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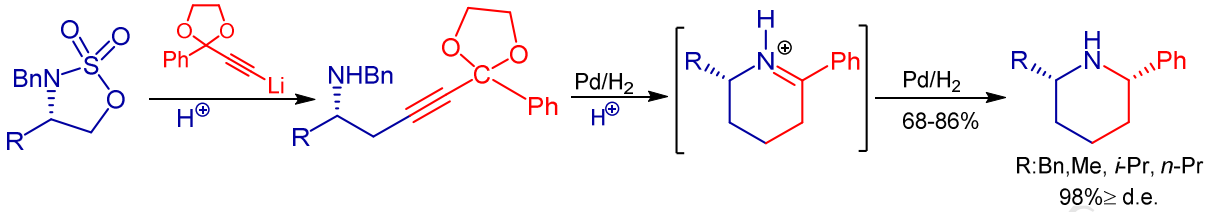
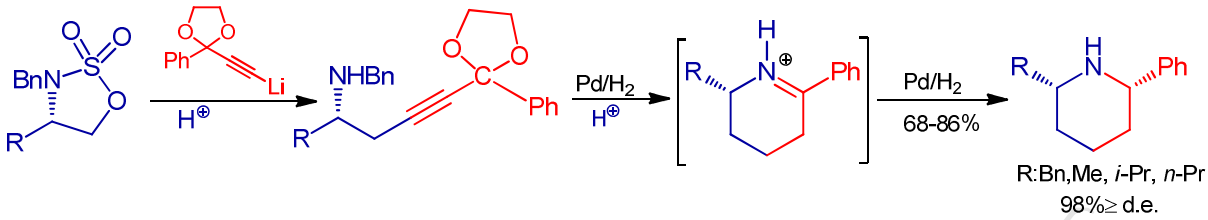
Graphical Abstract



Graphical Abstract



Stereoselective Synthesis of *cis*-2,6-Disubstituted Piperidines from 1,2-Cyclic Sulfamidates

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Abstract

Diastereoselective synthesis of *cis*-2,6-disubstituted piperidines from 1,2-cyclic sulfamidates is described. Regioselective ring-opening reactions of 1,2-cyclic sulfamidates derived from L-phenylalanine, alanine, valine, norvaline with the ketal protected acetylide with a phenyl substituent proceed smoothly to form the *N*-sulfamate intermediates which on acidic hydrolysis give alkynylated amines with the ketal group intact. Hydrogenation of the alkynylated amines, debenzylation, ketal deprotection, subsequent cyclization (of aminoketones) and stereoselective hydrogenation of the cyclic iminium ion intermediates afford the corresponding *cis*-2,6-disubstituted piperidines in high diastereoselectivity (98%≥d.e.) with good chemical yields (68-86%). The present approach provides a novel route for the stereoselective synthesis of *cis*-2,6-disubstituted piperidines.

Key Words: 1,2-cyclic sulfamidates, acetylide, ketal, stereoselective synthesis, cyclization, piperidines.

1. Introduction

The piperidine, 6-membered nitrogen saturated heterocycle is arguably one of the most observed structural units in natural products and pharmaceuticals.[1] Accordingly stereoselective synthesis of substituted piperidines has attracted great deal of interest over the years.[2] The piperidine ring system possessing a chiral centre at C-2 and-6 positions is particularly common substitution system. The 2,6-disubstituted piperidine framework is present in monocyclic piperidine as well as bicyclic indolizidine alkaloids, and has been found to occur not only in plants but also insects and amphibians. (-)-Pinidinol **1**, (+)-epidihydropinidine **2**, (-)-solenopsin A **3**, isosolenopsin A **4**, (+)-monomorine I **5** and (-)-indolizidines 209D **6** are some representative examples of 2,6-disubstituted piperidine alkaloids (**Figure 1**). (-)-Pinidinol **1** and (+)-epidihydropinidine **2** are naturally occurring defense alkaloids isolated from *Picea* (spruce) and/or *Pinus* (pine) species and various insects.[3] (-)-Solenopsin A **3** and isosolenopsin A **4** are example constituents of fire ant venom

(genus *Solenopsis*).[4] (+)-Monomorine I **5** and (-)-Indolizidine 209D **6** are representative indolizidine alkaloids that contain *cis*-2,6-disubstituted piperidine substructure. Most of the indolizidine alkaloids possess alkyl side chains at the 5 positions (3-and 5-positions for disubstituted indolizidines). (+)-Monomorine I **5** is a rail pheromone of the pharaoh ant (*Monomotium pharaonis*).[5] (-)-Indolizidine 209D **6** alkaloids is a representative alkaloid which can be isolated from the poison frogs dendrobatid species.[6]

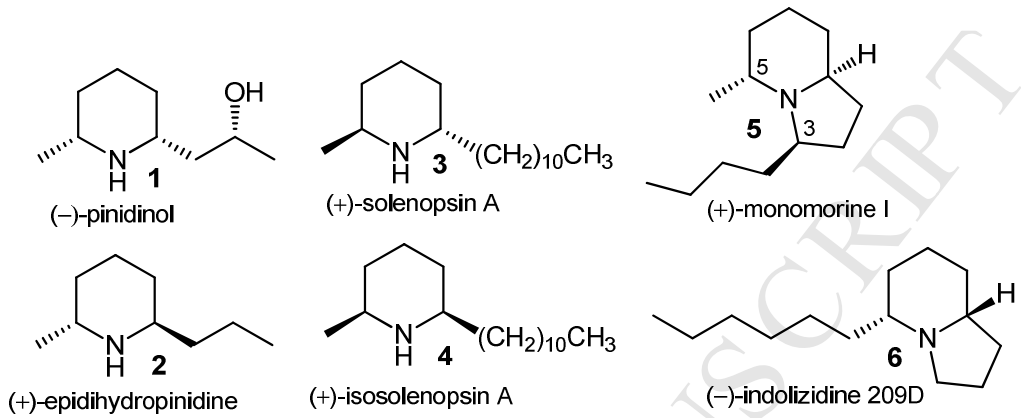


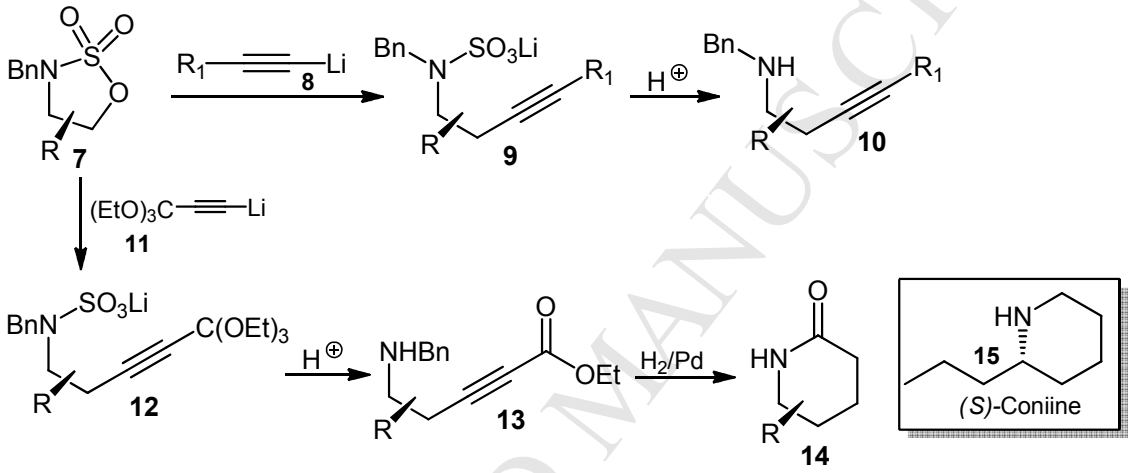
Figure 1. Represantative 2,6-disubstituted piperidine motif containing natural products.

