# Michael Addition of Carbonyl Compounds to α,β-Unsaturated Nitroalkenes

Subjects: Chemistry, Organic

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The proline-catalyzed asymmetric Michael addition reaction of acetaldehyde with α,β-unsaturated nitroalkenes as synthetically useful routes to β-substituted derivatives of γ-Aminobutyric acid (GABA).

pharmaceuticals neurological drugs γ-aminobutyric-acid derivatives asymmetric Michael addition

## 1. Introduction

Tailor-made amino acids [1] play an indispensable role in the development of modern pharmaceuticals and drug formulations [2][3][4][5][6]. Thus, over 20% of newly approved small-molecule drugs contain structural fragments of AAs [7][8][9]. In particular, γ-aminobutyric-acid (GABA) derivatives bearing β-alkyl or β-aryl substituents, which include baclofen [10], phenibut [11][12][13], tolibut [14], and pregabalin [15][16][17], are recognized as an essential class of marketed pharmaceuticals for the treatment of neurological diseases (**Figure 1**). Similarly, piracetam-based GABA derivatives such as phenylpiracetam [18], brivaracetam [19][20][21], and rolipram [22] are also developed as pharmaceuticals. Introduction of β-alkyl or β-aryl substituent in the GABA backbone allows for the improvement of the lipophilic character of these compounds.

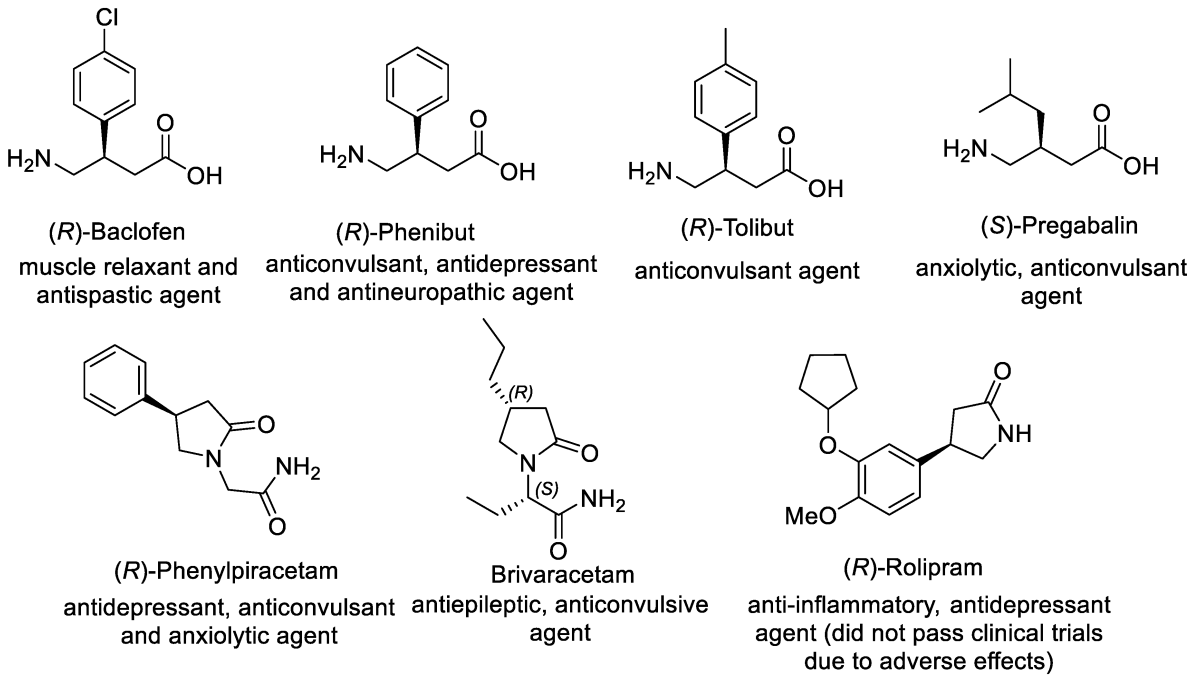


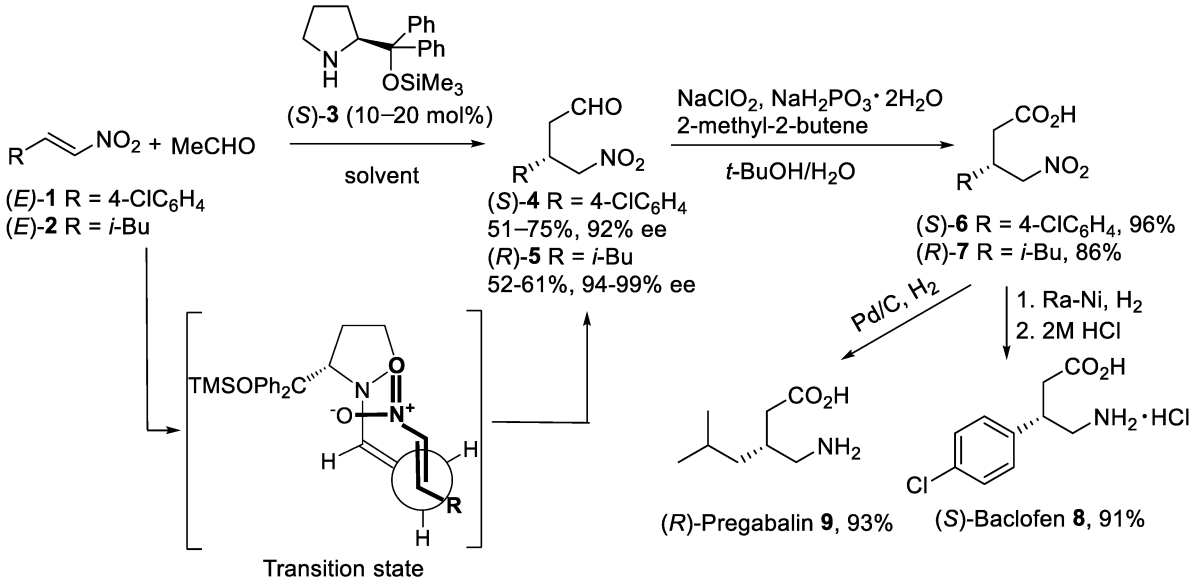

**Figure 1.** Representative β-substituted GABA derivatives with clinical applications.

Significantly, biological activity of β-substituted GABA derivatives depends on their absolute configuration. For example, (*R*)-enantiomers of Baclofen (antispastic agent and muscle relaxant) and Phenibut (tranquilizer and anticonvulsant) are considerably more active than the corresponding (*S*)-enantiomers, while anticonvulsant activity of Pregabalin (anti-epilepsy drug) is primarily related to (*S*)-enantiomer [23]. Consequently, considerable efforts were devoted to developing asymmetric synthesis of β-substituted GABA derivatives, including chemical and biocatalytic resolution, asymmetric reduction, desymmetrization, aldol addition, and nucleophilic substitution [24][25][26]. For the past decade, the asymmetric Michael addition of carbon nucleophile to α,β-unsaturated compound-bearing nitro or carbonyl groups gained impressive progress, providing straightforward access to γ-nitrocarbonyl compounds as key chiral intermediates that can be converted into β-substituted GABA derivatives via subsequent transformation of functional groups.

## 2. Michael Addition of Carbonyl Compounds to α,β-Unsaturated Nitroalkenes

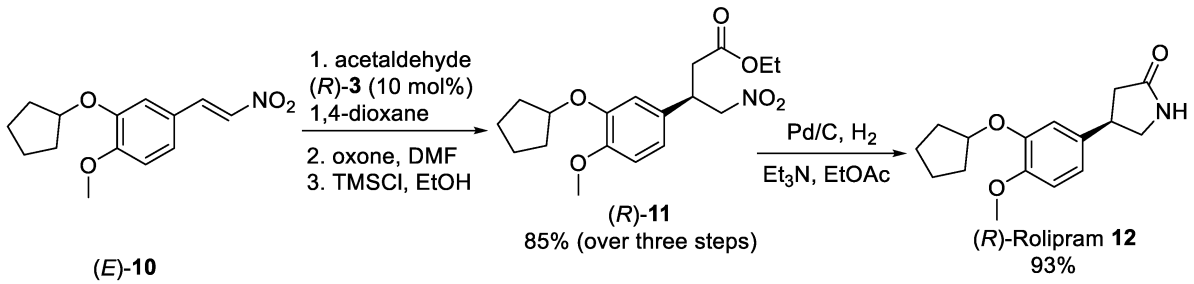
The proline-catalyzed asymmetric Michael addition reaction [27] of acetaldehyde with α,β-unsaturated nitroalkenes attracted considerable attention as synthetically useful routes to β-substituted derivatives of GABA. Thus, the addition of acetaldehyde to the nitroolefins (*E*)-**1** and (*E*)-**2** (Scheme 1) was carried out in the presence of enantiomerically pure (*S*)-diphenylprolinol silyl ether **3** as the catalyst [28][29]. After optimization of reaction conditions, the asymmetric Michael addition proceeded efficiently with 10–20 mol% of organocatalyst (*S*)-**3** in such solvents as MeCN, DMF/*i*-PrOH, and 1,4-dioxane to afford γ-nitro aldehydes (*S*)-**4** and (*R*)-**5** in reasonable yield and excellent enantiomeric excess. Oxidation of γ-nitro aldehydes (*S*)-**4** and (*R*)-**5** was successfully performed in aqueous *t*-BuOH using $NaClO_2$ and $NaH_2PO_4$ with 2-methyl-2-butene as a chlorine scavenger to afford carboxylic

acids (*S*)-**6** and (*R*)-**7** in good to excellent yields [30]. The reduction of the nitro acid (*S*)-**6** with Raney Ni in MeOH gave, after treatment with aqueous HCl, (*S*)-Baclofen **8** as hydrochloride salt in 91% yield. (*R*)-Pregabalin **9** was also synthesized by the reduction of the nitro group in (*R*)-**7** under Pd/C in 93% yield. The mechanism of the asymmetric Michael addition reaction of acetaldehyde with nitroalkenes promoted by diphenylprolinol silyl ether involves the formation of the enamine as a nucleophile. Thus, the organocatalyst would react with the acetaldehyde forming *anti*-enamine with the double bond oriented away from the diphenylsiloxymethyl group. In this case, the (diphenylmethyl)trimethylsiloxy group provides the formation of *anti*-enamine and shielding one face of the enamine double bond. The *anti*-enamine would add stereoselectively to the nitroolefin via the acyclic synclinal transition state proposed by Seebach [31] as shown in Scheme 1.



