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Asymmetric Synthesis of Substituted NH-Piperidines from Chiral Amines

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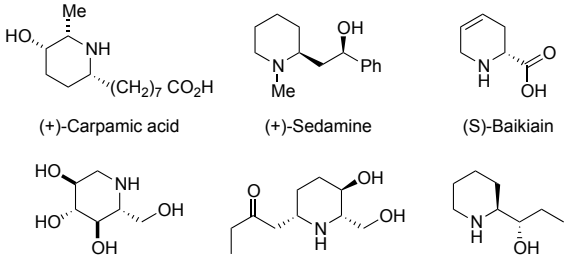
Previously, we reported an efficient asymmetric synthesis of substituted piperidines through exocyclic chirality induced nitroalkene/amine/enone (NAE) condensation reaction. Effective protecting group strategy was developed herein to achieve enantiopure piperidines (yields up to 92%) with complete chirality retention (ee > 95%). Simple derivatization of the obtained piperidines gave thiourea catalysts, indicating the strong potential of this method in producing new amine-based dual functional organocatalyst for future development.

Polysubstituted piperidines and its derivatives are important compounds in biological and medicinal research.[1] Currently, over 12,000 piperidines have been used in clinical trials or preclinical studies.[2] Several biologically and medicinally active piperidines are shown in **Scheme 1**.[3] As a result, new approaches that provide the stereoselective synthesis of chiral piperidines have been an important area in organic chemistry during the last decades.[4]

Scheme 1. Biologically active substituted piperidines.



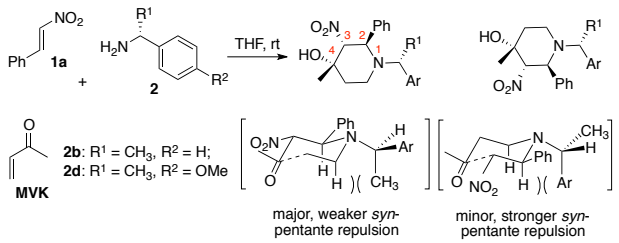
According to the chemical literature, asymmetric syntheses of piperidine derivatives revolve around the following four strategies:[5] (A) intramolecular S_N2 displacement of an amine to a precursor containing a leaving group;[6] (B) reduction or addition to pyridine/piperidine derivatives;[7] (C) ring expansion of prolinols,[8] and; (D) ring closing-metathesis (RCM).[9] Although considerable effort has been devoted to the preparation of these heterocycles, efficient, short, direct, multi-substituted and diversity-oriented asymmetric piperidine syntheses are rare and highly desirable.

We have previously demonstrated the step efficient diastereoselective synthesis of highly substituted piperidines.[10] Herein we extend this to an asymmetric method that provides N-H piperidines (>95% ee) when followed by a new mild deprotection method. The key improvement was the use a commercially available chiral amine auxiliary that could also be readily cleaved under the mild conditions of trifluoroacetic acid (TFA). This approach is delineated here, and afforded the highly enantioenriched NH-piperidines with good to excellent yield and diastereocontrol.

During the last four years, our group has been working on amine addition to the nitroalkene as a new reaction mode to facilitate complex hetereocycle synthesis in a multi-component fashion under mild conditions. The stereochemical outcome can be controlled by the exocyclic stereogenic center. Thus, using amino acids as the amine nucleophile, the N-substituted piperidines were prepared in modest to good yields (50% to 85%) and decent stereoselectivity of 3:1 to 4:1 dr. One major limitation to this strategy is how to prepare the NH-piperidine, which will be more attractive in general. To further extend this strategy for the synthesis of enantio-enriched NH-piperidines, we initiated the investigation of various chiral amines and examined the N-substitutent group deprotection process to achieve the asymmetric synthesis of NH-piperidine with high efficiency and excellent stereoselectivity.

