Thiourea catalysts for synthesis of Active Pharmaceutical Ingredients

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Abstract

Thiourea is an important building block found in several drug molecules such as thioacetazone, enzalutamide, thiocarlide etc. Thiourea derivatives have been used for activation of carbonyl and imine compounds to facilitate Michael addition reactions, and as an oxyanion stabilizer for [Ir] catalyzed amination of alcohols without using any base or acid. Chiral bifunctional thiourea catalysts have been successfully applied for asymmetric synthesis of several drug molecules.

Keywords: Thiourea, Sitagliptin, Zanamavir, Laninamivir, Baclofen.

1. Introduction:

Thiourea was synthesized by the Polish chemist Marceli Nencki in the year 1873, as the first urea analogue.[1] Thiourea moiety is present in a variety of drugs and bioactive such as anti-viral, anti-convulsant, anti-inflammatory, antimicrobial and anti-tumor effects (Scheme 1).[2]

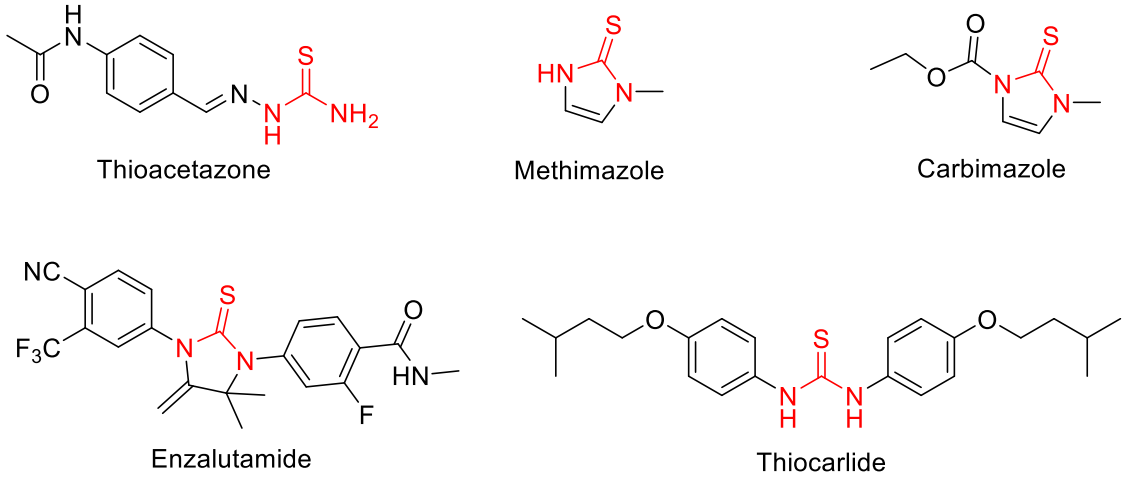


Figure 1. Thiourea containing drug molecules.

Thiourea catalysts act as hydrogen bond donor catalysts and activate electrophiles such as carbonyl compounds, imines, nitro functional group to react with nucleophiles.[3a] Schreiner reported *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea as a hydrogen bond donor catalyst, which has been widely used for several nucleophilic addition and other reactions.[3b] Loh and co-workers has reported thiourea as a Brønsted acid for glycosylation reaction.[4] Thiourea can also act as a Lewis base for oxidation of alcohols as described by Mukherjee and co-workers.[5] Schreiner,[6] Kass[7] proved that the oxyanion stabilization by thiourea as double hydrogen bond donor for addition of alcohols to tetrahydropyran is feasible, and thioureas can also catalyse acetalization of carbonyl compounds by oxyanion stabilization.[8] Many bifunctional thioureas such as Takemoto,[9(a-d)] Jacobsen, and other heterocyclic containing thiourea catalysts have been synthesized, which utilize both hydrogen bonding interactions and enamine formation.[9(e-f)]

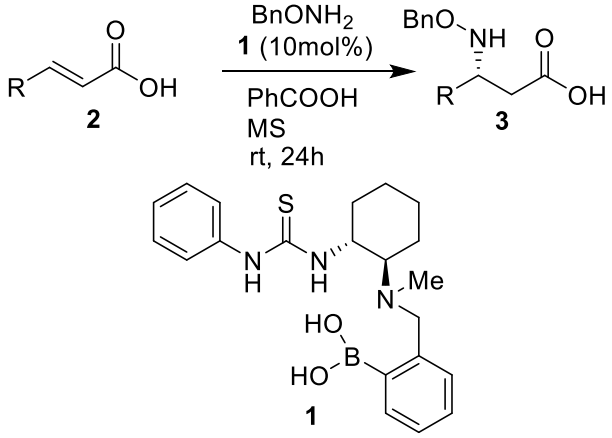
The pharmaceutical industries are keen to develop green processes for the synthesis of heterocyclic compounds and active pharmaceutical ingredients (API).[10] They are spending on research and development for generating environment friendly process and eliminating hazardous chemicals. and Thiourea catalysts have been utilised by chmists for green synthesis of heterocyclic compounds.[11,12]