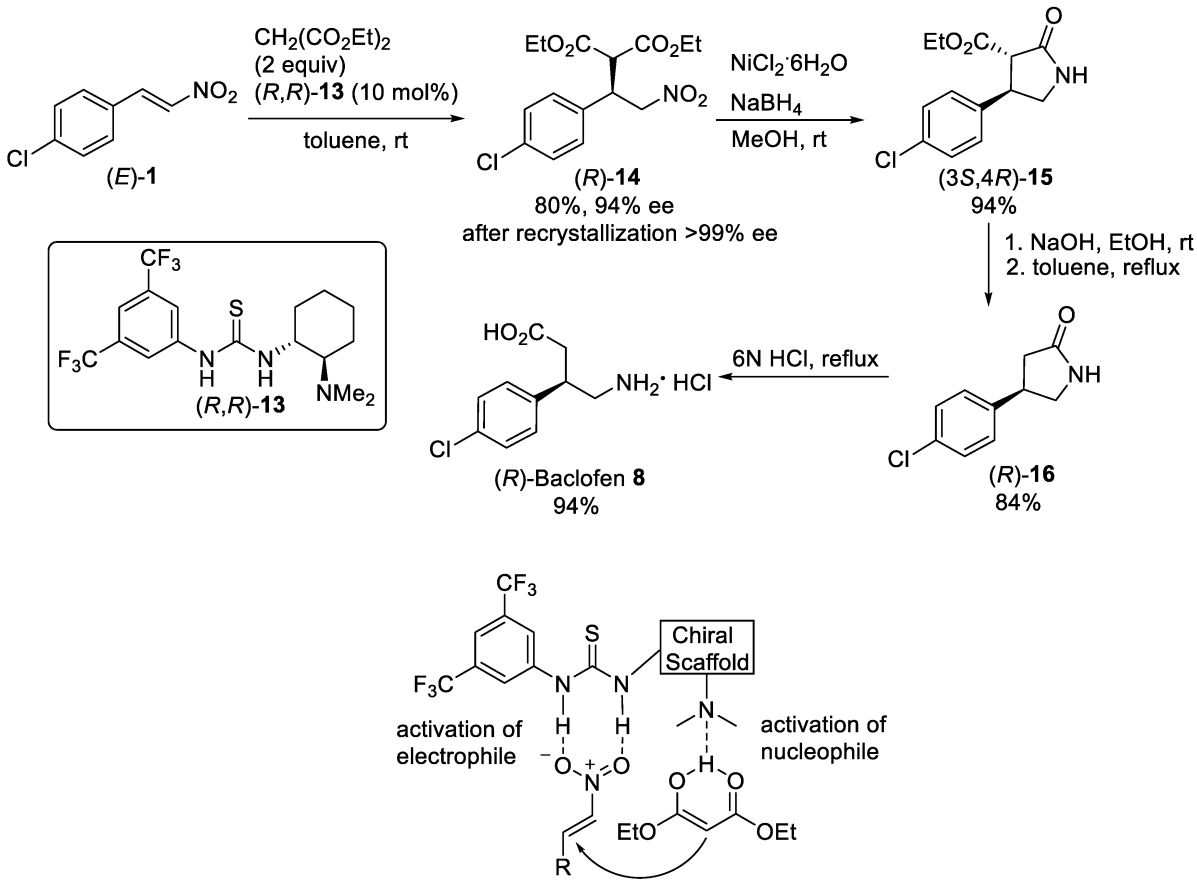

**Scheme 1.** Organocatalytic asymmetric Michael reaction of acetaldehyde with nitroalkenes (*E*)-**1** and (*E*)-**2**.

In a similar way, the nitro olefin (*E*)-**10** (Scheme 2), easily available from isovanillin via *O*-alkylation and Henry condensation, reacted with acetaldehyde in the presence of a catalytic amount of diphenylprolinol silyl ether (*R*)-**3** (10 mol%) affording corresponding nitro aldehyde adduct which upon oxidation with oxone and esterification successfully transformed into ester derivative (*R*)-**11** in 85% yield [32]. The nitroester (*R*)-**11** underwent intramolecular reductive lactamization under $H_2$ in presence of catalytic amount of Pd/C to furnish (*R*)-Rolipram **12** in 93% yield and >99% ee. The present method was also utilized to prepare enantiomerically pure (*S*)-Rolipram using (*S*)-diphenylprolinol silyl ether-mediated asymmetric Michael addition reaction as the key step. Recently, water-soluble diarylprolinol silyl ether containing the dimethylamine functionality was found to be very effective for the Michael additions of the acetaldehyde with nitroolefins. These reactions took place in brine with good yields and high enantioselectivities for a broad range of nitroolefins [33][34][35].



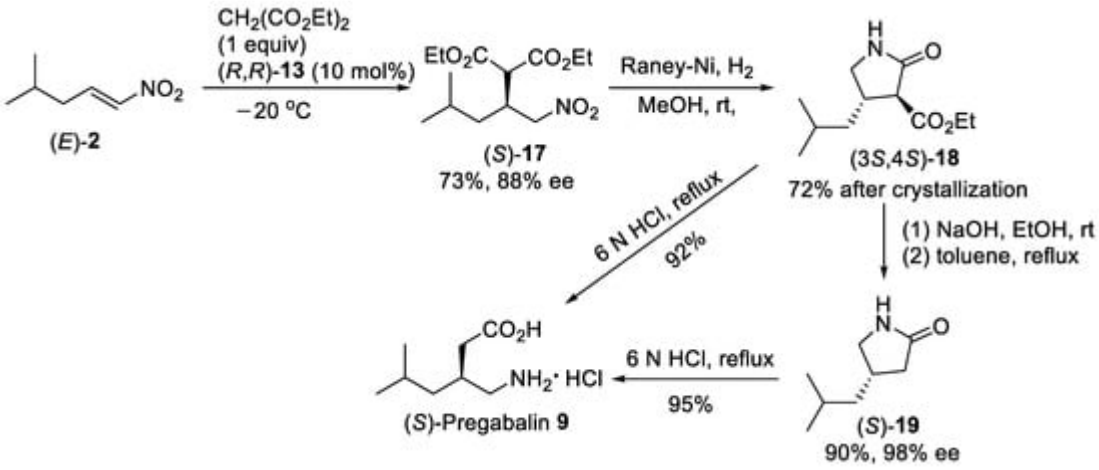

**Scheme 2.** Synthetic approach of (*R*)-Rolipram **12** employing the organocatalyzed asymmetric Michael addition acetaldehyde to nitro olefin (*E*)-**10**.

Enantioselective conjugate addition of malonates and their equivalents to nitroolefins promoted by bifunctional organocatalysts bearing a hydrogen-bonding donor group and Lewis base (tertiary amine) is considered as one of the most simple and efficient routes for constructing chiral β-substituted derivatives of GABA and their lactam analogs, especially from the perspective of green chemistry. The success of bifunctional organocatalysts was based on their ability to increase the reactivity of both nitroolefins and nucleophiles as well as control the approach of nucleophiles to nitroolefins in the transition state [36][37]. For example, the Michael reaction of nitroalkene (*E*)-**1** (Scheme 3) with diethyl malonate was performed in the presence of Takemoto thiourea catalyst (*R*,*R*)-**13** bearing 3,5-bis(trifluoromethyl)benzene and tertiary amino group [38]. The use of 2 equiv of diethyl malonate in toluene and 10 mol% catalyst loading was required to provide the Michael adduct (*R*)-**14** in 80% yield with 94% ee. A single recrystallization made it possible to increase the enantiomeric purity of the product (*R*)-**14** to 99% ee. Then, reductive cyclization of (*R*)-**14** with $NaBH_4/NiCl_2$ in methanol gave γ-lactam (3*S*,4*R*)-**15** as thermodynamically more stable *anti*-diastereomer [39][40], which after hydrolysis and decarboxylation was converted into lactam (*R*)-**16** in 84%. Finally, acidic hydrolysis of (*R*)-**16** gave (*R*)-Baclofen **8** as hydrochloride salt in 94% yield. A high level of enantioselectivity in organocatalytic Michael addition reaction was achieved as a result of dual activation through deprotonation of the acidic proton of diethylmalonate by tertiary amino group of the organocatalyst and the hydrogen-bond formation between the nitro group and the thiourea moiety [41].



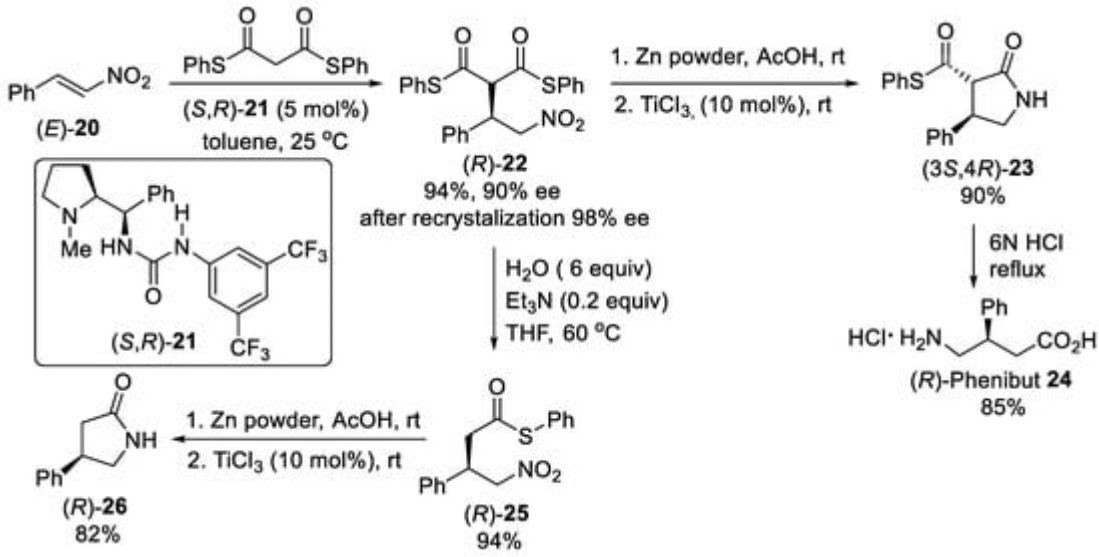

**Scheme 3.** Enantioselective Michael reaction of (*E*)-**1** with diethyl malonate in the presence of thiourea (*R*,*R*)-**13**.