Their relatively simple ring structure makes this class of molecules **1-6** an attractive vehicle for demonstrating the utility of a new synthetic method. Thus, there are variety of methods developed in the literature for stereoselective synthesis of the 2,6-disubstituted piperidine ring core. These methods include reduction of 2,6-dialkylpyridines,[7] metal-catalysed intramolecular cyclizations,[8] intramolecular cyclization *via* aza-Micheal addition,[9] rearrangement of oxime sulfonates,[10] alkylation of pyridinium salts and piperidine derivatives,[11] reductive aminocyclization,[12] iminium-type alkylations,[13] cycloaddition,[14] enzymatic[15] reactions.[16] Given widespread distribution and broad range of interesting biological activities of 2,6-disubstituted piperidine core containing molecules in nature, new routes for stereoselective synthesis of 2,6-disubstituted piperidines are always valuable.

Cyclic sulfamidates are readily available and often enantiopure aminoalcohol-derived reactive electrophiles that have found increasing synthetic utility in organic synthesis. Formation of sulfamidates activates the hydroxyl towards nucleophilic displacements while providing concurrent protection to the nitrogen atom.[17] The reactivity profile of cyclic sulfamidates from 1,2-and 1,3-aminoalcohols is considered to be an effective alternative to the reactivity of the related aziridines and azetidines. Nucleophilic cleavage with sulfamidates occur in a regiospecific manner at the C–O bond, and the nucleophilic attack at the C–N bond is not generally observed. There is also no specific requirement for the presence and subsequent removal of an activating group on the nitrogen. These features make cyclic sulfamidates synthetically versatile electrophilic synthons in synthesis. As a result, reaction of sulfamidates with a wide variety of nucleophiles including carbon,[18] nitrogen,[19] oxygen,[20] sulfur,[21] phosphour[22] and fluoride[23] has been reported.[24]

Of particular value is the ring opening reactions with carbon-based nucleophiles that enables the synthesis of functionalized amine compounds. The reactivity of cyclic sulfamidates towards synthetically functionalized carbon-based nucleophiles has being explored in organic synthesis over the years.[18] We previously reported a synthetically useful level of reactivity of cyclic sulfamidates towards acetylides (**Scheme 1**).[25] Nucleophilic cleavage of 1,2-cyclic

sulfamidates **7** with acetylides **8** proceeded smoothly in a regioselective fashion to form *N*-sulfamate **9** which on acidic hydrolysis produced the alkynylated amines **10**. Primary carbon-centered sulfamidates were found to be particularly effective in the alkylation reaction furnishing the related alkynylated amines in high yields. Once the acetylide component possesses an orthoester functionality, nucleophilic addition of triethylorthopropiolate **11** gave *N*-sulfamate intermediate **12**.[26] Acidic hydrolysis not only cleaved the *N*-sulfamate but also led to concurrent hydrolysis of orthoester to the corresponding ethylester. Thermal cyclization of amino-α,β-unsaturated esters **13** upon hydrogenation enabled synthesis of the alkyl substituted piperidine lactams **14**, in which [N─C─C] fragment from the sulfamidate and [C─C─C] fragment from the propiolate are combined to form the piperidine ring. This approach represents a new cyclization strategy for the synthesis of the substituted piperidin-2-ones. The efficiency of the cyclization process was demonstrated by the synthesis of the hemlock alkaloid (*S*)-coniine **15** from L-norvaline.



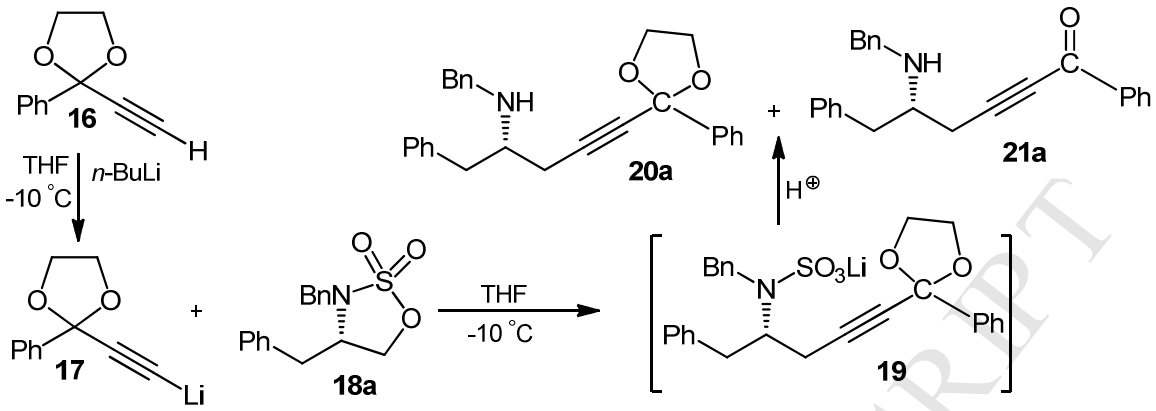
Scheme1. Reactivity of 1,2-cyclic sulfamidates towards acetylides.

Inspired by the synthesis of the substituted piperidin-2-one system, we envisaged that once a ketal protected acetylide is used as the nucleophilic component, a similar cyclization approach could enable the stereoselective synthesis of 2,6-disubstituted piperidines. In this communication we report our preliminary results for stereoselective synthesis of *cis*-2,6-disubstituted piperidines from 1,2-cyclic sulfamidates and the ketal protected acetylide with a phenyl substituent.

