (2H, m), 6.94 (1H, brs), 7.02 (1H, d, *J* = 8.1 Hz), 7.11-7.14 (1H, m), 7.19-7.22 (6H, m), 7.32-7.35 (1H, m), 7.58 (2H, d, *J* = 8.2 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.2, 26.9, 39.3, 48.0, 97.7, 122.7, 122.8, 125.5, 126.6, 127.5, 128.7, 128.8, 128.9, 129.6, 129.8, 136.8, 137.7, 140.1, 143.0, 149.5, 166.4, 172.8, 177.1. IR (neat, cm^{-1}): 3291, 3266, 3065, 2986, 1742, 1700, 1645, 1596, 1540, 1451, 1351, 1210, 1162, 1121, 1031, 757, 698, 573, 543. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{30}H_{31}N_3O_6SNa$: 584.1826; found: 584.1822.

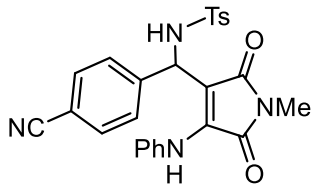
N-((4-methoxyphenyl)(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl) methyl)-4-methylbenzenesulfonamide, **65**



Yellow solid. mp: 201-202 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.37 (3H, s) , 2.83 (3H, s), 3.75 (3H, s), 5.11 (1H, d, *J* = 10.4 Hz), 6.06 (1H, d, *J* = 10.4 Hz), 6.71 (2H, d, *J* = 8.8 Hz), 6.84 (1H, brs), 6.88 (2H, d, *J* = 8.6 Hz), 7.05 (2H, d, *J* = 7.2 Hz), 7.17 (2H, d, *J* = 8.1 Hz), 7.27-7.33 (3H, m), 7.54 (2H, d, *J* = 8.2 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.5, 51.7, 55.2, 98.6, 113.8, 124.1, 127.2, 127.2, 128.4, 129.0, 129.6, 130.2, 136.4, 137.7, 138.9, 143.1, 159.0, 167.0, 173.0. IR (neat, cm^{-1}): 3298, 3238, 1699, 1647, 1535, 1510, 1449, 1251, 1164, 1029, 756, 697, 571. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_5SNa$: 514.1407; found: 514.1402.

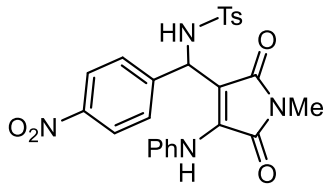
N-((4-cyanophenyl)(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide, **66**



Yellow solid. mp: 219-221 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.38 (3H, s), 2.86 (3H, s), 5.21 (1H, d, *J* = 10.3 Hz), 6.24 (1H, d, *J* = 10.3 Hz), 6.98 (1H, brs), 7.01 (2H, d, *J* = 8.3 Hz), 7.08-7.09 (2H, m), 7.18 (2H, d, *J* = 8.1 Hz), 7.34-7.38 (3H, m), 7.44 (2H, d, *J* = 8.3 Hz), 7.53 (2H, d, *J* = 8.2 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.7, 51.7, 96.8, 111.5, 118.4, 124.7, 127.0, 127.7, 127.9, 129.2, 129.9, 132.2, 136.0, 137.4, 139.6, 143.6, 143.8, 166.6, 172.9. IR (neat, cm^{-1}): 3306, 3238, 2229, 1762, 1697, 1647, 1595, 1532, 1448, 1348, 1164, 1086, 1041, 765, 698, 571. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{26}H_{22}N_4O_4SNa$: 509.1254; found: 509.1257.