Based on our previous report, we evaluated benzyl amines as alternative nucleophiles for this condensation reaction. Under the optimized conditions (THF solvent, 0.5M concentration, 1 equiv nitroalkene, 1.5 equiv amine, and 2.0 equiv MVK, rt), the desired *N*-benzyl-piperidines **3** were prepared in excellent yields (generally >90% with the combination of all stereoisomers **Figure 1**).[10]

Figure 1. Benzyl-amine in NAE reaction

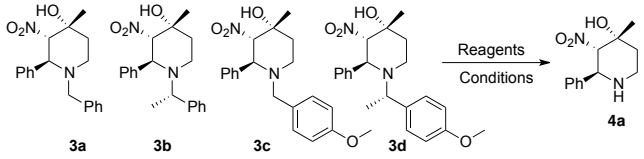


3b: d.r. (5:1:0:0), 68% yield of major isomer; **3d**: d.r. (16:3:1:0), 72% yield of major isomer

As shown in **Figure 1**, benzyl amines are suitable for this nitroalkene/amine/enone condensation (NAE), giving > 95% yields (combining all stereoisomers) in most of the cases. Notably, the reaction can be easily scaled up. The major isomer of piperidine **3a** was synthesized on a 10 g scale. With enantiopure chiral amines, good stereoselectivity were observed (**3b**, **3d**). Given that there are two stereogenic centers in the products, four isomers could be potentially formed. However, only two major products were observed for piperidine **3b** (5:1 dr), and very little third stereoisomer observed in piperidine **3d** (16:3:1). Notably, the absolute stereochemistry of **3d** was assigned based on compound **3b**, whose structure has been confirmed by X-ray crystallography as reported previously (see X-ray structure in supporting information).[11] Subsequent deprotection of the amine (*vide infra*) confirmed that the two major stereoisomers in both cases as the pseudo-enantiomers (not the C-4 isomer). In all cases, the major stereoisomers were isolated with yields higher than 65%. Compared with benzyl amine, the *p*-OMe benzyl (PMB) amine gave slightly higher yield and better stereoselectivity, presumably a consequence of the improved nucleophilicity.

These results demonstrate that readily available chiral benzyl amine derivatives may be used as the amine source for this NAE condensation reaction. In view of our interest in developing an efficient synthesis of NH-piperidines, we then focused our investigation on the benzyl deprotection process. The major stereoisomers of piperidines **3a-3d** were isolated and subjected to various deprotection conditions. The results are summarized in **Table 1**.

Table 1. Benzyl amine deprotection[a,b]

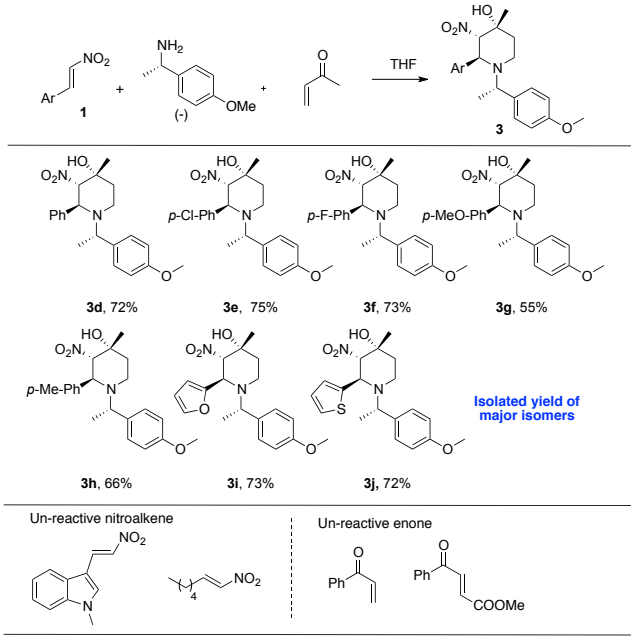


Entry	Conditions	3a (%)	3b (%)	3c (%)	3d (%)
1	Raney Ni, H_2, Ac_2O, MeOH, 20-40 psi, 24 h	<5	<5	<5	<5
2	$Pd(OH)_2$, H_2, Boc_2O, MeOH, 20-40 psi, 24 h	<5	<5	<5	<5
3	Pd/C, H_2, AcOH, MeOH, 20-40 psi, 24 h	<5	<5	<5	<5
4	Na, NH_3, -78°C THF, 12 h	<5	<5	<5	<5
5	Et_3SiH, HCOOH, 90°C, 12h	<5	<5	<5	<5
6	CAN, AcOH/H_2O, rt, 12 h	37	29	42	35
7	DDQ, DCM/H_2O, rt, 12 h	39	30	43	28
8	TMSCl, DCM, rt, 12 h	nr	nr	25	32
9	HCl, Dioxane, RT-70°C, 12 h	nr	nr	38	46
10	TFA:DCM (1:1), rt, 12 hr	nr	nr	48	90[d]
11	TFA, rt, 12 h	nr	nr	30	48[d]

[a]General reaction conditions: Piperidines **3a-3d** (1.0 eq.), reagents were used excess except for entry 4, 5, 6 & 7 (2.1 eq.). [b]Reactions were monitored by TLC/crude NMR till SM totally consumed. [c]Yield refers to crude NMR. [d] Isolated yield of product, nr = no reaction/inert.