2. Results and discussion

Ketal protected terminal alkyne **16** was lithiated with *n*-butyllithium in THF at -10 °C for 1h (**Scheme 2**).[27] The resulting acetylide **17** solution was reacted with **18a** as the model sulfamidate for 24h to form *N*-sulfamate **19**. Treatment with 5M HCl solution is generally considered to be the standard acidic conditions for cleavage of *N*-sulfamate.[25] Under these conditions (5M HCl) the hydrolysis reaction on **19** afforded alkynylated amine **20a** with ketal group intact along with ketal group hydrolyzed product **21a** in varying yields. We previously observed that the acetal group was adequately stable to 5M HCl allowing the corresponding alkynylated acetal product to be isolated in good yield. The relative unstability of the ketal group to 5M HCl called for investigations of hydrolysis conditions in more details. After extensive experimentation, we were able to obtain the desired alkynylated amine **20a** with the ketal group intact in good yields. The best conditions that avoids the ketal hydrolysis was found to be dropwise addition of H_2O and conc. H_2SO_4 to the etheric *N*-sulfamate solution.

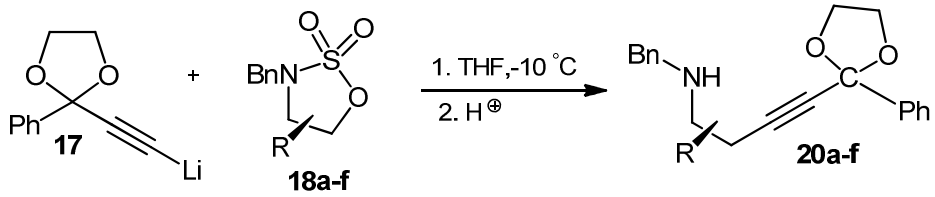
The labile ketone by product **21a** could be obtained as the sole reaction product when the hydrolysis was performed with conc. HCl solution.



Hydrolysis conditions for 1mmol **19**		% isolated yields		Hydrolysis conditions for 1mmol **19**		% isolated yields	
		20a	**21a**			**20a**	**21a**
1	0,5 mL, 5M HCl; 0,5h	26	67	7	0,5 mL, 12 M HCl; 1h	-	89
2	0,5 mL, 5M HCl; 1h	41	49	8	1 mL, 10% H_2SO_4; 8h	66	28
3	0,5 mL, 5M HCl; 3h	56	41	9	0,3 mL, 70% H_2SO_4; 10 min.	87	-
4	0,6 mL, 5M HCl; 1h	22	55	10	0,4 mL, 50% H_2SO_4; 45 min.	88	-
5	0,5 mL, 1M HCl; 1h	hydrolysis not finished		11	15 drops H_2O;15 drops con.H_2SO_4; 2,5h	73	23
6	0,5 mL, 2,5 M HCl; 1h	hydrolysis not finished		12	4 drops H_2O;4 drops con.H_2SO_4; 2,5h	92	-

Scheme 2. Nucleophilic substitution of phenylalanine derived sulfamidate **18a** with acetylide **17**.

Having established the optimum hydrolysis conditions, the scope of the acetylenic substitution reactions was examined with the structural variations in sulfamidates **18a-f** (**Scheme 3**). A representative set of 1,2-cyclic sulfamidates **18a-f** was synthesized for scaning of the structural affects on substitution.[26] We preferred to use the benzyl group for *N*-protection considering the ease of installation and subsequent removal by hydrogenation as well as its stability under the basic conditions. Enantiomerically pure primary carbon-centered sulfamidates **18a–d** were prepared from L-phenyalanine, alanine, valine, norvaline. Optically pure secondary carbon-centered 1,2-cyclic sulfamidate **18e** was prepared from (*S*)-ethyl lactate. Primary carbon-centered sulfamidates **18a-d** were all found to be effective in the alkylation reaction delivering the expected β-alkynylated amines **20a-d** in good yields. The lability of the sulfamidate **18f** toward elimination was already reported.[25a] Using the similiar reaction conditions, the alkylation reaction of **18f** led to the formation of the substitution product **20f** in 22% yield along with *N*-benzyl cinnamylamine **22** in 54% yield. This result is in paralel to our previous observations; sulfamidate **18f** generally favors the elimination pathway in displacement reactions. Ring-opening reactions of **18a-f** usually required two equivalent of acetylide **17** for completion in 24h. Inclusion of 7,5% HMPA by volume was found to enhance reaction rates such that 1.1 equivalent of **17** was suffice for the reaction to be completed in several hours. Therefore, HMPA was frequently used as polar additive in reaction mixtures to avoid the excess use of synthetically valuable alkyne **16**.



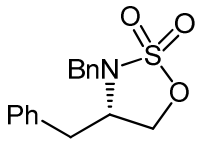
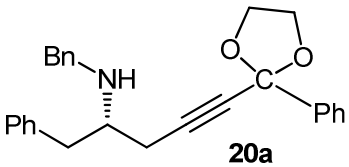
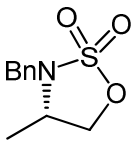
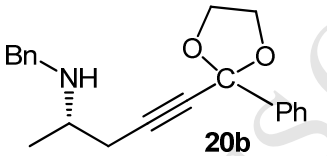
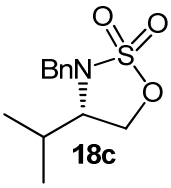
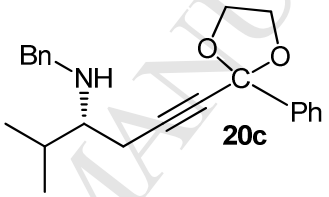
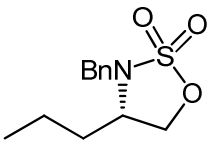
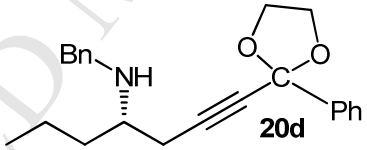
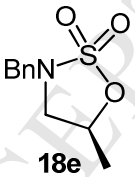
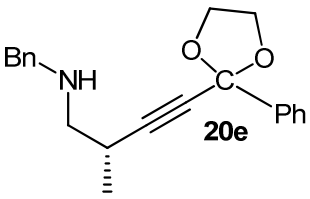
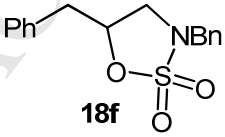
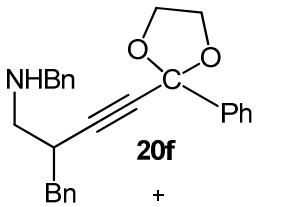
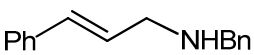
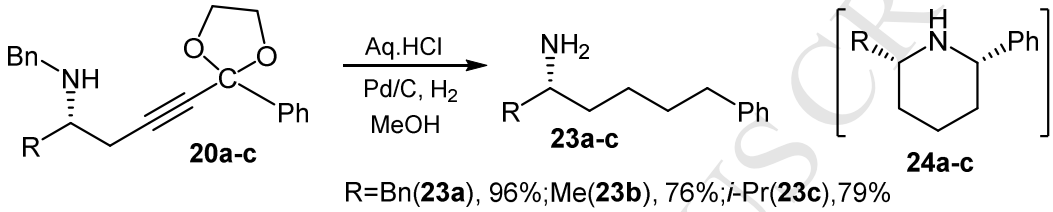
Entry	1,2-Cyclic sulfamidate **18a-f**	Substitution product **20a-f**	% isolated yield
1	 **18a**	 **20a**	92
2	 **18b**	 **20b**	83
3	 **18c**	 **20c**	89
4	 **18d**	 **20d**	88
5	 **18e**	 **20e**	80
6	 **18f**	 **20f** +  **22**	22 54

Table 1. Nucleophilic substitution reactions of various 1,2-cyclic sulfamidates **18a-f** with ketal protected acetylide **17**.