4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(4-nitrophenyl)methyl)benzenesulfonamide, **67**

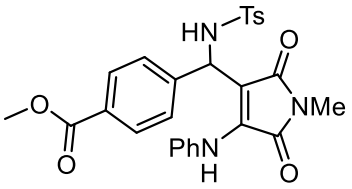


Yellow solid. mp: 209-211 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.37 (3H, s), 2.87 (3H, s), 5.26 (1H, d, *J* = 10.3 Hz), 6.29 (1H, d, *J* = 10.3 Hz), 7.00 (1H, brs), 7.05 (2H, d, *J* = 8.7 Hz), 7.11 (2H, d, *J* = 6.9 Hz), 7.18 (2H, d, *J* = 8.2 Hz), 7.34-7.40 (3H, m), 7.54 (2H, d, *J* = 8.2 Hz), 7.99 (2H, d, *J* = 8.7 Hz). ^{13}C NMR

($CDCl_3$, δ): 21.4, 23.7, 51.5, 96.7, 123.6, 124.8, 127.0, 127.9, 127.9, 129.2, 129.9, 136.0, 137.4, 139.7, 143.6, 145.8, 147.2, 166.6, 172.9. IR (neat, cm^{-1}): 3306, 3244, 1697, 1649, 1595, 1522, 1448, 1346, 1162, 758, 698, 666, 570. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{25}H_{22}N_4O_6SNa$: 529.1152; found: 529.1172.

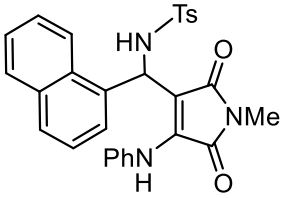
4-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)((4-methylphenyl)sulfonamido)methyl)benzoate, **68**



Yellow solid. mp: 222-223 ºC.

^1H NMR ($CDCl_3$, δ): 2.37 (3H, s), 2.85 (3H, s), 3.89 (3H, s), 5.21 (1H, d, *J* = 10.4 Hz), 6.19 (1H, d, *J* = 10.4 Hz), 6.91 (1H, brs), 6.98 (2H, d, *J* = 8.3 Hz), 7.07-7.08 (2H, m), 7.17 (2H, d, *J* = 8.0 Hz), 7.29-7.35 (3H, m), 7.54 (2H, d, *J* = 8.3 Hz), 7.83 (2H, d, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, δ): 19.0, 21.6, 48.2, 48.4, 76.2, 128.1, 128.7, 129.0, 135.3, 204.2. IR (neat, cm^{-1}): 3293, 3231, 3056, 2952, 1721, 1700, 1649, 1594, 1535, 1282, 1163, 1111, 764, 696, 572. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{27}H_{25}N_3O_6SNa$: 542.1356; found: 542.1355.

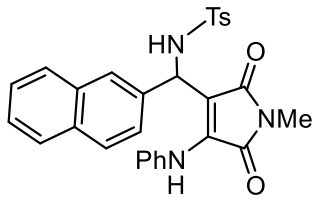
4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(naphthalen-1-yl)methyl)benzenesulfonamide, **69**



Yellow solid. mp: 214-216 ºC.

^1H NMR ($CDCl_3$, δ): 2.39 (3H, s), 2.79 (3H, s), 5.77 (1H, d, *J* = 10.7 Hz), 5.97 (1H, d, *J* = 10.7 Hz), 6.76-6.82 (4H, m), 6.87 (1H, brs), 6.93-6.96 (1H, m), 7.21 (2H, d, *J* = 8.1 Hz), 7.32-7.40 (3H, m), 7.45-7.48 (1H, m), 7.62 (2H, d, *J* = 8.2 Hz), 7.72 (1H, d, *J* = 8.5 Hz), 7.78-7.83 (2H, m). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.4, 49.6, 97.8, 123.2, 123.8, 124.7, 125.3, 125.9, 126.6, 126.8, 127.5, 128.2, 128.9, 129.4, 129.6, 131.2, 132.7, 133.6, 136.2, 137.4, 139.9, 143.3, 166.6, 173.4. IR (neat, cm^{-1}): 3291, 3270, 3098, 1594, 1523, 1492, 1449, 1393, 1289, 1118, 1085, 1041, 732, 647, 616, 554, 546, 538, 513, 508. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{29}H_{25}N_3O_4SNa$: 534.1458; found: 534.1490.