2. Applications of thiourea catalysts for synthesis of Active Pharmaceutical Ingredients (API).

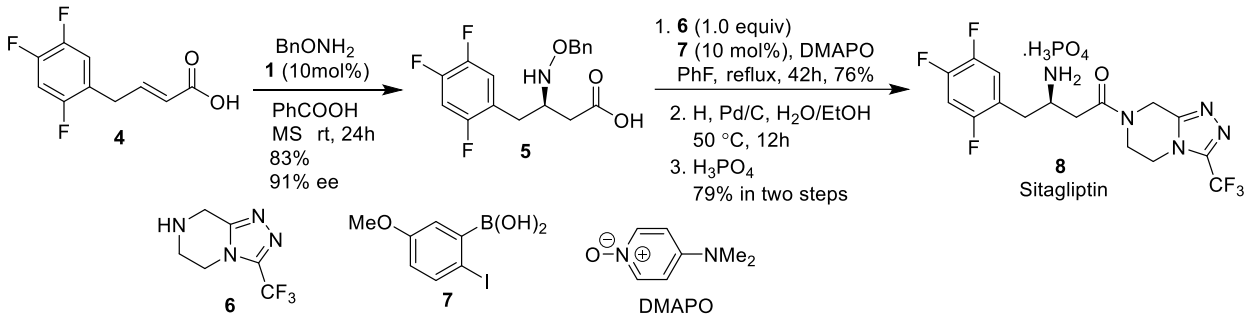
2.1. Asymmetric Aza-Michael Addition: synthesis of sitagliptin[13]

Aza-Michael addition reaction is a classical method for synthesizing β-amino acids. Takemoto and co-workers explored the possibility of intermolecular aza-Michael addition of benzylhydroxylamine to carboxylic acids **2** using the hybrid thiourea catalyst **1**. The reaction was carried out in carbon tetrachloride in the presence of a 10 mol% catalyst and 4 Å molecular sieves (MS). The chiral thiourea hybrid catalyst also contains a boronic acid moiety. The 4 Å MS facilitated the catalytic reaction efficiently. The methodology was successfully applied for the formal asymmetric synthesis of sitagliptin (antidiabetic drug). Sitagliptin synthesis was accomplished in four steps, starting from the α,β-unsaturated carboxylic acid **4** without using any chiral auxiliary or protecting groups (Scheme 2). The thiourea catalyzed reaction provided the β-amino acid in 83% yield and good enantioselectivity (91%ee). Then it was coupled with amine 6,

followed by deprotection of -OBn group by hydrogenation. Finally, the phosphoric acid salt was made to get the desired sitagliptin (**8**).