The typical reduction conditions did not work well (entries 1-5) due to the rapid, preferential reduction of nitro group.[11] Under the hydrogenation conditions (entries 1-3), only nitro reduction was observed. Reactions of piperidines **3a-d** with Na/NH_3 and Et_3SiH gave partial benzyl reduction products after an extended reaction time.[12] However, the resulting diamines were unstable and hard to be isolated from the reaction mixtures. The oxidative conditions (entries 6-7),[13] on the other hand, led to the decomposition of resulting amine, generating the *NH* amine in poor yields. To circumvent these problems, we focused on acidic conditions that target the benzyl amine over the nitro group. After exploring several typical acid deprotection conditions (entries 8-11), the 1:1 TFA:DCM solution was identified as the optimal pair of reagent, that gave the *NH*-piperidine in excellent yield (entry 10).[14] Notably, the PMB was required for this deprotection and benzyl amine could not be deprotected under this conditions.[15]

Figure 2. NAE Reaction scope



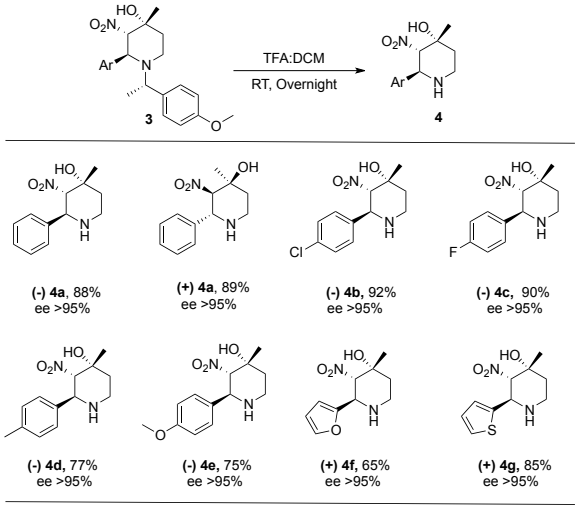
[a]General reaction conditions: Nitroalkene (1.0 eq.), Chiral amine (1.5 eq.), and MVK (2.0 eq.) mixed in THF (0.5M). [b]The reactions were monitored by TLC till nitro-alkene was totally consume. [c]Isolated yield of major diastereomer. dr and structure determined by NMR of crude reaction (see supporting information).

As summarized in **Figure 2**, the aromatic nitroalkene was generally suitable to NAE reaction. With the optimal conditions in hand, subsequently we evaluated the reaction scope. Good to excellent diastereoselectivities were observed with the major isomer being isolated in good yields. In contrast, aliphatic nitroalkenes do not work under this condition. This result may be due to the low reactivity of olefin with electron donating alkyl group and the undesired double bond rearrangement side reaction. Similar results were obtained when *para*-methoxy nitroalkene was used (**3g**). The reaction was extremely slow and a limited yield was noticed even after increasing the reaction time (72 h). The *p*-chloro-substituted nitroalkene reacted much faster and a higher yield was obtained. Indole and protected indole nitroalkene also did not work in this reaction due to the same reason. In addition, aromatic vinyl ketones did not work in this reaction, likely caused by the challenging cyclization due to the steric hindrance at the C-4 position. An unfavored electronic effect was also observed in β-substituted enone, which gave no cyclization products even after extended reaction time. Despite this limitation, the fact that single enantiomer of substituted piperidines was produced in good yields in one step from

simple starting materials emphasizes the high efficiency of this transformation.

With these chiral *N*-piperidines in hand, we explored the deprotection conditions described in **Table 1**. The goal was to evaluate whether or not racemization occurred during the process. Surprisingly, enantiomerically pure *NH*-piperidines were obtained (>95% ee) in all cases. The result is shown in **Figure 3**.