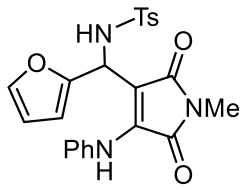
4-methyl-N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(naphtha len-2-yl)methyl)benzenesulfonamide, **70**



Yellow solid. mp: 221-223 °C.

^{1}H NMR ($CDCl_3$, δ): 2.31 (3H, s), 2.88 (3H, s), 5.34 (1H, d, *J* = 10.4 Hz), 6.28 (1H, d, *J* = 10.4 Hz), 6.90 (1H, s), 7.08-7.13 (5H, m), 7.19 (1H, brs), 7.30-7.32 (3H, m), 7.43-7.45 (2H, m), 7.54 (2H, d, *J* = 8.3 Hz), 7.61-7.63 (1H, m), 7.66 (1H, d, *J* = 8.6 Hz), 7.74-7.76 (1H, m). ^{13}C NMR ($CDCl_3$, δ): 14.2, 21.0, 27.0, 29.5, 32.3, 35.9, 41.0, 41.6, 49.9, 55.7, 60.4, 63.3, 113.1, 120.9, 126.6, 127.1, 128.3, 128.5, 130.7, 145.6, 149.7, 150.5, 160.5, 171.1, 195.6. IR (neat, cm^{-1}): 3293, 3235, 3060, 1700, 1649, 1595, 1537, 1449, 1341, 1164, 1028, 752, 693, 570. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{29}H_{25}N_3O_4SNa$: 534.1458; found: 534.1473.

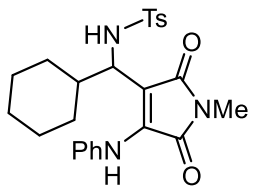
N-(furan-2-yl(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide, **71**



Yellow solid. mp: 197-199 °C.

^{1}H NMR ($CDCl_3$, δ): 2.31 (3H, s), 2.88 (3H, s), 5.34 (1H, d, *J* = 10.4 Hz), 6.28 (1H, d, *J* = 10.4 Hz), 6.90 (1H, s), 7.08-7.13 (5H, m), 7.19 (1H, brs), 7.30-7.32 (3H, m), 7.43-7.45 (2H, m), 7.54 (2H, d, *J* = 8.3 Hz), 7.61-7.63 (1H, m), 7.66 (1H, d, *J* = 8.6 Hz), 7.74-7.76 (1H, m). ^{13}C NMR ($CDCl_3$, δ): 14.2, 21.0, 27.0, 29.5, 32.3, 35.9, 41.0, 41.6, 49.9, 55.7, 60.4, 63.3, 113.1, 120.9, 126.6, 127.1, 128.3, 128.5, 130.7, 145.6, 149.7, 150.5, 160.5, 171.1, 195.6. IR (neat, cm^{-1}): 3297, 1760, 1695, 1639, 1597, 1514, 1452, 1334, 1159, 1034, 817, 758, 669, 573. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{23}H_{21}N_3O_5SNa$: 474.1094; found: 474.1095.

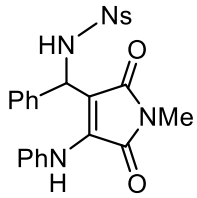
N-(cyclohexyl(1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)methyl)-4-methylbenzenesulfonamide, **72**



Pale yellow solid. mp: 204-206 ºC.