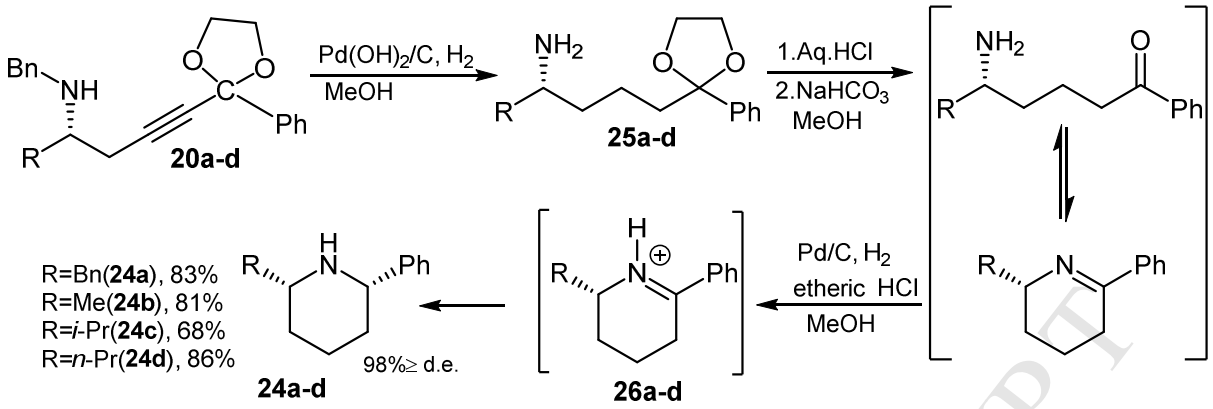
We envisaged that ketal amine **20a-e** could be converted readily into disubstituted piperidines **24a-c** in a stereoselective manner using palladium-catalyzed hydrogenation. Combination of

aqueous HCl and Pd/C in MeOH was successfully used in several stereoselective synthesis of substituted piperidines.[13c,18c] Attempts to construct the piperidine ring from amines **20a-e** using acidic palladium-catalyzed hydrogenation in one pot operation failed (**Scheme 3**). All attempts led to isolation of unexpected acyclic amines **23a-c** instead. Formation of acyclic amines **23a-c** could be explained on the basis of kinetics of the reactions involved in this one pot multistep process; saturation of triple bond, ketal deprotection, debenzylation, cyclization and reduction of the activated aromatic carbonyl group in acidic environment. Saturation of triple bond, ketal deprotection, carbonyl reduction are apparently kinetically more favourable reactions as indicated by the isolation of acyclic amines from the reactions. Sluggish debenzylation step could be responsible for the failure. Direct conversion of the ketone **21a** into the corresponding piperidine using HCl and Pd/C in MeOH conditions in one pot operation was not successful either.



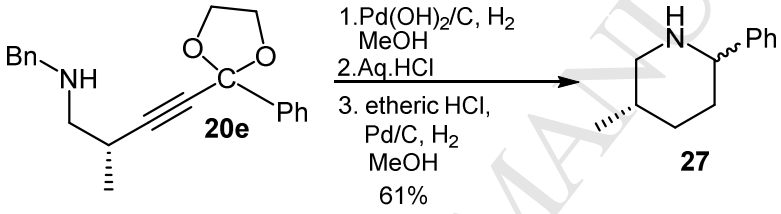
Scheme 3. Palladium catalyzed hydrogenation of **20a-c**.

Fortunately, performing the reactions in step-wise manner allowed us to overcome formation of acyclic amines. Thus, alkynylated ketal amines **20a-e** was initially hydrogenated in the absence of acid to carry out saturation and sluggish debenzylation reactions (**Scheme 4**). The crude debenzylated amines **25a-d** were subject to the kinetically fast ketal deprotection reaction with aqueous HCl conditions which led to *insitu* formation of cyclic imines (by TLC). At this stage, cyclic imines could not be characterized spectroscopically due to decomposition on chromatography. It is important that the crude cyclic imines isolated should be strictly free of water for smooth stereoselective hydrogenation. Exposure of the crude cyclic imines in MeOH containing etheric anhydrous HCl to palladium-catalyzed hydrogenation gratifyingly afforded the corresponding *cis*-disubstituted piperidines **24a-d** in excellent diastereoselectivity with good chemical yields over three steps.[28] ^{1}H NMR spectrum of *cis*-disubstituted piperidines showed the presence of only one diastereoisomer which indicates hydrogenation operating with 98%≥d.e stereoselectivity. It is critical that atmospheric palladium-catalyzed hydrogenation be performed under anhydrous conditions; otherwise formation of acyclic amines may cause a problem to varying extents, thereby rendering efficiency of the hydrogenation step.



Scheme 4. Stereoselective synthesis of disubstituted piperidines **24a-d**.

Application of the step-wise reaction strategy to lactate-derived alkynylated amine **20e** did not lead to good stereoselectivity for synthesis of 2,4-disubstituted piperidine system. In this case, 2,4-disubstituted piperidine **27** was obtained as approximately a 4:1 inseparable mixture of two diastereosimers (**Scheme 5**).



Scheme 5. Synthesis of disubstituted piperidine **27** from lactate derived alkynylated amine **20e**.