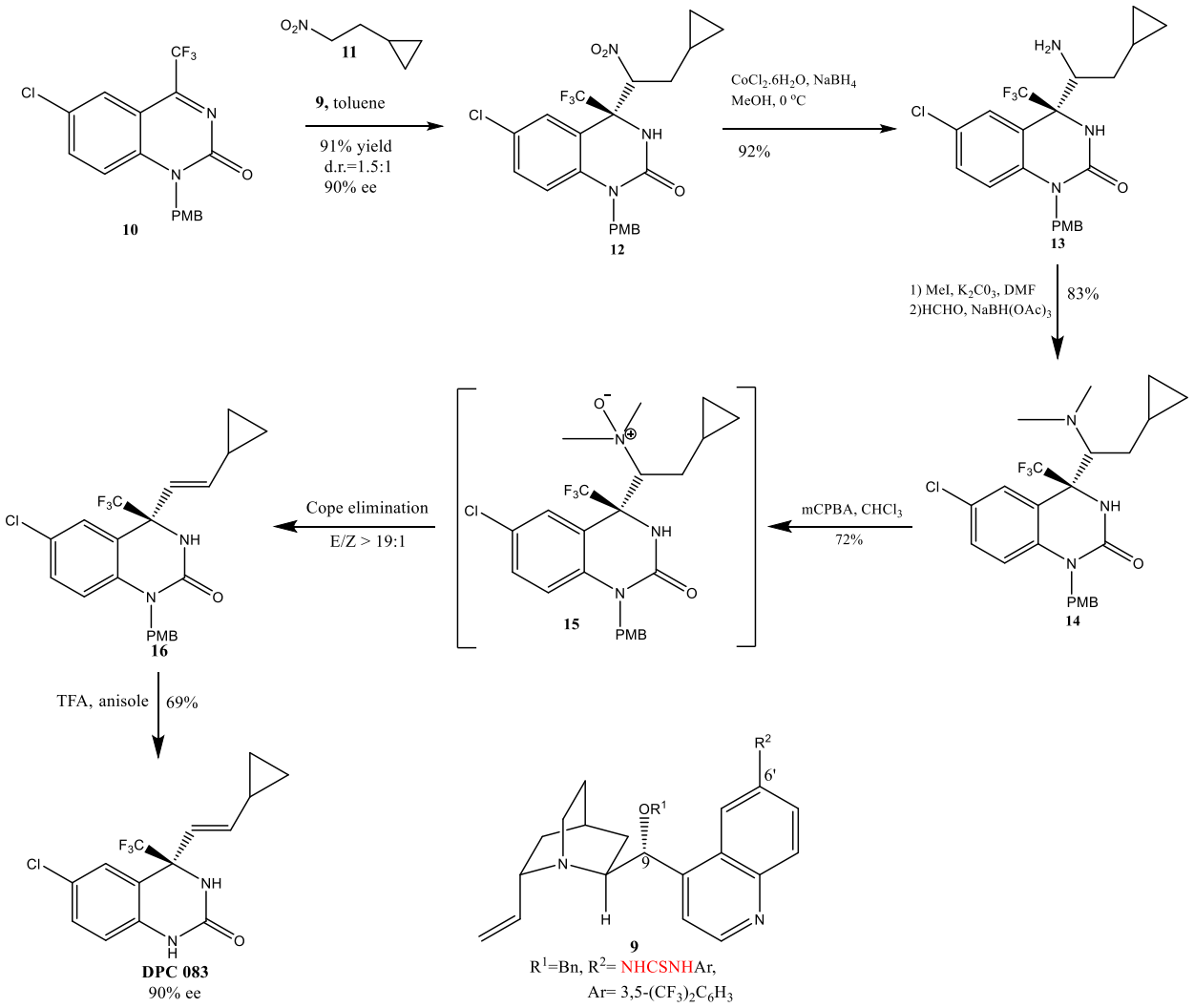
Scheme 1. Thiourea catalyzed asymmetric Michael addition reaction.



Scheme 2. Synthesis of Sitagliptin catalyzed by chiral thiourea catalyst.

2.2.Enantioselective Aza-Henry Reaction: Synthesis of Anti-HIV Drug DPC 083[14]

Dihydroquinazolinones, are an important class of heterocyclic compounds which possess broad biological activities such as antiviral, antiobesity, used for the treatment of cardiovascular diseases, inflammation and pain. A drug candidate called DPC 083 developed by Dupont, bearing a dihydroquinazolinone ring along with a chiral trifluoromethyl moiety is a potent inhibitor of HIV-1 nonnucleoside reverse transcriptase.



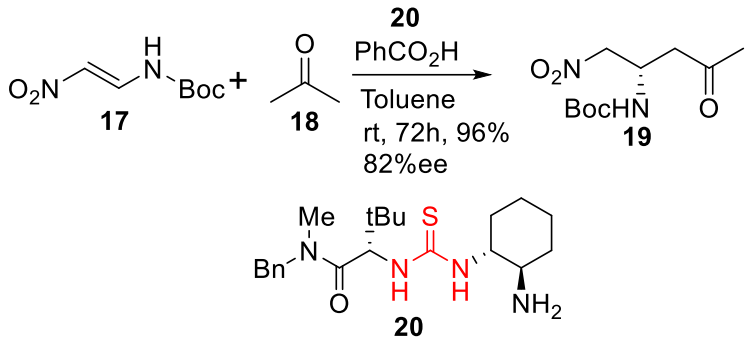
Scheme 3. Generation of quaternary chiral carbon centre and synthesis of DPC 083.

Wang and co-workers[14] developed chorial thiourea **9**-catalyzed aza-Henry reaction for the synthesis of trifluoromethylquinazolin-2(1H)-ones in high yields and good to excellent enantioselectivities. A variety of the nitroalkanes 2 were also investigated. This asymmetric aza-Henry reaction was applied for the synthesis of anti-HIV drug DCP 083 (Scheme 3). The thiourea-catalyzed aza-Henry reaction between dihydroquinazolinone **10** and nitrocyclopropylalkane **11** generated quaternary stereogenic center in 91% yield, with diastereomeric ration 1.5:1 and 90% enantiomeric excess. The diastereomers were easily separated by silica gel column chromatography. The synthesis of target molecule DPC 083 was accomplished in five steps. Reduction of the nitro group in compound **12** in presence of $CoCl_2 \cdot 6H2O$ and $NaBH_4$ in MeOH

produced amine compound **13** in 92% yield. N-dimethylation of the amino group using excess of iodomethane (>3 equiv) resulted in a mixture of mono- and bisproducts. Hence, monomethylation with MeI in the presence of K_2CO_3 and followed by bismethylation by reductive amination with formaldehyde and $NaBH(OAc)_3$ generated compound **14** in 83% yield. N-oxide and spontaneous Cope elimination reactions afforded olefin compound **16** in 72% over the two steps (E/Z> 19:1). Finally, the deprotection of the PMB group was performed by treating with TFA in the presence of anisole to provide the target DPC 083 in 69% and no racemization of the quaternary stereogenic center was observed as analysed by chiral HPLC.