Under solvent-free conditions reducing the amount of diethyl malonate from 2 to 1 equiv did not significantly influence both the yield and enantioselectivity of Michael addition to nitroalkenes promoted by thiourea (*R*,*R*)-**13** catalysts. Thus, Michael addition of diethyl malonate to alkyl-substituted nitroalkene (*E*)-**2** (Scheme 4) in the presence of 10 mol% of (*R*,*R*)-**13** under solvent-free conditions produced the nitro ester (*S*)-**17** in 73% yield and 88% enantiomeric excess [42]. Hydrogenation of (*S*)-**17** over Raney Ni provided the pyrrolidin-2-one (3*S*,4*S*)-**18** [43] in 72% after crystallization, which was subjected to ester hydrolysis followed by decarboxylation to give γ-lactam (*S*)-**19** in 90% yield and 98% enantiomeric excess. Hydrolysis of γ-lactam (*S*)-**19** with 6N HCl gave the enantiomerically pure (*S*)-Pregabalin **9** hydrochloride in 95% yield. Additionally, treatment of pyrrolidin-2-one derivative (3*S*,4*S*)-**18** with 6N HCl at reflux also directly produced the (*S*)-Pregabalin **9** hydrochloride in 92% yield.



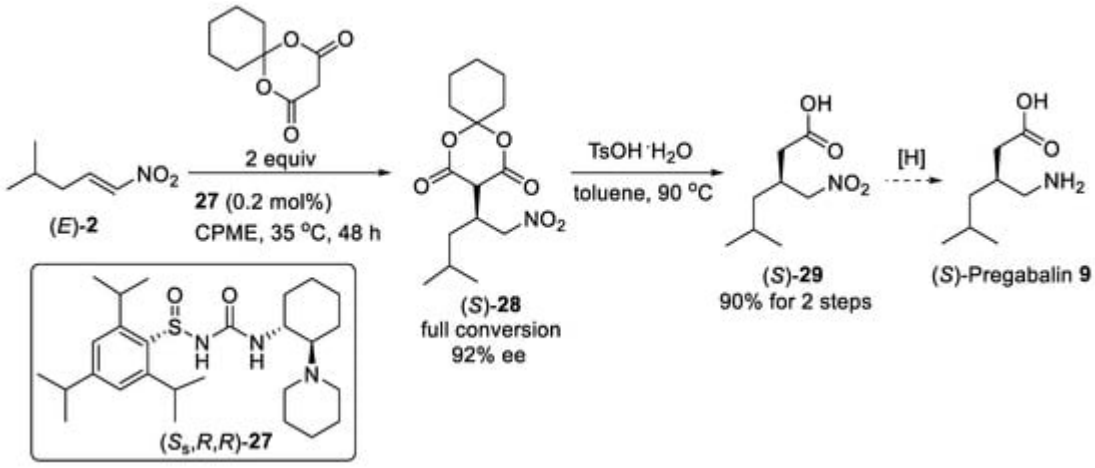

**Scheme 4.** Enantioselective Michael reaction of (*E*)-**2** with diethyl malonate in the presence of thiourea (*R*,*R*)-**13** under solvent-free conditions.

A series of Takamoto-type bifunctional organocatalysts were examined for the asymmetric Michael addition of malonate derivatives to nitroalkenes and showed very effective catalytic activity. For example, L-proline-derived bifunctional urea-pyrrolidine organocatalyst (*S*,*R*)-**21** (Scheme 5) was demonstrated to catalyze the enantioselective Michael addition of diphenyl dithiomalonates to nitrostyrene (*E*)-**20** in toluene as the best solvent at 25 °C [44]. The reaction performing with 5 mol% of (*S*,*R*)-**21** was complete in 1.5 h, affording Michael adduct (*R*)-**22** in 90% enantiomeric excess, which was improved to 98% after recrystallization from ethanol. Reduction of the nitro group using zinc in acetic acid and substoichiometric amounts of $TiCl_3$ followed by intermolecular cyclization enabled the formation of the lactam (*R*)-**23** in excellent yields of 90%. Hydrolysis of the lactam (*R*)-**23** was finally achieved with 6N HCl and the resulting (*R*)-Phenibut **24** was isolated as hydrochloride in 85% yield. Additionally, mild basic hydrolysis-decarboxylation of Michael adduct (*R*)-**22** provided γ-nitrothioester (*R*)-**25** in 94% yield, which reduced and cyclized under the above described conditions (Zn/AcOH/$TiCl_3$) to lactam (*R*)-**26** that was isolated in 82% yield.



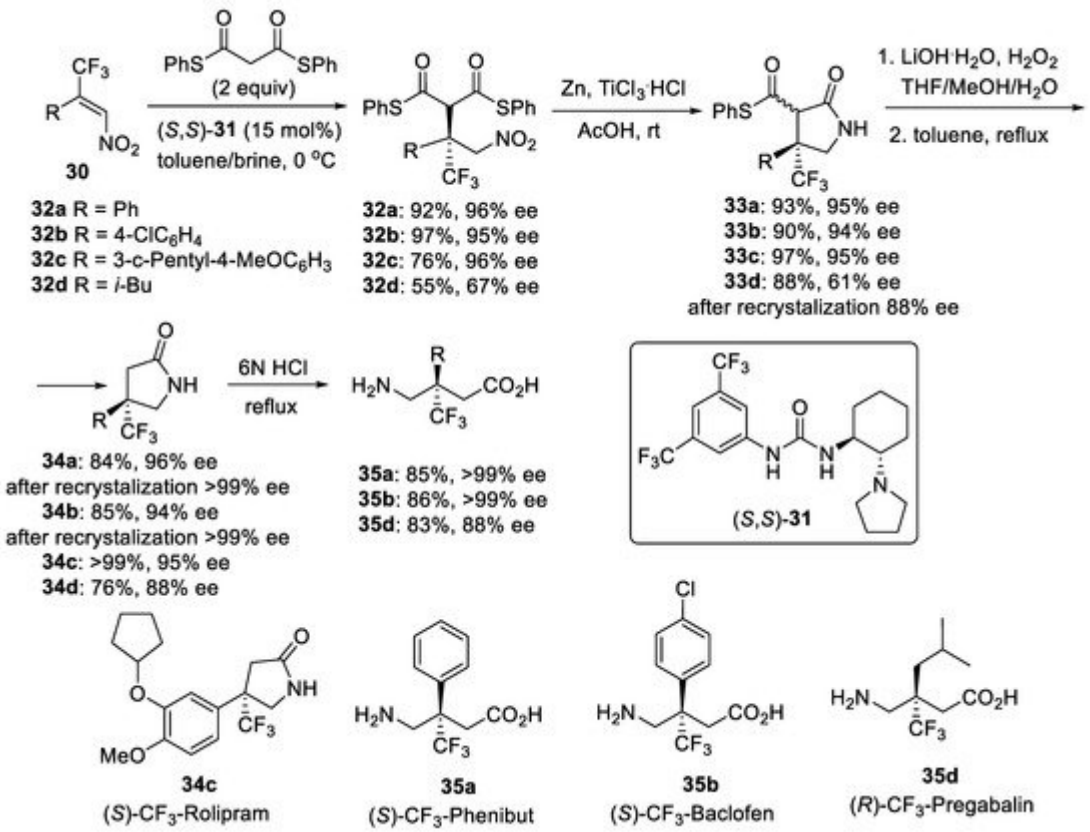
**Scheme 5.** Enantioselective Michael addition of diphenyl dithiomalonates to β-nitrostyrene (*E*)-**20** catalyzed by L-proline-derived urea (*S*,*R*)-**21**.

When the addition of cyclohexyl Meldrum's acid to aliphatic nitroalkene (*E*)-**2** (Scheme 6) was carried out with only 0.2 mol% of *N*-sulfinyl urea catalysis ($S_S$,*R*,*R*)-**27** in cyclopentyl methyl ether (CPME), complete conversion of starting nitroalkene (*E*)-**2** proceeded at 35 °C for 48 h providing the Michael adduct (*S*)-**28** in 92% ee [45]. Using *n*-sulfinyl urea catalysis ($S_S$,*R*,*R*)-**27** bearing cyclic tertiary amine was found to be essential for achieving high conversion and enantioselectivity. Direct hydrolysis/decarboxylation of addition product (*S*)-**28** without purification led to one mole scale synthesis of γ-nitroacid (*S*)-**29** in 90% overall yield from nitroalkene (*E*)-**2**. (*S*)-Pregabalin **9** could be provided by heterogeneous catalytic hydrogenation of (*S*)-**29**.



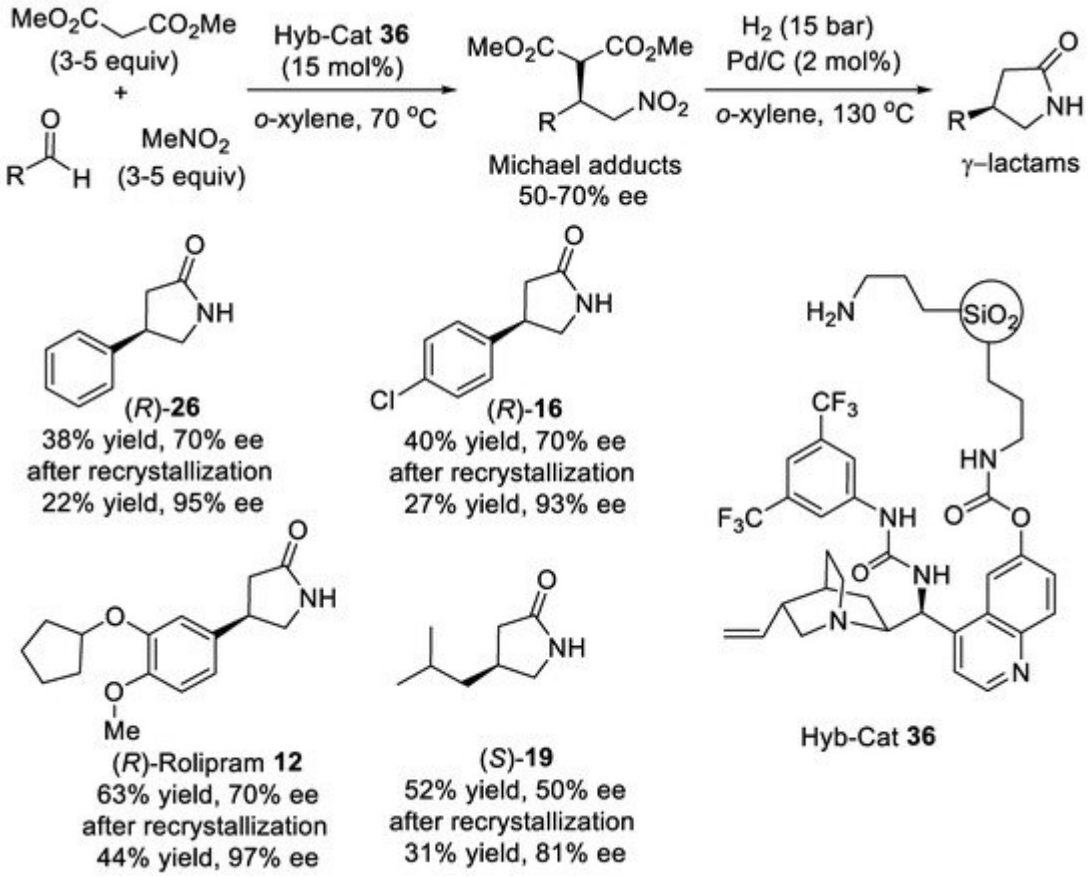

**Scheme 6.** Catalytic enantioselective addition of cyclohexyl Meldrum's acid to nitroalkene (*E*)-**2** using *N*-sulfinyl urea catalysis ($S_S$,*R*,*R*)-**27**.