Characterization data for known alanine-derived *cis*-piperidine **24b** ((2*S*,6*S*)-2-methyl-6-phenylpiperidine, $[\alpha]_D^{20}$= -35.6 (*c*=1,38 $CHCl_3$)) and alanine-derived *trans*-piperidine ((2*S*,6*R*)-2-methyl-6-phenylpiperidine, $[\alpha]_D^{20}$= +33.4 (*c*=1,25 $CHCl_3$)) was already available in the literature.[13f] Optical rotation for (2*S*,6*S*)-2-methyl-6-phenylpiperidine **24b** was measured in this work as $[\alpha]_D^{30}$= -34.2 (*c*=1, $CHCl_3$). Comparision of NMR data and optical rotation of **24b** with literature data indicated disubstituted piperidine **24b** in *cis* configuration. Configuration of other disubstituted piperidines **24a**, **24c**, **24d** was assigned as *cis*-configuration using the analogy to **24b** and NOESY NMR. The observed stereochemical outcome of palladium catalyzed hydrogenation can be explained on the base that attack of hydrogen from the less hindered side of cyclic iminium intermediate **26a-d** in the transition state leading to *cis*-2,6-disubstituted piperidines (**Figure 2**).[29]

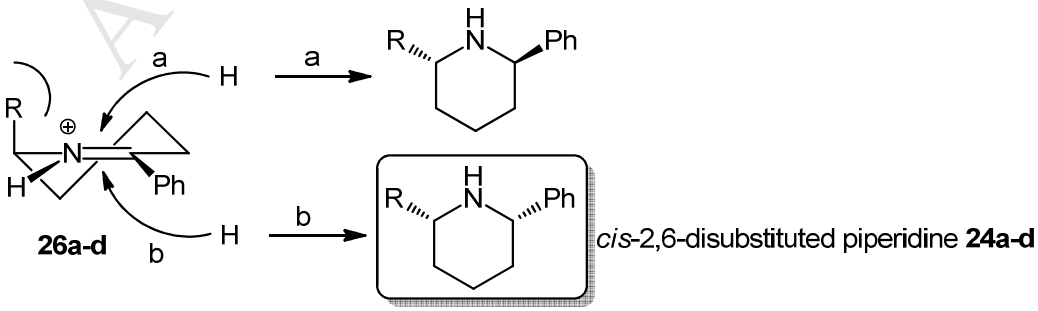


Figure 2. Transition states of hydrogenation of cyclic iminium intermediates **26a-d**.

3. Conclusions

In summary a new method for stereoselective synthesis of *cis*-2,6-disubstituted piperidines from 1,2-cyclic sulfamidates is developed. Regioselective ring-opening reactions of 1,2-cyclic sulfamidates derived from L-phenylalanine, alanine, valine, norvaline with ketal protected acetylide with a phenyl substituent proceed efficiently to give alkynylated amines with the ketal group intact after acidic hydrolysis. Hydrogenation of the alkynylated amine products, debenzylation, ketal deprotection, subsequent cyclization and stereoselective hydrogenation of the cyclic iminium ion intermediates afford the corresponding *cis*-disubstituted piperidines in high diastereoselectivity (98%≥d.e.). The present approach represents a novel route for the stereoselective synthesis of *cis*-2,6-disubstituted piperidines. Application of this methodology with the use of the ketal protected acetylides with an alkyl group for natural product synthesis containing 2,6-disubstituted piperidine unit is currently ongoing in our laboratory and will be reported elsewhere.

4. Experimental section

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian AS 400 MHz NMR spectrometer with TMS as an internal. Chemical shifts are expressed in δ (parts per million) units downfield from TMS. IR spectra were recorded on a Perkin Elmer Spectrum BX spectrometer as thin films on NaCl plates. Optical rotations were measured with Rudolph Research Analytical Autopol I Automatic Polarimeter. LC/MS Q-TOF were taken from Giresun Univesity, Giresun, Turkey with an Agilent 6230 Q-TOF LC/MS instrument. THF and ether were freshly distilled from $LiAlH_4$ before use. TLC was performed using aluminum plates coated with silica gel (254 nm) and use of the basic permanganate dying system. Flash column chromatography was carried out using silica gel (0.063-0.2 mm). Removal of solvents in *vacuo* was achieved using a IKA rotary evaporator at room temperature unless otherwise stated. Yields refer to isolated material, homogeneous by TLC and NMR spectroscopy, unless otherwise stated. Phenyl ketal alkyne **16** was synthesized from propiophenone according to literature protocols.[27] 1,2-Cyclic sulfamidates **18a-f** were prepared according to literature protocols.[26]

4.2. General procedure for the nucleophilic substitution of 1,2-cyclic sulfamidates 18a-f with phenyl ketal alkyne 16

To a solution of terminal alkyne **16**, 2 mmol in 10 mL freshly distilled dry THF under argon atmosphere, cooled at -10 °C over ice-salt bath was added dropwise *n*-butyllithium (1.3 mL, 2.1 mmol, 15% solution in hexane) and the solution was stirred at this temperature for 1 h (1.1 mmol **16** and 1.2 mmol *n*-butyllithium were sufficient if 0.75 mL HMPA was used as co-solvent). A solution of 1,2-cyclic sulfamidate (1 mmol) in 3 mL dry THF was then added to the resulting acetylide solution via a syringe. After stirring at –10 ºC for 5-6 h, the reaction mixture was allowed to warm up to room temperature gradually with stirring overnight (a few hours if HMPA was used, overnight for **18e**). TLC monitoring showed complete consumption of sulfamidate. The resulting mixture was then added one drop conc. H_2SO_4 and one drop H_2O sequentially (total 4 drops H_2SO_4 and 4 drops H_2O) with stirring for 1-2h to hydrolyze the *N*-sulfamate intermediate before neutralization with saturated $NaHCO_3$ solution. Extraction with ether (3x20mL) and drying over anhydrous Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. Purification by column chromatography using

EtOAc/Hexane solvent systems (containing 0.5% triethylamine) afforded compounds **20a-f** and **22** as an oil. Ketal protected alkynylated amines **20a-f** are sensitive compounds for chromatographic purification; a small extent of decomposition was sometimes observed.

4.2.1. (*S*)-*N*-Benzyl-1-phenyl-5-(2-phenyl-1,3-dioxolan-2-yl)pent-4-yn-2-amine 20a

Obtained as a pale yellow oil (358 mg, 90% yield). TLC, R*f*: 0.42 [(EtOAc:hexane) 1:3]; $[\alpha]_D^{30}$=+0.36 (*c*=6.0, $CHCl_3$); IR (film); υ_{max}/cm^{-1}; 3357 (NH), 2234 (C≡C); ^{1}H NMR δ_H (400 MHz, $CDCl_3$) (ppm) 2.37 (1H, dd, *J*=5.6 and 16.8), 2.43 (1H, dd, *J*=6.0 and 16.8), 2.80 (1H, dd, *J*=7.2 and 13.6), 2.86 (1H, dd, *J*=6.0 and 13.6), 2.98-3.04 (1H, m), 3.76 (1H, d, *J*=13.2), 3.84 (1H, d, *J*=13.2), 4.07-4.15 (2H, m), 4.19-4.25 (2H, m), 7.14-7.38 (13H, m, Ar-H), 7.69-7.72 (2H, m, Ar-H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) (ppm) 23.67, 4074, 51.32, 57.40, 65.23, 80.89, 84.33, 102.63, 126.17, 126.65, 127.19, 128.28, 128.50, 128.67, 128.74, 129.38, 129.63, 138.97, 139.82, 140.50; LC/MS Q-TOF (m/z): $[M+H]^+$ found 398.2116, $C_{27}H_{28}NO_2$ requires 398.2120.