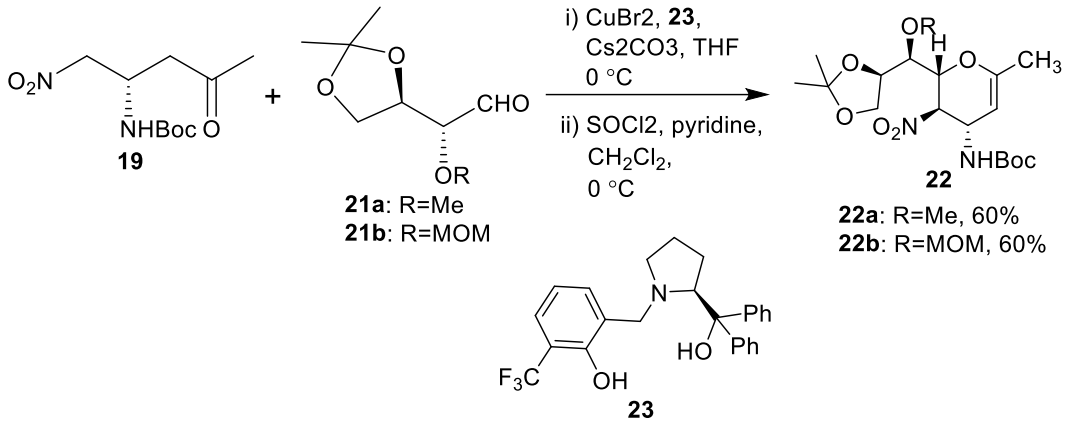
2.3. Michael addition of acetone with tert-butyl (2-nitrovinyl)carbamate[15]

Zanamivir, laninamivir, and CS-8958 are neuraminidase inhibitors used for treatment of influenza virus infection. Ma and co-workers[15] studied asymmteric Michael addition reaction of acetone with less reactive tert-butyl (2-nitrovinyl)carbamate **17** (Scheme 4). Use of chiral bifunctional primary amine–thiourea catalyst **20** (20 mol%) for give rise to desired Michael addition product **19** in 96% yield with 82%ee. The reduction of catalyst to 5 mol% did not reduce enantioselectivity, but yield was reduced to 82%.