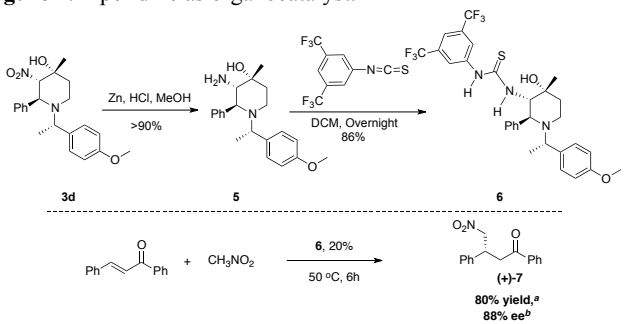
Figure 3. Preparation of enantiomeric pure NH-piperidine[a]



General reaction conditions: Substrate **3** (1eq.), TFA:DCM (1:1) at RT, 12-18hr, The reactions were monitored by TLC, yield is both crude ^{1}H NMR/ isolated, *ee* determined by chiral HPLC analysis; (+) & (-) determined from optical rotation.

The optimal deprotection conditions worked well for all these substrates, giving the *NH*-piperidine in excellent yields. The products were confirmed by ^{1}H-NMR, ^{13}C-NMR and HRMS. The *ee* were determined by HPLC analysis. With this new strategy, both piperidine enantiomers can be prepared from the corresponding chiral amines.

Figure 4. Piperidine as organocatalyst.



[a]Yield of isolated product after chromatography. [b]Absolute configuration was determined by comparing the specific rotation with that of literature data.[17d]

Although our NAE condensation strategy suffers from limited substrate scope, one unique advantage of this reaction is the incorporation of NO_2 and amine functional groups through simple steps. As shown in **Figure 4**, compound **3d** can be readily converted to thiourea through amine nitro-reduction.[16] The amine-thiourea **6** was prepared in excellent yields. Applying piperidine **6** as a dual functional organocatalyst gave the nitro methane Michael addition product in good yield with excellent *ee*.[17] Exploration of other of applications this new class of organocatalyst is currently under investigation.

Conclusions

In conclusion, we report herein the asymmetric synthesis of *NH*-piperidines. With the application of chiral amine, the enantiomerically pure piperidines were achieved through the nitroalkene-amine-enone condensation. Further demonstration of these compounds in organocatalysis revealed a promising future for these compounds and highlighted the significance of this highly efficient asymmetric synthesis.

Experimental Section

General Information

All of the reactions dealing with air and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen using oven/flame-dried glassware and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian 600 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) for ^{1}H-NMR and $CDCl_3$ (δ 77.0 ppm) for ^{13}C-NMR. Flash column chromatography was performed on 230-430 mesh silica gels. Analytical thin layer chromatography was performed with precoated glass baked plates (250μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios. Optical rotations were measured on a commercial automatic polarimeter and reported as follows: $[\alpha]^T$D (c = g/100 mL, solvent). Melting points were measured on a Mel-Temp 1001D apparatus and uncorrected. HRMS were recorded on LTQ-FTUHRA spectrometer. Anhydrous tetrahydrofuran (THF) was purchased from Acros and distilled with sodium, immediately before use. Anhydrous dichlomethane (CH_2Cl_2) was distilled with CaH_2.

General Procedure for the Preparation of Substituted *N*-protected Piperidine (3d-3j):

To a solution of nitroalkene **1a** (149 mg, 1 mmol, 1 eq.) in dry THF (2 mL, 0.5 M), were added successively Chiral 4-methoxy-phenylethanamine (227 mg, 1.5 mmol, 1.5 eq.) and MVK (140 mg, 2.0 mmol, 2.0 eq.) under N_2 atmosphere. The mixture was stirred at room temperature for 36 hr and monitored by TLC. After removing the solvent, the residue was purified by flash silica gel chromatography (Hexane-EtOAc v/v 8:1), which gave a major diastereomeric **piperidine 3d** (266 mg, 0.72 mmol, yield: 72%) as white solid.

General Procedure for the Preparation of *NH*-piperidine (4a-4g):

TFA was added dropwise to a stirred solution of the substrate **3d** (266 mg, 0.72 mmol) in minimum amount of DCM and stirred at

room temperature 12-18hr (TFA:DCM = 1:1). After concentration in rotary evaporator, the residue was partitioned between saturated aqueous sodium bicarbonate solution (8ml) and Dichloromethane (8ml). The separated aqueous phase was extracted with Dichloromethane (3×8ml), and the combined organic extracts dried over sodium or magnesium sulfate for 2hr then filtered through the cotton plug. Finally, the dilute solution was concentrated in vacuo and the residue was purified by column chromatography using solvent system (Dichloromethane: Methanol from 200:1 to 50:1) to afford piperidine **4a**. Using the same mentioned procedure other *NH*-piperidines were prepared from **3d-3j**.