4.2.2. (*S*)-5-(benzylamino)-1,6-diphenylhex-2-yn-1-one 21a

Obtained as a pale yellow oil (312 mg, 89% yield). TLC, R*f*: 0.47 [(EtOAc:hexane) 1:3]; δ_H (400 MHz, $CDCl_3$) (ppm) 2.60 (1H, dd, *J*=5.2 and 17.2), 2.68 (1H, dd, *J*=5.6 and 17.2), 2.89-2.99 (2H, m), 3.14-3.20 (1H, m), 3.84 (1H, d, *J*=13.2), 3.93 (1H, d, *J*=13.2), 7.21-7.33 (10H, m, Ar-H),7.45-7.50 (2H, m, Ar-H), 7.59-7.63 (1H, m, Ar-H), 8.16-8.19 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 24.32, 40.84, 51.43, 57.11, 81.82, 94.00, 126.85, 127.30, 128.24, 128.70, 128.78, 128.85, 129.56, 129.82, 134.22, 137.14, 138.41, 140.12, 178.22; LC/MS Q-TOF (m/z): $[M+H]^+$ found 354.1867, $C_{25}H_{23}NO$ requires 354.1858. The title compound was prone to decomposition.

4.2.3. (*S*)-*N*-Benzyl-5-(2-phenyl-1,3-dioxolan-2-yl)pent-4-yn-2-amine 20b

Obtained as a pale yellow oil (267 mg, 83% yield). TLC, R*f*: 0.35 [(EtOAc:hexane) 1:1]; $[\alpha]_D^{30}$= -15.0 (*c*=1.0, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3317 (N–H),3029, 2964, 2927, 2892, 2233 (C≡C), 1493, 1451, 1275, 1152, 1067, 1028, 966, 754, 698; δ_H (400 MHz, $CDCl_3$) (ppm) 1.19 (3H, d, *J*=6.4), 2.44 (2H, d, *J*=6.0), 2.95 (1H, septet, *J*=6.0), 3.80 (2H, br, s), 4.09-4.24 (4H, m), 7.24-7.38 (8H, m, Ar-H), 7.69-7.72 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 20.42, 26.41, 51.09, 51.25, 65.04, 80.16, 84.25, 102.40, 125.85, 126.92, 128.04, 128.18, 128.42, 129.07, 139.45, 140.31; LC/MS Q-TOF (m/z): $[M+H]^+$ found 322.1819, $C_{21}H_{23}NO_2$ requires 322.1807.

4.2.4. (*R*)-*N*-Benzyl-2-methyl-6-(2-phenyl-1,3-dioxolan-2-yl)hex-5-yn-3-amine 20c

Obtained as a pale yellow oil (310 mg, 89% yield). TLC, R*f*: 0.38 [(EtOAc:hexane) 1:3]; $[\alpha]_D^{30}$= -31.0 (*c*=2.0, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3337 (N–H), 3028, 2958, 2891, 2232 (C≡C), 1493, 1450, 1274, 1152, 1066, 1028, 965, 750, 697; δ_H (400 MHz, $CDCl_3$) (ppm) 0.95 (3H, d, *J*=6.8), 0.98 (3H, d, *J*=6.8), 1.87-1.95 (1H, m), 2.43 (1H, dd, *J*=6.4 and 16.8), 2.51-2.61 (2H, m), 3.77 (1H, d, *J*=12.8), 3.88 (1H, d, *J*=12.8), 4.09-4.15 (2H, m) 4.17-4.24 (2H, m), 7.25-7.39 (8H, m, Ar-H), 7.70-7.73 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 18.54, 18.76, 21.00, 30.83, 51.65, 61.10, 65.03, 79.81, 84.96, 102.44, 125.87, 126.82, 128.13, 128.17, 128.31, 129.04, 139.51, 140.78 ; LC/MS Q-TOF (m/z): $[M+H]^+$ found 350.2124, $C_{23}H_{27}NO_2$ requires 350.2120.

4.2.5. (*S*)-*N*-Benzyl-1-(2-phenyl-1,3-dioxolan-2-yl)hept-1-yn-4-amine 20d

Obtained as a pale yellow oil (307 mg, 88% yield). TLC, R*f*: 0.39 [(EtOAc:hexane) 1:2]; $[\alpha]_D^{30}$= -25.7 (*c*=1.0, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3326 (N–H), 3030, 2952, 2924, 2890, 2235 (C≡C), 1490, 1451, 1272, 1152, 1065, 1026, 965, 752, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 0.92 (3H, t, *J*=7.2), 1.34-1.44 (2H, m), 1.47-1.57 (2H, m), 2.43 (1H, dd, *J*=5.6 and 16.8), 2.54 (1H, dd, *J*=5.6 and 16.8), 2.80 (1H, quintet, *J*=6.0), 3.76 (1H, d, *J*=12.80), 3.84 (1H, d, *J*=12.80), 4.09-4.15 (2H, m), 4.21-4.24 (2H, m), 7.23-7.40 (8H, m, Ar-H), 7.69-7.74 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 14.19, 16.07, 23.90, 36.57, 50.96, 55.30, 65.04, 80.06, 84.40, 102.43, 125.87, 126.87, 128.09, 128.17, 128.36, 129.06, 139.48, 140.55; LC/MS Q-TOF (m/z): $[M+H]^+$ found 350.2121, $C_{23}H_{27}NO_2$ requires 350.2120.

4.2.6. (*S*)-*N*-Benzyl-2-methyl-4-(2-phenyl-1,3-dioxolan-2-yl)but-3-yn-1-amine 20e

Obtained as a pale yellow oil (257 mg, 80% yield). TLC, R*f*: 0.27 [(EtOAc:hexane) 1:1]; $[\alpha]_D^{30}$= -24.7 (*c*=1.3, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3333 (N–H), 3025, 2974, 2935, 2890, 2229 (C≡C), 1493, 1451, 1272, 1172, 1068, 1029, 965, 744, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 1.22 (3H, d, *J*=6.8), 2.70 (2H, m), 2.82 (1H, septet, *J*=6.8), 3.78 (1H, d, *J*=13.2), 3.84 (1H, d, *J*=13.2), 4.07-4.14 (2H, m), 4.18-4.23 (2H, m), 7.23-7.38 (8H, m, Ar-H), 7.67-7.71 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 18.41, 26.62, 53.34, 54.24, 65.00, 79.28, 89.51, 102.42, 125.89, 126.95, 128.02, 128.17, 128.40, 129.07, 139.44, 140.02; LC/MS Q-TOF (m/z): $[M+H]^+$ found 322.1807, $C_{21}H_{23}NO_2$ requires 322.1807.