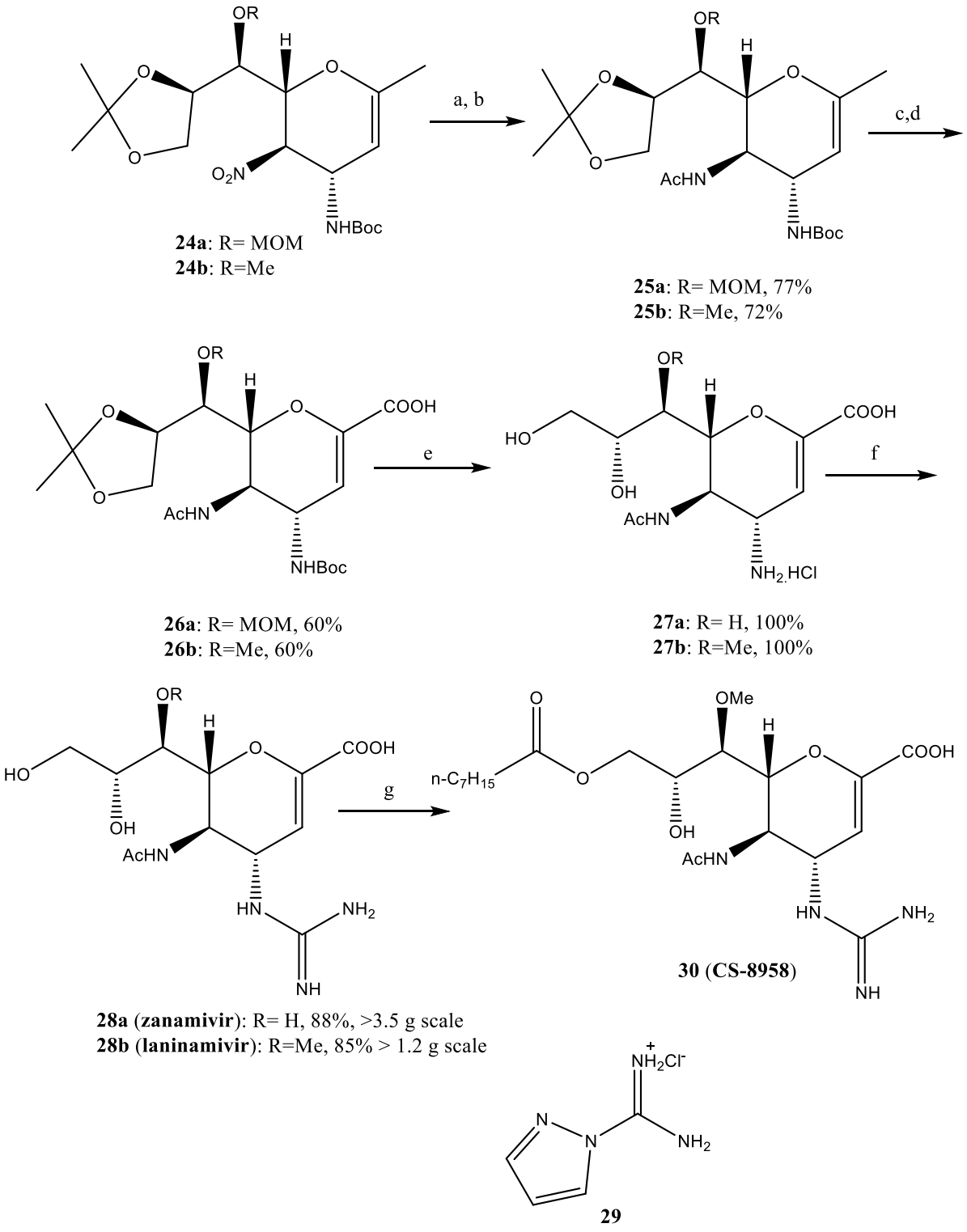
Scheme 4. Thiourea-catalyzed asymmetric Michael addition reaction of acetone with nitro vinyl compound.

The core moiety of zanamavir and laninamivir **22** was synthesized by asymmetric Henry reaction using chiral proline catalyst **22**.



Scheme 5. Chiral synthesis of zanamavir and laninamivir core moiety.

Reduction of nitro group in presence of Zn and followed by acetylation provided desired compound **25a** in 77% yield and **25b** in 72% yield. Oxidation of methyl group with SeO2 and further oxidation with sodium chlorite produced acid compounds **26a** and **26b** in 60% yield. Deprotection of amine (Boc protection) by treating with HCl provided free amine compound **27a** and **27b** in 100% yield. Reaction of amine compound **27a** and **27b** with **29** generated zanamivir (**28a**) in 88% yield and laninamivir (**28b**) in 85% yield. The esterification of **28b** with n-$C_7H_{15}C(OMe)_3$ in methanolic HCl gave CS-8958 (**30**) in 92% yield.



24a: R= MOM
24b: R=Me

25a: R= MOM, 77%
25b: R=Me, 72%

26a: R= MOM, 60%
26b: R=Me, 60%

27a: R= H, 100%
27b: R=Me, 100%

28a (**zanamivir**): R= H, 88%, >3.5 g scale
28b (**laninamivir**): R=Me, 85% > 1.2 g scale

30 (**CS-8958**)

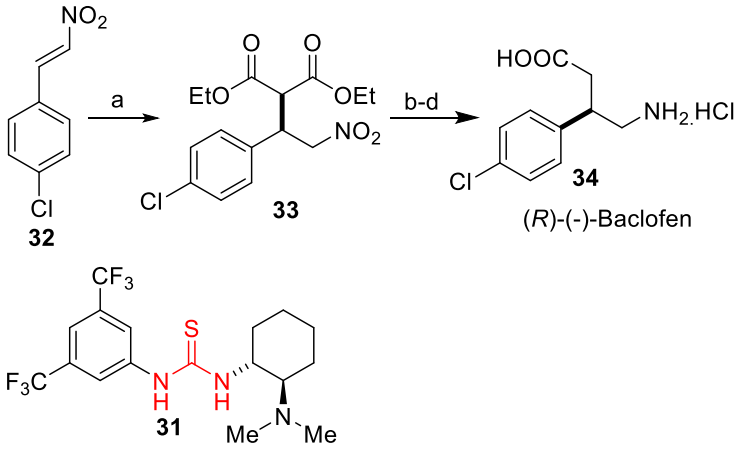
29

Scheme 6. Synthesis of zanamavir and laninamivir. Reagents and conditions: a) Zn, HOAc; b) AcCl, Et3N; c) SeO2, pyridine, 4A molecular sieves, dioxane/THF; d) $NaClO_2$, NaH_2PO_4,

2-methylbutene, ^{t}BuOH/THF/H2O; e) HCl, THF; f) **29**, DIPEA, DMF, 50 ◦C; g) n-$C_7H_{15}C(OMe)_3$, HCl, MeOH,92%.