^{1}H NMR ($CDCl_3$, δ): 0.37-0.45 (1H, m), 0.51-0.59 (1H, m), 0.84-1.04 (3H, m), 1.12 (1H, d, *J* = 12.8 Hz), 1.23-1.29 (1H, m), 1.48-1.64 (4H, m), 2.39 (3H, s), 2.81 (3H, s), 3.81-3.84 (1H, m), 5.87 (1H, d, *J* = 10.2 Hz), 6.79 (1H, brs), 7.21 (4H, t, *J* = 8.4 Hz), 7.33 (1H, t, *J* = 7.5 Hz), 7.43-7.46 (2H, m), 7.66 (2H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.5, 25.8, 25.9, 29.2, 29.7, 42.9, 54.0, 98.7, 125.3, 127.1, 127.3, 129.0, 129.4, 136.4, 138.1, 139.3, 143.0, 173.3. IR (neat, cm^{-1}): 3461, 3336, 3313, 3028, 2944, 2847, 1768, 1701, 1631, 1596, 1506, 1499, 1437, 1378, 1282, 1163, 1006, 760, 673, 562. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{25}H_{29}N_3O_4SNa$: 490.1771; found: 490.1776.

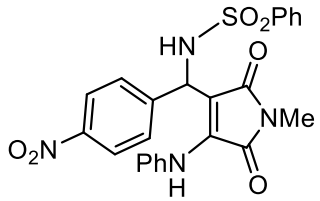
N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl)-4-nitrobenzenesulfonamide, **75**



Yellow solid. mp: 201-203 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.92 (3H, s), 5.32 (1H, d, *J* = 9.8 Hz), 6.67-6.70 (3H, m), 7.02-7.11 (4H, m), 7.18 (2H, d, *J* = 7.6 Hz), 7.37-7.46 (3H, m), 7.69 (2H, d, *J* = 8.9 Hz), 8.08 (2H, d, *J* = 8.9 Hz). ^{13}C NMR ($CDCl_3$, δ): 23.8, 52.5, 98.3, 123.6, 124.8, 126.8, 127.6, 127.8, 128.1, 128.6, 129.8, 136.1, 138.0, 138.4, 146.5, 149.5, 167.0, 173.3. IR (neat, cm^{-1}): 3321, 3095, 1694, 1651, 1536, 1449, 1348, 1163, 759, 747, 737, 691, 562. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{24}H_{20}N_4O_6SNa$: 515.0996; found: 515.1013.

N-((1-methyl-2,5-dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)(4-nitrophenyl)methyl)benzenesulfonamide, **76**

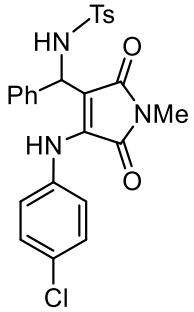


Yellow solid. mp: 191-193 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.88 (3H, s), 5.28 (1H, d, *J* = 10.2 Hz), 6.38 (1H, d, *J* = 10.2 Hz), 7.0 (1H, brs), 7.03 (2H, d, *J* = 8.6 Hz), 7.12 (2H, d, *J* = 6.8 Hz), 7.35-7.41 (5H, m), 7.48-7.51 (1H, m), 7.65-7.66 (2H, m), 7.99 (2H, d, *J* = 8.8 Hz). ^{13}C NMR ($CDCl_3$, δ): 23.8, 51.5,

96.6, 123.7, 124.8, 127.0, 127.8, 128.0, 128.7, 129.9, 132.6, 135.9, 139.5, 140.3, 145.7, 147.2, 166.6, 172.9. IR (neat, cm^{-1}): 3307, 3061, 1698, 1645, 1595, 1519, 1447, 1347, 1166, 759, 729, 691, 592, 554. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{24}H_{20}N_4O_6SNa$: 515.0996; found: 515.1014.

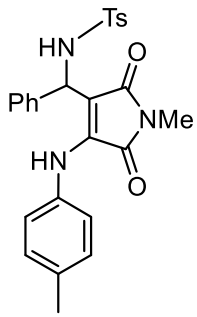
3-((4-chlorophenyl)amino)-1-methyl-4-(phenyl(phenylamino)methyl)-1H-pyrrole-2,5-di one, **77**



Yellow solid. mp: 201-203 ºC.