4.2.7. *N*,2-Dibenzyl-4-(2-phenyl-1,3-dioxolan-2-yl)but-3-yn-1-amine 20f

Obtained as an orange oil (88 mg, 22% yield). TLC, R*f*: 0.39 [(EtOAc:hexane) 1:1]; IR (film) υ_{max}/cm^{-1}: 3327 (N–H), 3064, 3025, 2896, 2845, 2229 (C≡C), 1493, 1454, 1272, 1146, 1065, 1026, 967, 744, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 2.72-2.91 (4H, m), 2.97-3.04 (1H, m), 3.77 (1H, d, *J*=13.2), 3.84 (1H, d, *J*=13.2), 4.04-4.11 (4H, m), 7.20-7.37 (13H, m, Ar-H), 7.60-7.63 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 34.47, 38.71, 52.26, 53.50, 64.95, 81.00, 87.93, 102.37, 125.96, 126.37, 126.96, 128.04, 128.14, 128.25, 128.41, 129.08, 129.23, 139.02, 139.14, 140.20 ; LC/MS Q-TOF (m/z): $[M+H]^+$ found 398.2104, $C_{27}H_{27}NO_2$ requires 398.2120.

4.2.8. *N*-Benzyl cinnamylamine 22

Obtained as a pale yellow oil (120 mg, 54% yield). TLC, Rf: 0.19 [(EtOAc:hexane) 1:1]; IR (film) υ_{max}/cm^{-1}: 3312 (N–H), 1646 (C=C), 1599, 1491, 1449 (aromatic), 736, 698; δ_H (400 MHz, $CDCl_3$) (ppm) 3.46 (2H, dd, *J*=1,2 and 6.0), 3.86 (2H, br s), 6.34 (1H, dt, *J*=6.4 and 16.0), 6.56 (1H, d, *J*=15.6), 7.21-7.40 (10H, m, Ar-H).

4.3. General procedure for synthesis of acyclic amines 23a-c

To a solution of the aminoketal alkynes **20a-c** (1.18 mmol) in methanol (15 mL) containing 1,5 mL 1N HCl was added Pd/C (80 mg) at room temperature. The resulting solution was flushed with argon several times and a stream of hydrogen was bubbled through the solution for 72 hours. After completion of the reaction, mixture was filtered through a pad of Celite® and evaporation of the volatiles in *vacuo* give the crude product. The resulting residue was dissolved in DCM and washed with saturated $NaHCO_3$ (3x10 mL), drying over anhydrous Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. Purification by flash column chromatography eluting with the (DCM/MeOH 90:10 to 95:5 gradient) solvent system (containing 0.5% triethylamine) afforded the acyclic amines **23a-c**.

4.3.1. (*R*)-1,6-Diphenylhexan-2-amine 23a

Obtained as an off-white solid (287 mg, 96% yield); mp 81-84 °C TLC, R*f*: 0.4 [(MeOH:DCM) 1:9]; $[\alpha]_D^{30}$= -12.8 (*c*=1.33, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3652, 3366, 3282 (N–H), 3025, 2929, 2853, 2851, 1602, 1496, 1454, 1029, 744, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 1.37-1.72 (6H, series of multiplet), 2.49 (1H, dd, *J*=8.8 and 13.6), 2.65 (2H, t, *J*=7.6), 2.81 (1H, dd, *J*=4.8 and 13.6), 2.97-3.04 (1H, m), 7.18-7.34 (10H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 25.91, 31.56, 35.89, 37.39, 44.62, 52.69, 125.66, 126.19, 128.27, 128.38, 128.42, 129.29, 139.57, 142.57 ; LC/MS Q-TOF (m/z): $[M+H]^+$ found 254.1913, $C_{18}H_{23}N$ requires 254.1909.

4.3.2. (*S*)-6-phenylhexan-2-amine 23b

Obtained as a viscous pale yellow oil (159 mg, 76% yield). TLC, R*f*: 0.1 [(MeOH:DCM) 1:9]; $[\alpha]_D^{30}$= +3.2 (*c*=4.67, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3351, 3280, 3170 (N–H), 3084, 3061, 3026, 2929, 2856, 1663, 1603, 1583, 1495, 1453, 1372, 747, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 1.05 (3H, d, *J*=6.0), 1.33-1.67 (6H, series of multiplet), 2.61 (1H, d, *J*=7.6), 2.63 (1H, d, *J*=7.6), 2.83-2.90 (1H, m), 7.15-7.18 (3H, m, Ar-H), 7.25-7.29 (2H, m, Ar-H) ; LC/MS Q-TOF (m/z): $[M+H]^+$ found 178.1599, $C_{12}H_{19}N$ requires 178.1596.

4.3.2. (*R*)-2-methyl-7-phenylheptan-3-amine 23c

Obtained as an off-white solid (191 mg, 79% yield); mp 63-65 °C ; TLC, R*f*: 0.46 [(MeOH:DCM) 1:9]; IR (film) υ_{max}/cm^{-1}: 3372, 3299 (N–H), 3084, 3025, 2931, 2857, 1603, 1495, 1453, 1366, 1030, 747, 698; δ_H (400 MHz, $CDCl_3$) (ppm) 0.86 (3H, d, *J*=6.8), 0.90 (3H, d, *J*=7.2), 1.25-1.68 (6H, series of multiplet), 2.50-2.54 (1H, m), 2.62 (2H, t, *J*=8.0), 7.15-7.18 (3H, m, Ar-H), 7.25-7.29 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 17.11, 19.23, 26.31, 31.66, 33.21, 34.49, 35.95, 56.49, 125.59, 128.22, 128.35, 142.66; LC/MS Q-TOF (m/z): $[M+H]^+$ found 206.1903, $C_{14}H_{23}N$ requires 206.1909.

4.4. General procedure for synthesis of piperidines 24a-d and 27

To a solution of the aminoketal alkynes **20a-d** (1.15 mmol) in methanol (25 mL) was added Pd/C (35 mg) and $Pd(OH)_2$ (35 mg) at room temperature. The resulting solution was flushed with argon several times and a stream of hydrogen was bubbled through the solution for overnight. After completion of the reaction, mixture was filtered through a pad of Celite® and evaporation of the volatiles in *vacuo* give the crude product. The residue was dissolved in MeOH (30 mL) and 1N HCl (2 mL) was added under argon atmosphere. After stirring at room tempature for 5h, the volatiles was evaporated in *vacuo*. The residue was dissolved in DCM (10 mL) and washed with saturated $NaHCO_3$ (3x10 mL), drying over anhydrous Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. The crude product was dissolved in MeOH (30 mL) and Pd/C (80 mg) and 0.8 mL anhydrous eteric HCl was added. The resulting solution was flushed with argon several times and a stream of hydrogen was bubbled through the solution for overnight. After completion of the reaction, mixture was filtered through a pad of Celite®. The resulting residue was dissolved in DCM (10 mL) and washed with saturated $NaHCO_3$ (3x10 mL), drying over anhydrous Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. Purification by flash column chromatography eluting with Hexane/EtOAc 5:1 to 2:1 gradient for **24a,c,d**; with acetone for **24b**; with DCM/MeOH 90:10 to 95:5 gradient solvent systems for **27** afforded the piperidines.