2.4. Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to Nitroolefins[16]

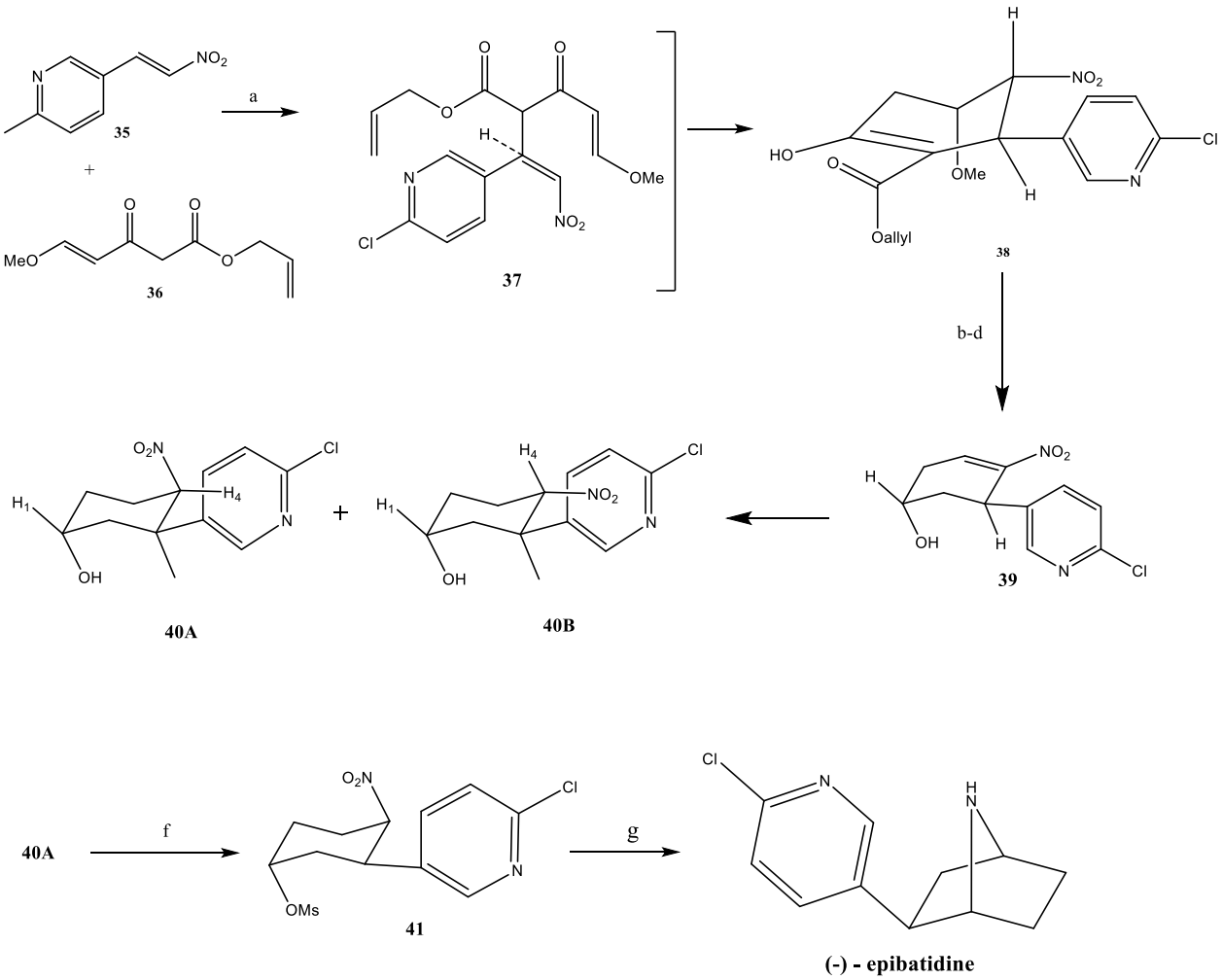
The Michael addition reaction of β-nitrostyrene compound **32** with diethyl malonate in toluene and 10 mol% of Takemoto chiral thiourea catalyst **31** (Scheme 7) gave the compound **33** in 80% yield and 99% ee. Both rigidity of the chiral diamine scaffold and cooperative function of two N–H bonds and the tertiary amino group in the catalyst were critical for the enantioselectivity reaction. Reduction of nitro group of compound 33 in presence of $NiCl_2$, $NaBH_4$; hydrolysis of ester in basic medium and finally decarboxylation of one carboxylic group in acidic medium generated baclofen. Baclofen is a derivative of GABA (γ-aminobutylic acid), and prescribed as an antispastic agent in racemic form.