Another urea catalyst (*S*,*S*)-**31** (Scheme 7) containing the pyrrolidine moiety was designed to catalyze in brine media [46] the enantioselective addition of dithiomalonate to otherwise unreactive β-$CF_3$-β,β-disubstituted nitroalkenes **30** providing corresponding Michael adducts **32** with a β-trifluoromethylated quaternary stereocenter [47]. In brine media the use of 15 mol% of urea catalyst (*S*,*S*)-**31** as well as the addition of *o*-xylene as additive was required for obtaining high yield and enantioselectivity of adducts **32** at 0 °C. In the absence of cosolvent, the achieved enantioselectivity of Michael adducts **32** was lower. These results could be explained by enforced hydrophobic interactions between catalysts and substrates when the reaction was carried out in brine media. Under optimal conditions, trifluoromethylated nitroalkenes **30** having substituted phenyl and *iso*-butyl groups were converted into the corresponding products **32** in 55–97% yields with 67–96% ee. So-obtained Michael products **32** were further subjected to reductive cyclization to furnish γ-lactam thioesters **33**. Hydrolysis of γ-lactam thioesters **33** followed by a decarboxylation provided β-trifluoromethylated analogues of rolipram **34c**, phenibut **35a**, baclofen **35b**, and pregabalin **35d**. The enantiopurity of γ-lactam thioester **33d** and γ-lactams **34a**,**b** could be improved by recrystallization.



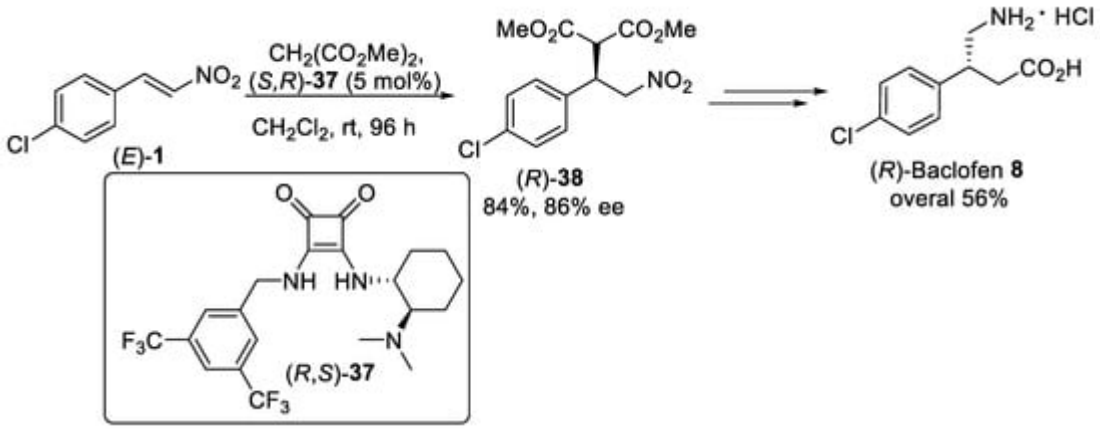

**Scheme 7.** Synthesis of GABA derivatives with a trifluoromethylated quaternary stereogenic center.

A three-component reaction of aromatic or aliphatic aldehydes, nitromethane and dimethyl malonate was found to catalyze by mesoporous siliceous material **36** (Scheme 8) incorporating urea-modified quinidine and propylamine groups in *o*-xylene at 70 °C leading to corresponding Michael adducts in reasonable yield [48][49]. The organic–inorganic hybrid catalyst **36** enabled access to Michael adducts with modest-to-good enantiomeric excess (50–70%). After removing the excess nitromethane by distillation, the *o*-xylene solution of Michael adducts was subjected to heterogeneous catalytic hydrogenation of the nitro group followed by cyclization and thermal decarboxylation to give γ-lactams with retention of enantiopurity. Thus, after column chromatography and recrystallization, (*R*)-Rolipram **12** and precursors of Phenibut (*R*)-**26**, Baclofen (*R*)-**16** and Pregabalin (*S*)-**19** were obtained in two-pot multicomponent operations with enantiopurity ranging from 81% ee to 97% ee. The solid hybrid catalyst could be reused three times without loss of activity.



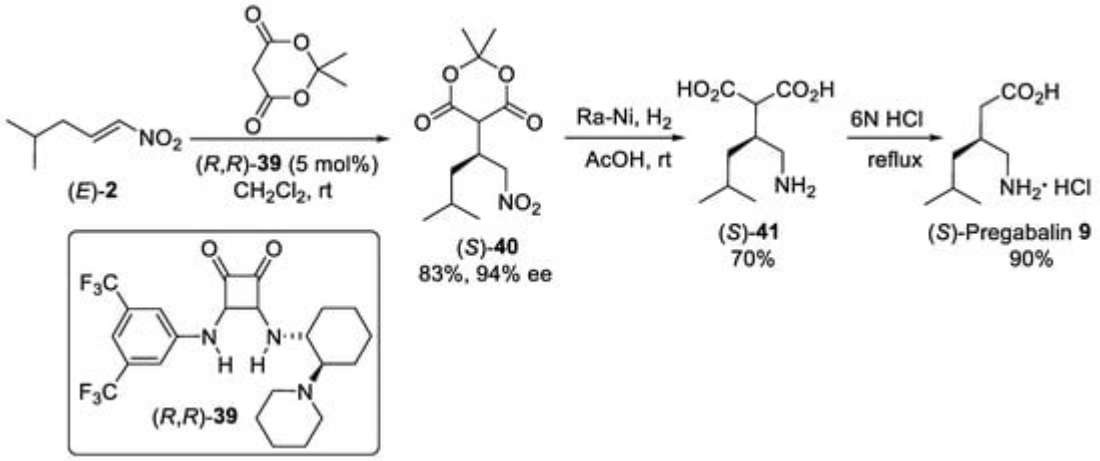

**Scheme 8.** Asymmetric three-component reaction of aldehydes, nitromethane, and malonate.

Conformationally rigid cyclobutene-ring-derivative squaramide (*R*,*S*)-**37** (Scheme 9) was shown to function in a complementary manner to thioureas as an effective hydrogen-bonding bifunctional organocatalyst for the Michael addition of dimethyl malonate to aromatic nitroalkene (*E*)-**1** [50][51]. It was supposed that two H-bonds formed between the squaramide (*R*,*S*)-**37** organocatalyst, incorporating tertiary nitrogen as Lewis base and chiral scaffold, and the nitroalkene substrate. Performing the reaction in dichloromethane as solvent with 5 mol% catalyst loading afforded the Michael product (*R*)-**38** in 84% yield and 86% ee, albeit in a long reaction time. Polymer-immobilized squaramide was also effective for the Michael addition of dimethyl malonate to nitroalkene (*E*)-**1**, but significant loss of activity was observed in the second and third cycles. The adduct (*R*)-**38** was further transformed to (*R*)-baclofen **8** hydrochloride in 56% overall yield through the procedure exemplified in Scheme 1.




**Scheme 9.** Michael addition of dimethyl malonate to β-nitrostyrene (*E*)-**1** using squaramide organocatalysis (*R*,*S*)-**37**.

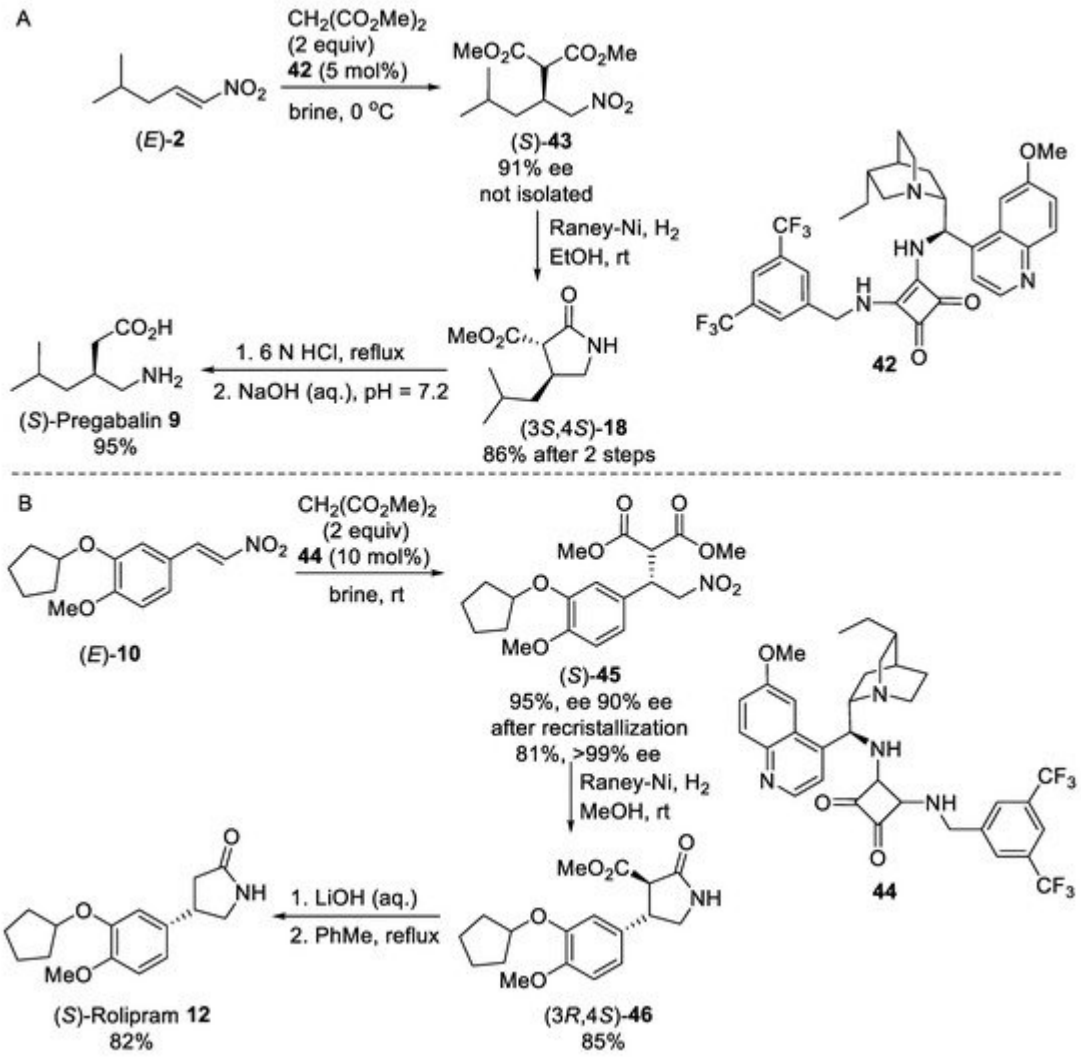
Squaramide (*R*,*R*)-**39** (Scheme 10), which possess an piperidine unit, was useful for the activation of Meldrum's acid in enantioselective Michael addition to aliphatic nitroalkenes. The reaction of Meldrum's acid and nitroalkene (*E*)-**2** was carried out with catalyst loading of 5 mol% in dichloromethane as the best solvent to obtain the nitro derivative (*S*)-**40** in 83% yield and 94% enantiomeric excess [52]. Squaramide (*R*,*R*)-**39** showed higher catalytic activity and enantioselectivity compared to quinidine-based thioureas organocatalysts [53]. Single-step catalytic hydrogenation and acid-catalyzed deprotection of (*S*)-**40** over Raney Ni in acetic acid than decarboxylation of the resulting malonic-acid derivative (*S*)-**41** with 6*N* HCl afforded (*S*)-Pregabalin **9** hydrochloride in 52% yield for three steps.