^1H NMR ($CDCl_3$, δ): 2.38 (3H, s), 2.85 (3H, s), 5.16 (1H, d, *J* = 10.3 Hz), 6.11 (1H, d, *J* = 10.3 Hz), 6.79 (1H, brs), 6.95-6.97 (2H, m), 7.01-7.04 (2H, m), 7.17-7.20 (5H, m), 7.27-7.28 (2H, m), 7.54 (2H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.6, 52.1, 99.3, 125.3, 127.0, 127.1, 127.8, 128.6, 129.1, 129.8, 132.7, 135.1, 137.5, 137.8, 138.6, 143.3, 166.9, 172.8. IR (neat, cm^{-1}): 3300, 3243, 1701, 1649, 1529, 1349, 1165, 825, 758, 718, 571, 543. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{25}H_{22}ClN_3O_4SNa$: 518.0912; found: 518.0915.

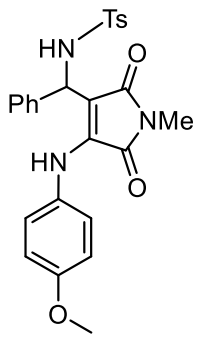
1-methyl-3-(phenyl(phenylamino)methyl)-4-(p-tolylamino)-1H-pyrrole-2,5-dione, **78**



Yellow solid. mp: 193-195 ºC.

^1H NMR ($CDCl_3$, δ): 2.35 (3H, s), 2.37 (3H, s), 2.82 (3H, s), 5.18 (1H, d, *J* = 10.4 Hz), 6.12 (1H, d, *J* = 10.4 Hz), 6.81 (1H, brs), 6.94-6.98 (4H, m), 7.09 (2H, d, *J* = 8.1 Hz), 7.16-7.19 (5H, m), 7.56 (2H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.1, 21.4, 23.5, 52.0, 97.7, 124.2, 127.1, 127.2, 127.6, 128.4, 129.0, 130.2, 133.7, 137.4, 137.7, 138.3, 139.4, 143.1, 167.0, 173.0. IR (neat, cm^{-1}): 3304, 3239, 3055, 3030, 1765, 1700, 1640, 1533, 1447, 1418, 1351, 1165, 824, 758, 721, 572, 543. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_4SNa$: 498.1458; found: 498.1456.

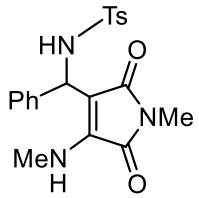
3-((4-methoxyphenyl)amino)-1-methyl-4-(phenyl(phenylamino)methyl)-1H-pyrrole-2,5-dione, **79**



Orange solid. mp: 183-185 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.37 (3H, s), 2.81 (3H, s), 3.81 (3H, s), 5.11 (1H, d, *J* = 10.4 Hz), 6.12 (1H, d, *J* = 10.4 Hz), 6.80-6.81 (3H, m), 6.94-6.96 (2H, m), 7.01-7.03 (2H, m), 7.16-7.18 (5H, m), 7.56 (2H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.4, 51.9, 55.5, 97.4, 114.7, 126.4, 127.0, 127.2, 127.6, 128.4, 128.9, 129.0, 137.7, 138.5, 140.0, 143.1, 158.8, 167.0, 173.0. IR (neat, cm^{-1}): 3296, 3223, 3059, 1701, 1645, 1530, 1510, 1253, 1161, 1030, 822, 758, 697, 571, 541. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_5SNa$: 514.1407; found: 514.1424.