Scheme 7. Synthesis of (-)-Baclofen. Reagents and Conditions: (a) Diethyl malonate, **31**, toluene, rt, 24h, 80% (>99% ee after single recrystallization from hexane/AcOEt); (b) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, rt, 7.5h, 94%; (c) NaOH, EtOH, rt, 45 h; then toluene, reflux, 6.5h, 84%; (d) 6N HCl, reflux, 24 h, 94%.

(−)-Epibatidine is a potent nicotinic acetylcholine receptor agonist. The reaction of γ,δ-unsaturated β-ketoester **36** with nitroalkene **35** in presence of chiral thiourea catalyst **31** gave 3,4-anti-4,5-syn cycloadduct **38** (Scheme 8) via Michael adduct intermediate **37** with excellent diastereoselectivity and moderate enantioselectivity (75%ee). This is the first reported asymmetric synthesis of three contiguous stereogenic centers by the tandem Michael addition

reaction with nitroalkenes. Then, the total synthesis of (−)-epibatidine was accomplished in six steps from the Michael adduct 36 (Scheme 8).



Scheme 8. Synthesis of (−)-epibatidine. Reagents and Conditions: **31**, toluene, 0 ◦C; KOH, EtOH, 0 ◦C ,77% (75% ee); (b) $Pd(OAc)_2$, PPh_3, HCOOH, Et_3N, THF, rt, 99%; (c) L-Selectride, THF, -78 ◦C, 71%; (d) NaOMe, ^tBuOH, 71%; (e) $NaBH_3CN$, AcOH, MeOH, -20 ◦C, 87% (**40A**/**40B** = 9/1); (f) MsCl, ET_3N, DMAP, CH_2Cl_2, 0 ◦C, 91%; (g) Zn, AcOH, THF, rt, $CHCl_3$, 60 ◦C, 85%.

2.5. **Michael-Michael Addition Reactions Promoted by Secondary Amine-Thiourea: stereocontrolled Construction of Barbiturate-Fused Tetrahydropyrano compounds**[17]

The barbituric acid scaffold is an important class of building block found in the pharmaceutical products. Drug molecules containing barbuturic acid moiety are widely used for treatment of many

diseases. Those are applied as sedative, anaesthetic, anxiolytic, anticonvulsant, analeptic, anticancer and anti-HIV treatments.[18] The tetrahydropyrano scaffold is a structural motif which attracts intensive attention.[19] Thus, as a combination of these two scaffolds, barbiturate-fused tetrahydropyrano compounds have a great importance for several biological activities, such as antimicrobial,[20] antiproliferative,[21] and antituberculosis activities (Fig.).[22]

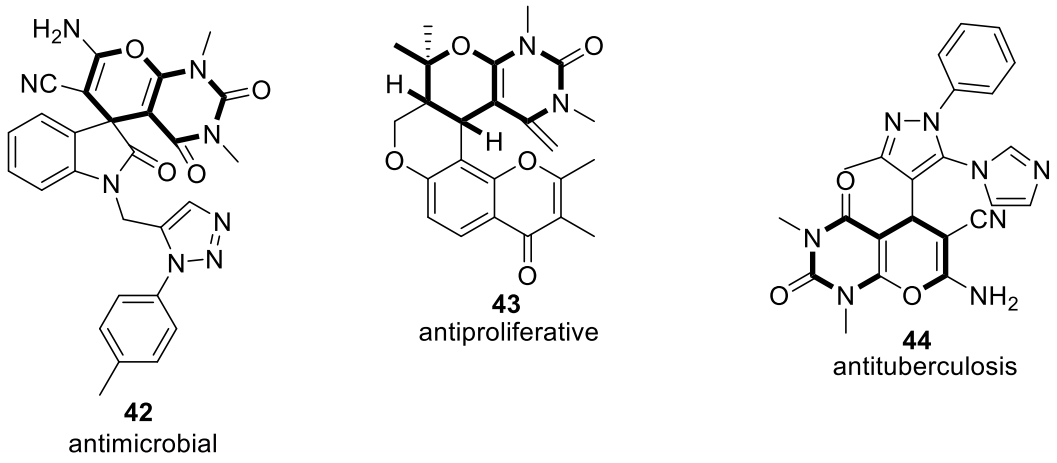
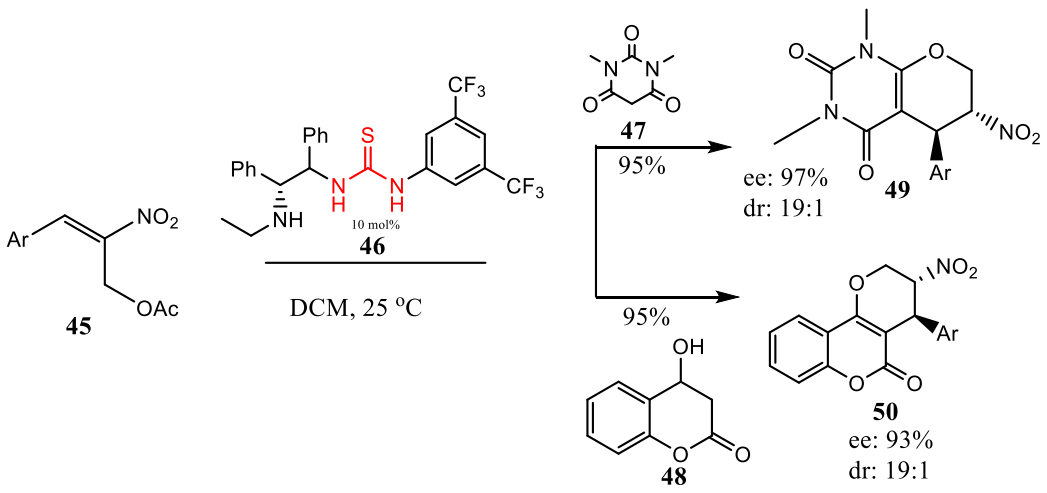