**Scheme 10.** The Michael addition of Meldrum's acid to nitroalkene (*E*)-**2** catalyzed by squaramide (*R*,*R*)-**39** catalyst.

The use of catalyst **42** (Scheme 11A) incorporating squaramide and hydroquinidine units allowed one to perform an enantioselective Michael addition of malonate to nitroolefin (*E*)-**2** in brine due to the "hydrophobic hydration effect" [54][55]. Under these conditions, hydrophobic hydroquinidine-squaramide catalyst **42** directed the reaction towards the corresponding Michael adduct (*S*)-**43** with high yield and enantioselectivity [43]. After the extraction of

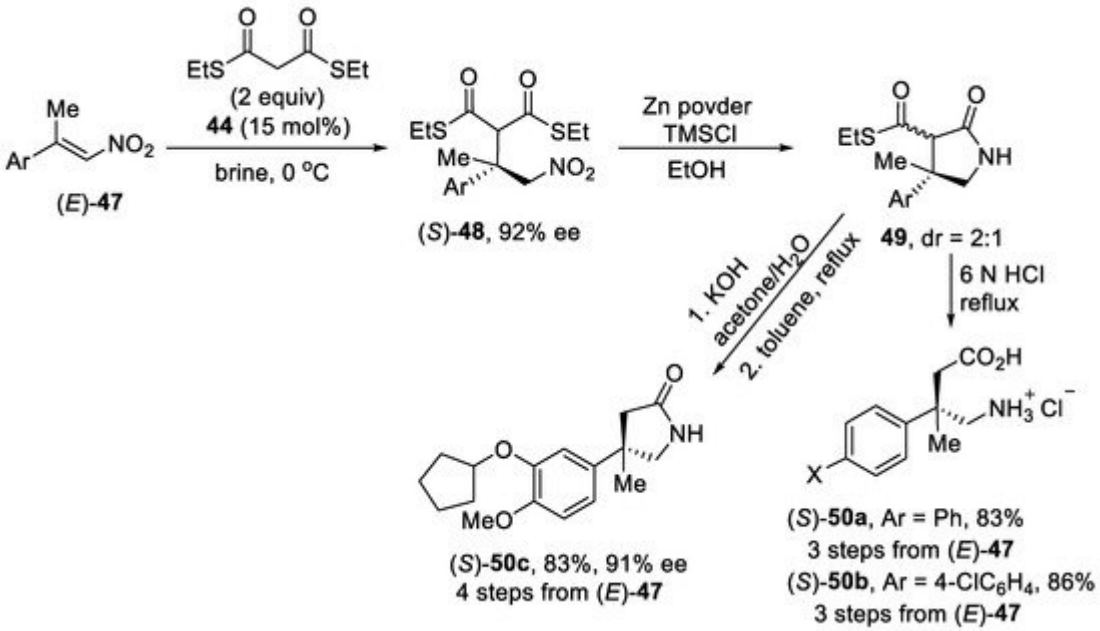
the Michael adduct (*S*)-**43** with methylcyclohexane, catalyst **42** was recoveried in quantitative yield (>99%) by simple filtration permitted the catalyst recycling. Hydrogenation of the crude Michael adduct (*S*)-**43** using Raney Ni followed by hydrolysis of resulting γ-lactam (3*S*,4*R*)-**18** with 6N HCl afforded (*S*)-pregabalin **9** in enantiomerically pure form after simple recrystallization from 2-propanol/water. The developed procedure in brine media was also applied for the scalable synthesis of enantiomerically pure (*S*)-Rolipram **12** (Scheme 11B) from aryl nitroolefin (*E*)-**10** using 10 mol% of hydroquinine-based squaramide catalyst **44**.




**Scheme 11.** Enantioselective syntheses of (*S*)-Pregabalin **9** (**A**) and (*S*)-Rolipram **12** (**B**) under "on water" conditions.

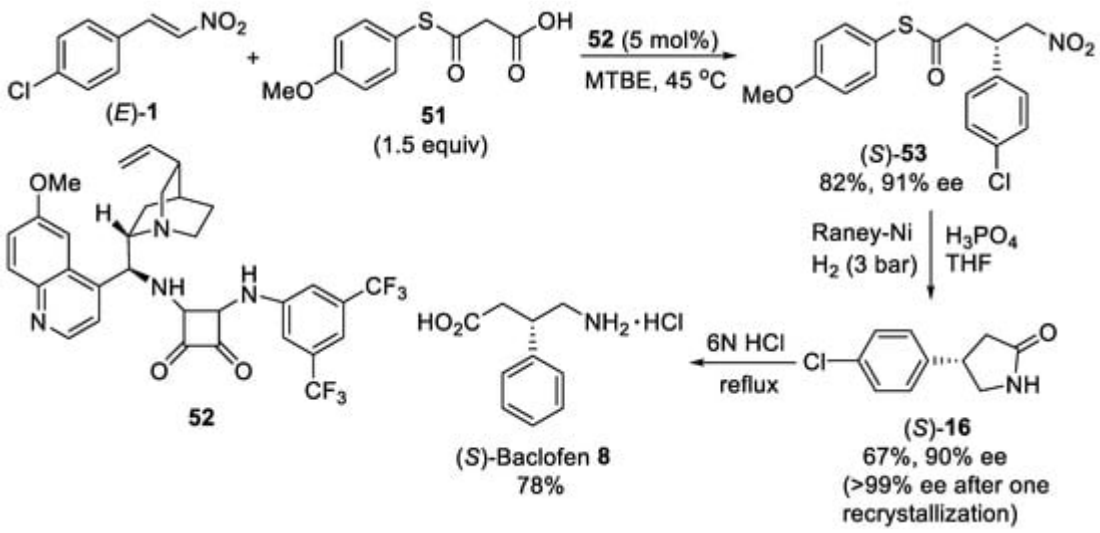
The hydrophobic dihydroquinine-squaramide derivative **44** (Scheme 11B) also demonstrated its efficiency in brine media for enantioselective Michael addition of the diethyl dithiomalonates to (*E*)-α-methyl-β-nitrostyrenes **47** (Scheme 12) [56]. In these cases, a high loading of **44** (15 mol%) and lowering the reaction temperature to 0 °C were required for the reaction to proceed with high enantioselectivities. At the same time, no reaction was observed when catalyst **44** was used in organic solvents. The resulting adducts (*S*)-**48** could further be converted into GABA analogs bearing an all-carbon quaternary stereocenter at the β-position. After the separation of the catalyst, the crude products (*S*)-**48** were subjected to reduction affording γ-lactam thioesters **49**,

which were hydrolyzed with 6N HCl into β-methylated analogs of Phenibut (*S*)-**50a** and Baclofen (*S*)-**50b** as hydrochloride salts. At the same time, the β-methylated analog of Rolipram (*S*)-**50c** was prepared by basic hydrolysis and decarboxylation of corresponding γ-lactam thioester **49**.



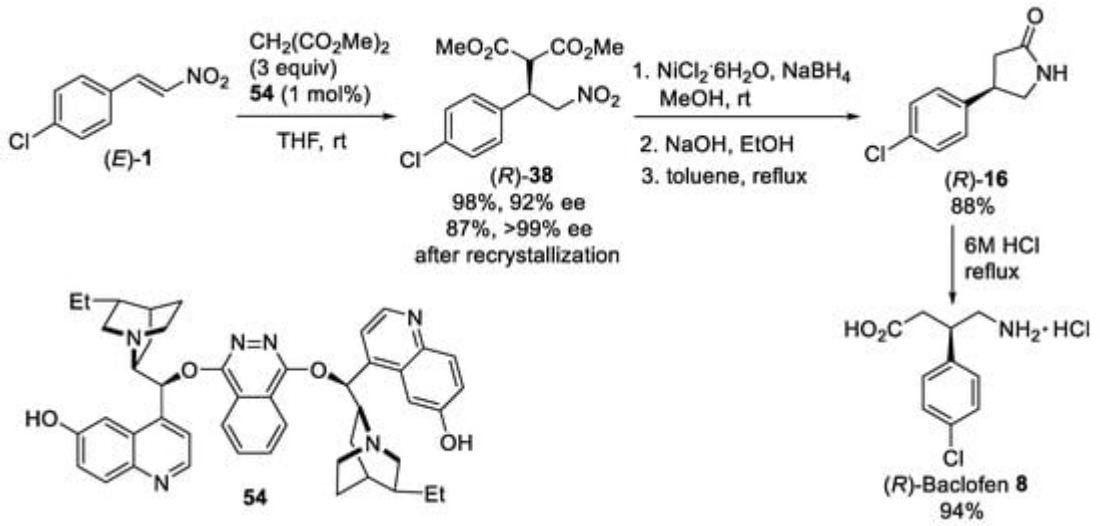

**Scheme 12.** Enantioselective Michael addition reaction of β,β-disubstituted nitroalkenes (*E*)-**47** with dithiomalonate using dihydroquinine-squaramide catalyst.