Preparation of Thiourea-Based-Piperidine:

To a solution of **3d** (major) (800 mg, 2.16 mmol, 1eq) were added 1N HCl in MeOH (25 mL, >10 eq.) and Zn powder (2.20 g, 34.6 mmol, 15 eq.). The mixture was then stirred at room temperature and monitored by TLC. After the complete consumption of **3d**, MeOH was completely evaporated followed by treatment with saturated aqueous $NaHCO_3$ until pH > 10, and CH_2Cl_2. Organic layer was extracted with CH_2Cl_2 (30 mL x 5). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was dissolved in minimum CH_2Cl_2 and purified by flash silica gel chromatography (CH_2Cl_2-MeOH v/v 100:1), which gave almost quantitative amount of **5** (700 mg, 2.0 mmol, yield 95%).

To a solution of amine **5** (700 mg, 2.0mmol) in 20 ml dichloromethane was added 3,5-di-trifluoromethyl-phenyl isothiocyanate (557 mg, 2.0 mmol, 1.0 eq.) and stirred for overnight. After, TLC showed the disappearance of **5**, the solution was evaporated and the residue was chromatographed in solvent system (EtoAc: Hexane, v/v 5:1 to 1:1) to afford white solid **6** (1.078 g, 1.78 mmol, yield: 86%).

Compound **6** was purified by flash silica gel chromatography (Hexane/EtOAc, v/v 5/1 to 1/1) as solid, 1.078g, yield 86 %. ^{1}H NMR (600 MHz, CDCl3): δ 8.09 (s, 2H), 7.73 (t, J = 10.0 Hz, 1H), 7.65 (s, 1H), 7.49 (m, 2H) 7.31 (d, J = 8.8 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 4.93 (s, 1H), 4.73 (s, 2H), 4.65 (t, J = 10.0 Hz, 1H), 3.73 (s, 3H), 3.70 (m, 1H), 3.60 (q, J = 6.85 Hz, 1H), 2.66 (m, 2H), 2.19 (m, 1H), 1.62 (m, 1H), 1.14 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (150 MHz, CDCl3): δ 185.7, 162.8, 147.2, 145.2, 140.8, 135.7, 135.3, 135.0, 134.7, 133.4, 132.1, 129.7, 127.0, 126.3, 120.8, 118.4, 74.9, 70.3, 68.1, 60.1, 58.9, 43.4, 43.0, 32.9, 13.3. HRMS Calculated for $C_{30}H_{32}F6N_3O_2S$ [M+H]+: 612.20747, Found: 612.20711.

Asymmetric Michael addition of Nitromethane to Chalcone with Chiral Organocatalysis:[18]

To a solution of chalcone (1 mmol, 1.0 equiv) and nitromethane (915 mg/0.80 ml, 15 mmol, 15.0 equiv) was added thiourea-catalyst **6** (122 mg, 0.2 mmol, 20 mol%). The reaction mixture was stirred in capped vial for 6 h at 50 °C. Then the volatiles were removed by concentration and the residue purified by silica gel flash column chromatography (ethyl acetate-petroleum ether 1:15 V/V) to afford the product as white solid (253 mg, 80% yield). Enantiomeric excess was determined by HPLC on Chiralpak AS-H column (n-hexane-isopropanol 90:10 V/V, flow rate 1.0 mL/min, 220 nm), major enantiomer t_R = 10.3 min, minor enantiomer t_R = 13.6 min, 88 % ee (R) $[a]_D^{25}$ = + 26.7 8 (c = 0.1, CH_2Cl_2, 88 % ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ =7.91–7.89 (m, 2H), 7.57–7.54 (m, 1 H), 7.46–7.42 (m, 2H), 7.32–7.27 (m, 5H), 4.81 (dd, *J* = 12.5, 6.6 Hz,1H), 4.68 (dd, *J* = 12.5, 8.0 Hz, 1H), 4.22 (ps quint, *J* = 7.1 Hz, 1H), 3.50-3.37 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 139.1, 136.3, 133.5, 129.3, 129.1, 129.0, 128.7, 127.4, 79.5, 41.5, 39.2.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental details, X-ray measurement and ^{1}HNMR, ^{13}NMR for all compounds. See http://dx.doi.org/10.1039/b000000x/

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