Figure 2. Drug molecules containing barbiturate-fused tetrahydropyrano moiety.

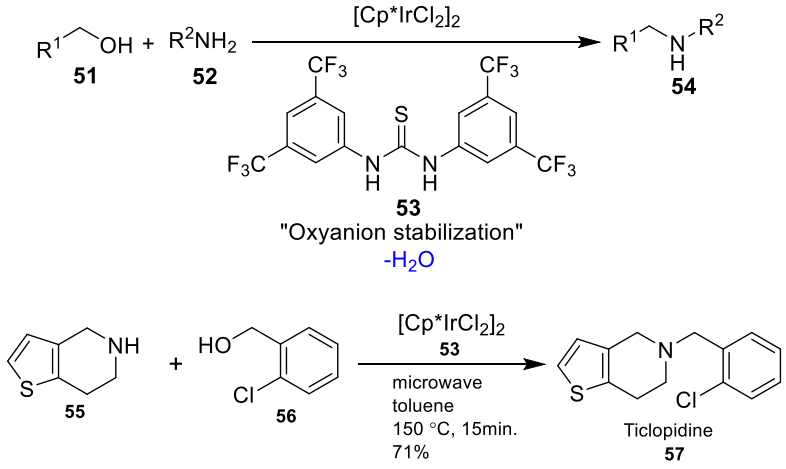
Bifunctional secondary amine-thiourea organocatalyst **46** was applied for asymmetric catalysis in the chiral synthesis of barbiturate-fused tetrahydropyrano moieties **49** and **50**. The catalyst **46** possessed excellent catalytic activity in the domino Michael-Michael reaction between N, N'-dimethylbarbituric acid **48** and Morita-Baylis-Hillman acetates of nitroalkenes to get pharmaceuticals in good yields with excellent enantioselectivities (97% ee), as described in Scheme 9. This catalytic reaction could also be applied to prepare active pyranocoumarin compounds.



Scheme 9. Thiourea catalyzed asymmetric synthesis of barbiturate-fused tetrahydropyrano moieties.

2.6. Thiourea as oxyanion stabilizer for amination of alcohols: Synthesis of cardiovascular drug ticlopidine[22]

Schreiner's thiourea can as an oxyanion stabilizer and facilitate [Ir] catalyzed amination of alcohols **51** without any base or strong acid (Scheme 10). Our laboratory has developed $[Cp^*IrCl_2]_2$ and thiourea catalyzed amination of alcohol in 60-82% yield. The method was successfully applied for the applied for the synthesis of cardiovascular drug ticlopidine in 71% yield (Scheme 10). This a green process for synthesis of ticlopidine, as H2O is the by product of the reaction.



Scheme 10. Synthesis of ticlopidine catalyzed by thiourea.

3. Conclusions

Thiourea was first applied by Schriener for activation of carbonyl, imine for Michael addition reaction. Jacobsen, Takemoto and other chemists developed several chiral thiourea catalysts, which were applied for asymmetric synthesis of several drug molecules. These thiourea catalysts were used for synthesis of sitagliptin, baclofen, zanamivir, laninamivir, ticlopidine etc.

Acknowledgements

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