An enantioselective decarboxylative Michael addition between malonic-acid half-thioester [57] and β-nitroolefins providing access to γ-nitro thioester was demonstrated to catalyze with cinchona-based squaramide [58] and cinchona-based urea [59] organocatalysts under mild reaction conditions. Performing the reaction of malonic-acid half-thioester **51** (Scheme 13) and β-nitrostyrene (*E*)-**1** with loading of 5 mol% of bifunctional quinine-based squaramide **52** as the most active and selective organocatalyst in methyl *tert*-butyl ether (MTBE) at 45 °C resulted in addition product (*S*)-**53** in high yield and excellent enantioselecitivity within 22 h [58]. It is noteworthy that using *E* or *Z* isomers of the starting β-nitrostyrene **1** afforded the (*S*)-enantiomer of the Michael adduct **53** with the same ee value. The nitro thioester (*S*)-**53** was converted with Raney Ni and $H_3PO_4$ in THF by intramolecular cyclization and recrystallization into enantiomerically pure γ-butyrolactam (*S*)-**16**. Finally, hydrolysis of resulting γ-butyrolactam (*S*)-**16** could be performed with 6N HCl under reflux to deliver the (*S*)-Baclofen **8** as its hydrochloride salt in 78% yield.




**Scheme 13.** Enantioselective Michael addition of malonic-acid half-thioester **51** to β-nitrostyrene (*E*)-**1**. Synthesis of (*S*)-baclofen **8**.

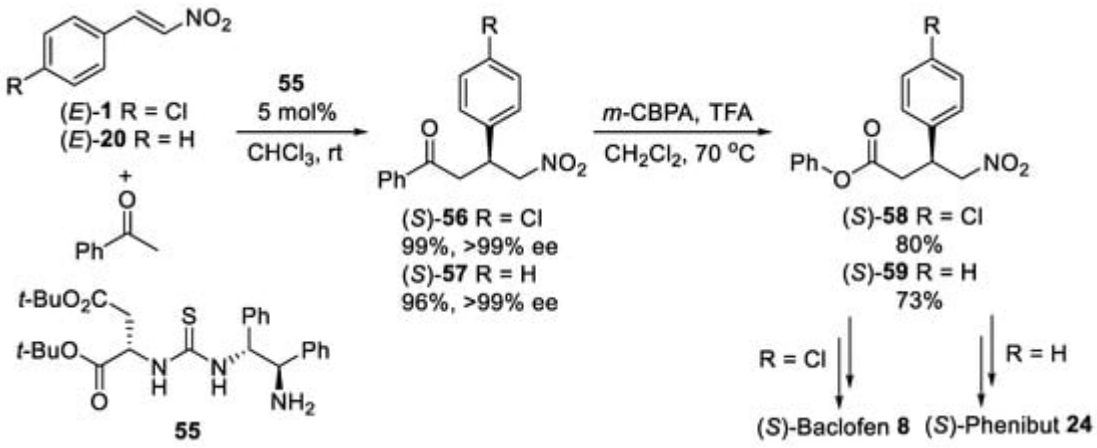
The bifunctional bisalkaloid organocatalyst **54** (Scheme 14) was developed and successfully tested for the enantioselective conjugate addition of malonates to nitroalkenes [60]. The best result in terms of reactivity and selectivity was achieved using dimethyl malonate, 1 mol% of organocatalyst **54** in THF at room temperature. Under optimal conditions, the Michael reaction of dimethyl malonate with β-nitrostyrene (*E*)-**1** proceeded well to give the corresponding adduct (*R*)-**38** with excellent yield and enantioselectivity (after recrystallization). The obtained adduct (*R*)-**38** was converted into (*R*)-Baclofen **8** hydrochloride according to the synthetic sequence demonstrated in Scheme 3.




**Scheme 14.** Asymmetric conjugate addition of dimethyl malonate to β-nitrostyrene (*E*)-**1**. Synthesis of (*R*)-Baclofen **8** hydrochloride.

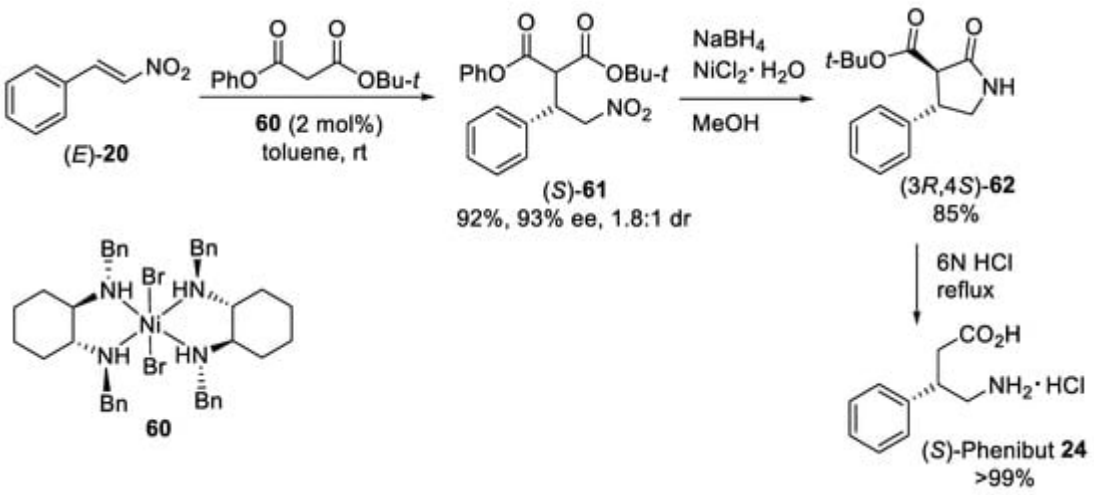
The highly stereoselective (>99% ee) conjugate addition of acetophenone to β-nitrostyrenes (*E*)-**1** and (*E*)-**20** (Scheme 15) was completed using primary amine-thiourea organocatalyst [61] based on (*S*)-di-*tert*-butyl

aspartate. With the optimal organocatalyst **55**, derived from (1*R*,2*R*)-diphenylethylenediamine the Michael addition provided adducts (*S*)-**56** and (*S*)-**57** at low catalyst loading (5 mol%) in excellent yield [62]. After Bayer–Villiger oxidation of (*S*)-**56** and (*S*)-**57**, corresponding γ-nitro esters (*S*)-**58** and (*S*)-**59** could be transformed into the (*S*)-Baclofen **8** and (*S*)-Phenibut **24** according to described above procedures. The enantiomer of **55** was also utilized as organocatalyst for the efficient synthesis of (*R*)-Baclofen **8**.



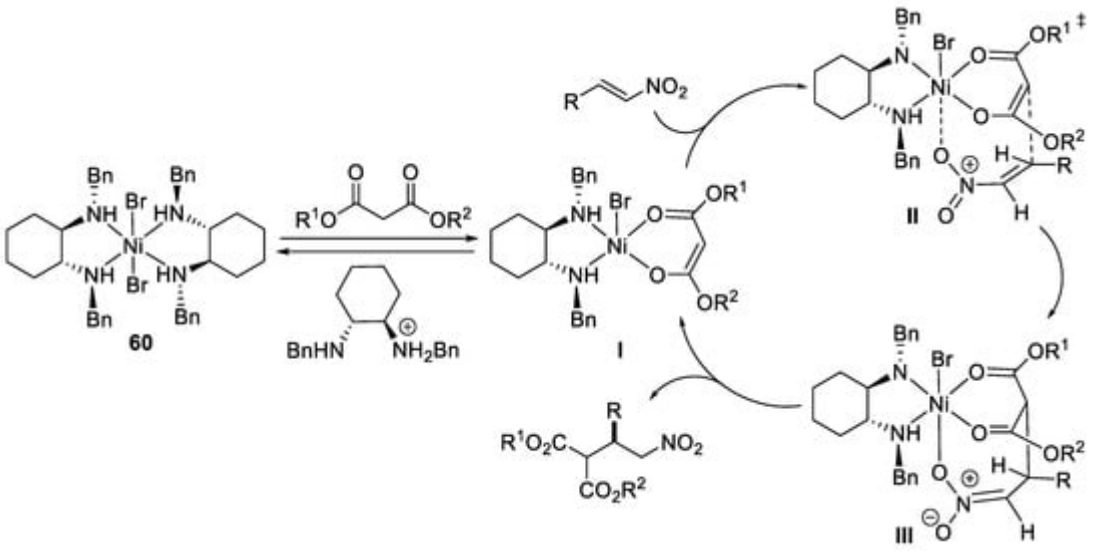

**Scheme 15.** Michael reaction between acetophenone and β-nitrostyrenes using primary amine-thiourea organocatalyst **55**.

Catalytic asymmetric version of the Michael addition reaction between malonates and nitroalkenes was also achieved by using chiral metal−ligand complexes [63][64]. For example, the highly enantioselective Michael addition of *tert*-butyl phenyl malonate to the β-nitrostyrene (*E*)-**20** (Scheme 16) was developed in toluene at room temperature using the easily accessible chiral bis-(cyclohexyldiamine)-based Ni(II) complex **60** (2 mol%) [65]. This process offered a route for the synthesis of β-nitro derivative (*S*)-**61** in 92% yield and 93% ee (1.8:1 diastereoisomeric ratio). Reduction and cyclization of (*S*)-**61** with the more reactive ester group afforded the γ-lactam (3*R*,4*S*)-**62** as one diastereomer. Final hydrolysis and decarboxylation of the γ-lactam (3*R*,4*S*)-**62** with 6N HCl under reflux produced the (*S*)-Phenibut **24** as the hydrochloride salt in quantitative yield. Later, several heterogeneous catalysts incorporating chiral bis(cyclohexyldiamine)-based Ni(II) complexes were developed for the asymmetric Michael addition of malonates to both aromatic [66][67] and aliphatic [68][69][70] nitroalkenes. These catalysts demonstrated good activities, enantioselectivities, reusability, and applicability for the multistep sequential flow synthesis of the (*S*)-Pregabalin [69].




**Scheme 16.** Enantioselective Michael additions of *tert*-butyl phenyl malonate to β-nitrostyrene (*E*)-**20** catalyzed by diamine−Ni(II) complex **60**.