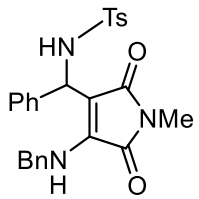
1-methyl-3-(methylamino)-4-(phenyl(phenylamino)methyl)-1H-pyrrole-2,5-dione, **80**



Pale yellow solid. mp: 186-188 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.36 (3H, s), 2.68 (3H, s), 3.12 (3H, d, *J* = 5.7 Hz), 5.35 (1H, brs), 5.75 (1H, d, *J* = 10.1 Hz), 6.13 (1H, d, *J* = 10.1 Hz), 7.18 (2H, d, *J* = 8.0 Hz), 7.25-7.37 (5H, m), 7.64 (2H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.2, 30.9, 52.2, 95.4, 126.7, 127.1, 127.8, 128.7, 129.0, 137.8, 139.5, 143.2, 143.4, 166.4, 172.5. IR (neat, cm^{-1}): 3330, 3300, 3028, 1705, 1645, 1523, 1415, 1326, 1160, 1049, 760, 669, 573, 544. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{20}H_{21}N_3O_4SNa$: 422.1145; found: 422.1145.

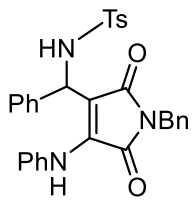
3-(benzylamino)-1-methyl-4-(phenyl(phenylamino)methyl)-1H-pyrrole-2,5-dione, **81**



Pale yellow solid. mp: 189-191 ºC.

^{1}H NMR ($CDCl_3$, δ): 2.36 (3H, s), 2.68 (3H, s), 3.12 (3H, d, *J* = 5.7 Hz), 5.35 (1H, brs), 5.75 (1H, d, *J* = 10.1 Hz), 6.13 (1H, d, *J* = 10.1 Hz), 7.18 (2H, d, *J* = 8.0 Hz), 7.25-7.37 (5H, m), 7.64 (2H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 23.2, 30.9, 52.2, 95.4, 126.7, 127.1, 127.8, 128.7, 129.0, 137.8, 139.5, 143.2, 143.4, 166.4, 172.5. IR (neat, cm^{-1}): 3441, 3352, 3324, 3284, 1698, 1651, 1532, 1455, 1447, 1341, 1162, 1030, 1023, 759, 701, 575, 545. HRMS (ESI): *m/z* $[M+Na]^+$, calcd for $C_{26}H_{25}N_3O_4SNa$: 498.1458; found: 498.1482.

1-benzyl-3-(phenyl(phenylamino)methyl)-4-(phenylamino)-1H-pyrrole-2,5-dione, **82**



Yellow solid. mp: 202-204 °C.

^{1}H NMR ($CDCl_3$, δ): 2.28 (3H, s), 4.51 (2H, s), 5.15 (1H, d, *J* = 10.4 Hz), 6.25 (1H, d, *J* = 10.4 Hz), 6.78 (1H, brs), 6.88 (2H, d, *J* = 8.0 Hz), 6.94-7.00 (4H, m), 7.16-7.18 (3H, m), 7.27-7.38 (8H, m), 7.43 (2H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, δ): 21.4, 41.5, 52.1, 98.2, 124.1, 126.9, 127.1, 127.3, 127.7, 128.0, 128.4, 128.8, 128.8, 129.1, 129.7, 136.0, 136.2, 137.5, 138.2, 138.8, 143.0, 166.6, 172.7. IR (neat, cm^{-1}): 3316, 3282, 3029, 1696, 1653, 1532, 1435, 1351, 1161, 1028, 760, 695, 542. HRMS (ESI): *m*/*z* $[M+Na]^+$, calcd for $C_{31}H_{27}N_3O_4SNa$: 560.1614; found: 560.1605.

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8. Catalog of reported papers

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Wei Han, Takeshi Oriyama

Bull. Chem. Soc. Jpn. **2020**, *93*, 988.

8.2 Synthesis of *N*-aryl-4-arylhexahydroquinoline derivatives by reaction of cyclic enaminones with arylidenemalononitriles in DMSO

Wei Han, Chika Inoue, Tsunaki Onizawa, and Takeshi Oriyama

Synthesis, **2021**, *53*, 1495.

8.3 DBU-catalyzed highly efficient synthesis of 1,4-dihydropyridine derivatives from arylidenemalononitriles and *β*-enamino imides

Wei Han, Kazuya Nakajima, Masashi Kajitani, and Takeshi Oriyama

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