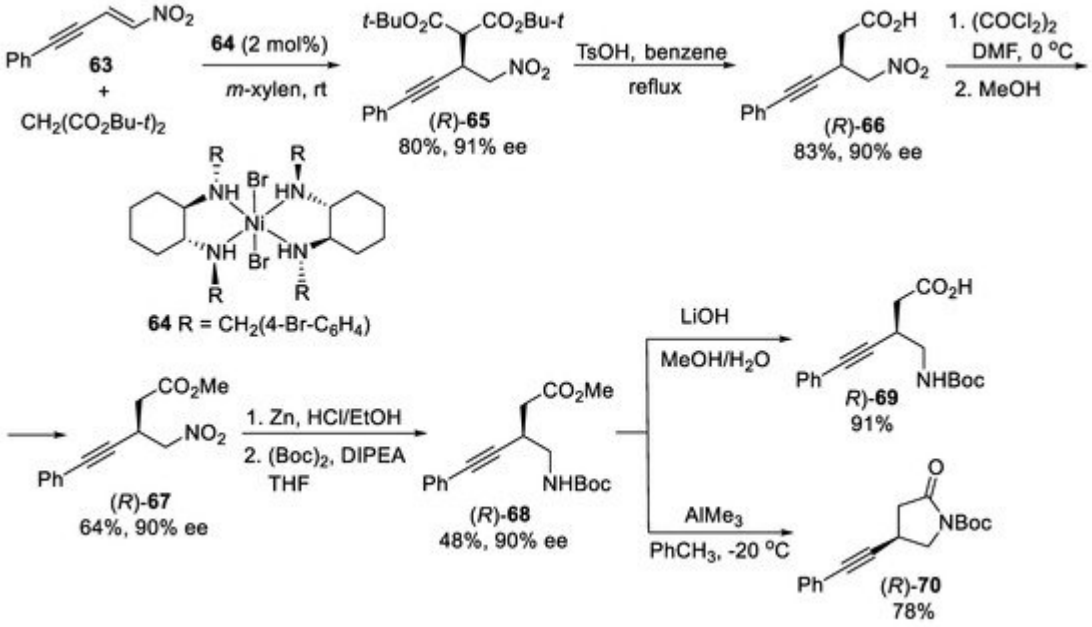
On the basis of mechanistic studies of conjugate addition reactions catalyzed by chiral nickel(II)-diamine complexes is proposed that the malonate displaces one diamine ligand of the catalyst generating the chiral enolate **I** (Scheme 17) [65]. Coordination of the nitroalkene to the nickel center of **I** leads to the intermediate **II**, and subsequent addition of enolate to the bound nitroalkene affords the 1,4-addition intermediate **III**. Then intermolecular proton transfer and displacement of the Michael product with another molecule of the malonate regenerates chiral enolate **I**.




**Scheme 17.** Proposed mechanism reaction.

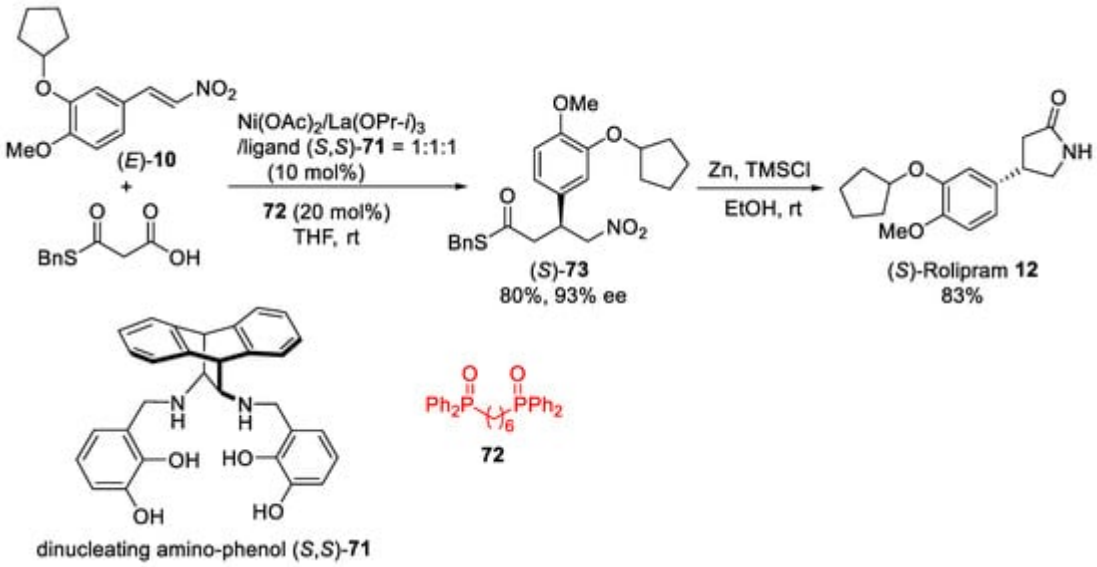
The application of the chiral nickel(II)-diamine catalysts was extended to 1,4-selective asymmetric addition of malonates to nitroenynes [71]. The 1,4-addition of di-*tert*-butyl malonate to nitroenyne **63** (Scheme 18) in the presence of 2 mol% of Ni(II) complex **64** as the catalyst proceeded regioselectively under mild conditions, affording β-alkynyl nitro acid (*R*)-**65** in good yield and high enantioselectivity (91% ee). Enantiomerical purity of product

(*R*)-**65** could be improved to 99% ee by single recrystallization. This protocol allowed to obtain β-alkynyl acid (*R*)-**66** after decarboxylation of (*R*)-**65** in the presence of TsOH under reflux. Reaction of β-alkynyl acid (*R*)-**66** with oxalyl chloride and MeOH gave β-alkynyl ester (*R*)-**67** in 64% yield, which by reduction of the nitro group followed by the treatment with di-t*ert*-butyl dicarbonate $(Boc)_2O$ afforded the *N*-Boc β-alkynyl-γ-amino ester (*R*)-**68**. The ester (*R*)-**68**, as the common intermediate, was converted to the β-alkynyl-γ-amino acid (*R*)-**69** and β-alkyny-γ-lactam (*R*)-**70** using standard procedures without loss of enantiomeric purity.




**Scheme 18.** Asymmetric synthesis of β-alkynyl-γ-amino acid (*R*)-**69** and β-alkyny-γ-lactam (*R*)-**70**.

The catalytic asymmetric decarboxylative 1,4-addition reaction of malonic-acid half-thioester to nitroalkene (*E*)-**10** (Scheme 19) was realized by employing heterobimetallic system [72] with transition metal, rare-earth metal, and dinucleating amino-phenol ligand (*S*,*S*)-71. Screening of the transition metal and rare-earth metal combination revealed that Ni/La/ligand (*S*,*S*)-**71** catalyst in the presence of phosphine oxide **72** as an achiral additive gave the best catalytic activity and selectivity delivering the addition product (*S*)-**73** in 80% yield and 93% ee [73]. The synthetic utility of the asymmetric decarboxylative 1,4-addition reaction was demonstrated by the reduction and cyclization of (*S*)-**73** with Zn and $(CH_3)_3SiCl$ to (*S*)-Rolipram **12** in 83% yield.




**Scheme 19.** Ni–La system for decarboxylative 1,4-addition of malonic-acid half-thioester to nitroalkene (*E*)-**10**.

Additionally, asymmetric 1,4-addition of dimethyl malonate to β-nitrostyrene (*E*)-**1** catalyzed by polymer-supported $CaCl_2$-pyridinebisoxazoline (Pybox) complex [74] was developed and implemented in continuous-flow synthesis of (*S*)-Baclofen precursor (3*R*,4*S*)-**74** using a series of different heterogeneous catalysts (**Figure 2**) [75]. In the first step, amine-modified silica gel/molecular sieves 4Å column reactor was used for condensation of *p*-chlorobenzaldehyde and nitromethane into β-nitrostyrene (*E*)-**1** in toluene. Then sequential-flow enantioselective asymmetric 1,4-addition of dimethyl malonate to β-nitrostyrene (*E*)-**1** proceeded into the second column reactor with polymer-supported $CaCl_2$-Pybox chiral catalyst to give adduct (*S*)-**38** with high enantioselectivity (92% ee). Further, the third column reactor containing dimethylpolysilane (DMPS)-modified Pt catalyst supported on activated carbon (AC) and calcium phosphate (CP) was successfully employed for flow chemoselective hydrogenation and intramolecular cyclization of adduct (*S*)-**38** to give 5 g of lactam (3*R*,4*S*)-**73** in 93–96% overall yield based on nitromethane with 92% *ee* during the 69-h process. Finally, (*S*)-Baclofen **8** was obtained according to the standard procedure. Slightly modifying the continuous flow system using polymer-supported $CaCl_2$-Pybox chiral catalyst was also employed in the synthesis of (*R*)-Phenibut [76] and (*R*)-Rolipram [77]. However, the polymer-supported $CaCl_2$-Pybox chiral catalyst demonstrated poor enantioselectivities in reactions of nitroolefins bearing primary aliphatic substituents.

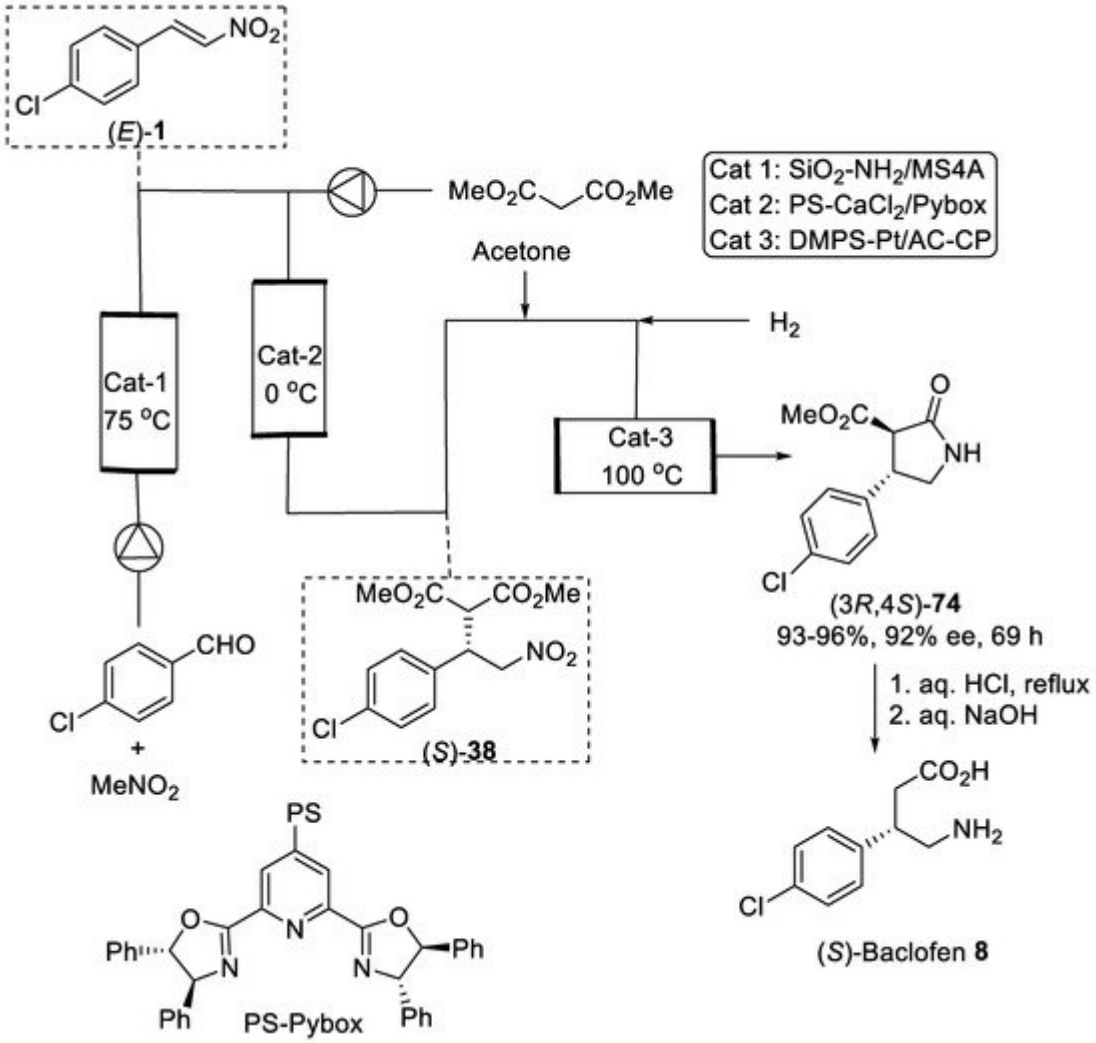
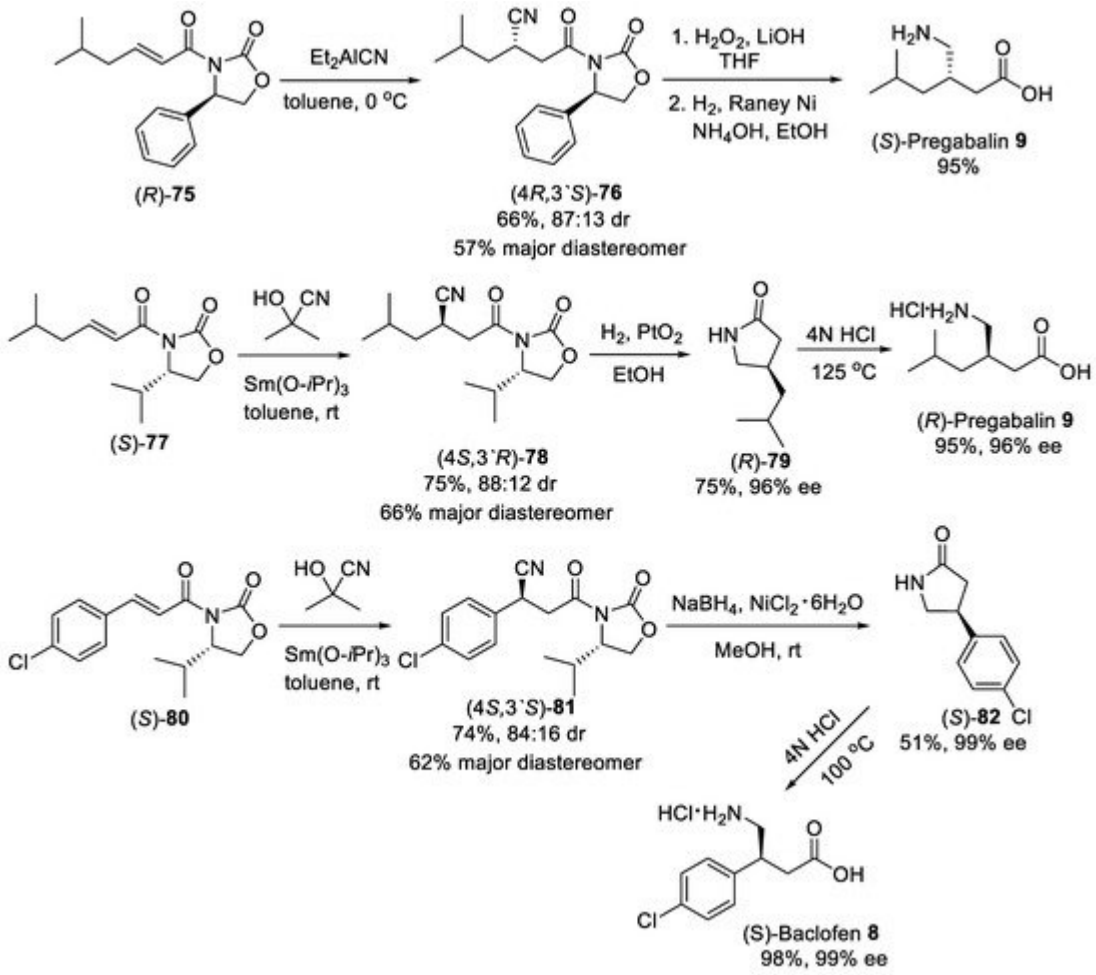



**Figure 2.** Sequential flow synthesis of Baclofen precursor (3*R*,4*S*)-**74**.

## 3. Michael Additions of Cyanide or Nitroalkanes to α,β-Unsaturated Carbonyl Compounds

Asymmetric conjugate addition of cyanide and nitroalkanes to α,β-unsaturated carbonyl substrates was another practical route for the synthesis of β-substituted GABA derivatives. For example, the Michael addition of diethylaluminum cyanide to substrate (*R*)-**75** (Scheme 20) bearing oxazolidinone chiral auxiliary [78] was conducted as the key step in the synthesis of (*S*)-Pregabalin **9** from commercially available starting materials [79]. Conjugate addition was performed in toluene at 0 °C to produce addition adduct (4*R*,3′*S*)-**76** in satisfactory yield and moderate dr (87:13). The diastereomerically pure (4*R*,3′*S*)-**76** was provided after purification with column chromatography on silica gel in a 57% yield. The observed stereoselectivity was attributed to the approach of the diethylaluminum cyanide mainly from the less hindered *Si* face opposite to phenyl group in the oxazolidinone auxiliary. The removal of oxazolidinone chiral auxiliary by treating with LiOH and $H_2O_2$ in aqueous THF and reduction of the cyano group by hydrogenolysis under Raney Ni afforded (*S*)-pregabalin **9** in 95% yield for two steps. Moreover, acetone cyanohydrin was also effectively used as cyanide source for diastereoselective conjugate

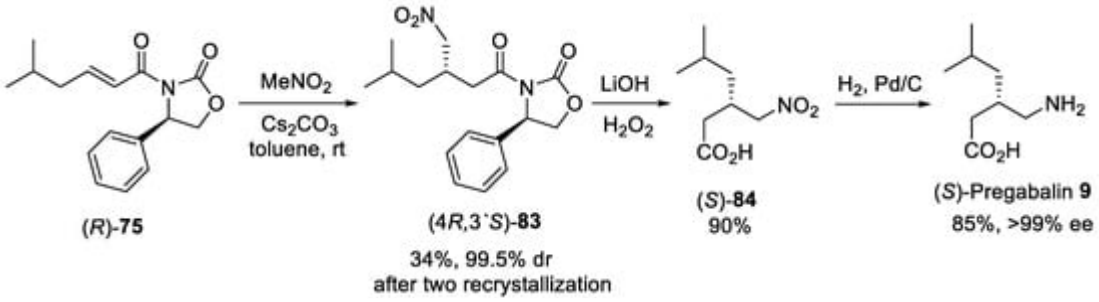
addition to α,β-unsaturated oxazolidinone (*S*)-**77** (Scheme 20) [80]. The hydrocyanation of (*S*)-**77** cleanly proceeded with two equivalents of acetone cyanohydrin and 10 mol% of Sm(III) isopropoxide as catalyst in toluene to give the addition adduct (4*S*,3′*R*)-**78** in 75% yield and 88:12 dr. The diastereomerically pure product (4*S*,3′*R*)-**78** was chromatographically isolated in 66% yield. The catalytic hydrogenation of the cyano group with simultaneous cleavage of oxazolidinone chiral auxiliary over platinum oxide afforded the lactam (*R*)-**79** in 75% yield and 96% ee, which acidic hydrolysis led to the (*R*)-Pregabalin **9** as hydrochloride in 95% yield with retention of the enantiomeric purity. A similar route was employed for the synthesis of (*S*)-Baclofen **8** using aryl-substituted substrate (*S*)-**80**, acetone cyanohydrin and Sm(O*i*-Pr)$_3$ as catalyst (Scheme 20) [80]. Under standard conditions, the diastereomerically pure nitrile adduct (4*S*,3′*S*)-**81** was obtained in 62% yield. Selective reduction of the cyano group with such reagents as $NaBH_4$ and $NiCl_2$ and hydrolysis of resulting lactam (S)-**82** provided (*S*)-Baclofen **8** in excellent yield and enantiomeric purity.




**Scheme 20.** Diastereoselective Michael addition of cyanide to α,β-unsaturated oxazolidinones.

Similarly, oxazolidinone as a chiral auxiliary was used to generate a new stereogenic center in the Michael addition between nitromethane and α,β-unsaturated oxazolidinone ®-**75** with $Cs_2CO_3$ as a base providing a diastereomerically pure addition adduct (4*R*,3′*S*)-**83** in 34% yield after two recrystallizations from isopropanol (Scheme 21) [81]. The oxazolidinone chiral auxiliary was removed by treating (4*R*,3′*S*)-**83** with alkaline hydrogen

peroxide to give the γ-nitroacid (*S*)-**84**. (*S*)-Pregabalin **9** was obtained after hydrogenation of γ-nitroacid (*S*)-**84** using Pd/C in 26% overall yield for three steps from ®-**75** with >99% ee.




**Scheme 21.** Preparation of (*S*)-Pregabalin **9**.

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