4.4.1. (*S*)-1-(2-phenyl-1,3-dioxolan-2-yl)heptan-4-amine 25d

The crude product was purified by passing through a small pad of silica gel. Obtained as colourless viscous oil (146 mg, 90% yield). TLC, R*f*: 0.18 [(MeOH:DCM) 1:9]; IR (film) υ_{max}/cm^{-1}: 3378, 3305 (N–H), 3058, 3030, 2952, 2929, 2879, 1664, 1462, 1448, 1118, 1040, 948, 766, 702; δ_H (400 MHz, $CDCl_3$) (ppm) 0.85-0.88 (3H, m), 1.17-1.46 (8H, m), 1.85-1.90 (2H, m), 2.61-2.67 (1H, m), 3.72-3.76 (2H, m), 3.97-4.00 (2H, m), 7.25-7.33 (3H, m, Ar-H), 7.41-7.44 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 14.12, 19.20, 20.13, 37.94, 40.06, 40.52, 50.79, 64.43, 110.34, 125.65, 127.68, 128.00, 142.62; LC/MS Q-TOF (m/z): $[M+H]^+$ found 264.1969, $C_{16}H_{25}NO_2$ requires 264.1964.

4.4.2. (2*R*,6*S*)-2-Benzyl-6-phenylpiperidine 24a

Obtained as a pale yellow oil which solidifies on storage in the refrigerator (240 mg, 83% yield); mp 46-47 °C; TLC, R*f*: 0.53 [(EtOAc:hexane) 1:3]; $[\alpha]_D^{30}$= -139.5 (*c*=2.67, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3308 (N–H), 3026, 2930, 2852, 2792, 2711, 1603, 1493, 1453, 1326, 1305, 1112, 752, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 1.27-1.37 (1H, m), 1.45-1.59 (2H, m), 1.74-1.84 (2H, m), 1.91-1.96 (1H, m), 2.71 (1H, dd, *J*=8.4 and 13.6), 2.84 (1H, d, *J*=5.2 and 13.6), 2.93-2.99 (1H, m), 3.59-3.63 (1H, m), 7.20-7.40 (10H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 25.34, 32.21, 35.02, 40.94, 59.03, 62.32, 126.21, 126.64, 126.93, 128.32, 128.45, 129.26, 139.27, 145.60; LC/MS Q-TOF (m/z): $[M+H]^+$ found 252.1744, $C_{18}H_{21}N$ requires 252.1752.

4.4.3. (2*S*,6*S*)-2-Methyl-6-phenylpiperidine 24b

Obtained as a pale yellow oil (163 mg, 81% yield). TLC, R*f*: 0.28 [(MeOH:DCM) 1:9]; $[\alpha]_D^{30}$= -34.2 (*c*=1.0, $CHCl_3$), Lit.,[13f] $[\alpha]_D^{20}$= -35.6 (*c*=1.38, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3307 (N–H), 3085, 3026, 2929, 2854, 2795, 2705, 1665, 1452, 1275, 1116, 752, 699; δ_H (600 MHz, $CDCl_3$) (ppm) 1.14 (3H, d, *J*=4.4), 1.16-1.28 (1H, m), 1.46-1.57 (2H, m), 1.77-1.81 (1H, m), 1.89-1.93 (1H, m), 2.81-2.87 (1H, m), 3.69 (1H, dd, *J*=1.6 and 7.2), 7.25-7.27 (1H, m, Ar-H), 7.32-7.35 (2H, m, Ar-H), 7.40-7.41 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 22.97, 25.37, 33.80, 34.18, 53.22, 62.47, 126.74, 126.99, 128.28, 145.30; LC/MS Q-TOF (m/z): $[M+H]^+$ found 176.1429, $C_{12}H_{17}N$ requires 176.1439.

4.4.4. (2*R*,6*S*)-2-Isopropyl-6-phenylpiperidine 24c

Obtained as a pale yellow oil (159 mg, 68% yield). TLC, R*f*: 0.45 [(EtOAc:hexane) 1:3]; $[\alpha]_D^{30}$= -65.8 (*c*=1.33, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3085, 3062, 3026, 2933, 2870, 2854, 2787, 2712, 1603, 1494, 1453, 1371, 1300, 1113, 753, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 0.97 (3H, d, *J*=3.6), 0.98 (3H, d, *J*=3.6), 1.15-1.25 (1H, m), 1.42-1.53 (2H, m), 1.63 (1H, septet, *J*=6.4), 1.70-1.81 (3H, m), 1.91-1.96 (1H, m), 2.45 (1H, ddd, *J*=2.8, 6.4 and 11.2), 3.66 (1H, dd, , *J*=2.4 and 10.4), 7.24-7.28 (1H, m, Ar-H), 7.32-7.36 (2H, m, Ar-H), 7.41-7.44 (2H, m, Ar-H),; δ_C (100 MHz, $CDCl_3$) (ppm) 18.92, 19.05, 25.51, 28.53, 33.40, 55.09, 62.60, 63.59, 126.74, 126.88, 128.28, 146.11; LC/MS Q-TOF (m/z): $[M+H]^+$ found 204.1748, $C_{14}H_{21}N$ requires 204.1752.

4.4.5. (2*S*,6*S*)-2-phenyl-6-propylpiperidine 24d

Obtained as a pale yellow oil (201 mg, 86% yield). TLC, R*f*: 0.25 [(EtOAc:hexane) 1:3]; $[\alpha]_D^{30}$= -52.9 (*c*=1.33, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3310 (N–H), 3064, 3025, 2952, 2929, 2851, 2789, 2711, 1602, 1493, 1454, 1325, 1303, 1113, 752, 699; δ_H (400 MHz, $CDCl_3$) (ppm) 0.94 (3H, t, *J*=7.2), 1.12-1.22 (1H, m), 1.34-1.54 (5H, m), 1.68-1.74 (1H, m), 1.76-1.81 (1H, m), 1.88-1.92 (2H, m), 2.65-2.71 (1H, m), 3.63-3.67 (1H, m), 7.22-7.41 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 14.25, 19.09, 25.41, 32.15, 34.79, 39.59, 57.55, 62.54, 126.75,

126.94, 128.30, 145.65; LC/MS Q-TOF (m/z): $[M+H]^+$ found 204.1755, $C_{14}H_{21}N$ requires 204.1752.

4.4.5. (*S*)-5-methyl-2-phenylpiperidine 27

Obtained as an inseparable 4:1 mixture of diastereomers, dark red oil (123 mg, 61% yield). TLC, R*f*: 0.19 [(MeOH:DCM) 1:9]; $[\alpha]_D^{30}$= +25.7 (*c*=1.0, $CHCl_3$); IR (film) υ_{max}/cm^{-1}: 3316 (N–H), 3081, 3058, 3030, 2924, 2868, 2845, 2784, 2733, 1602, 1493, 1454, 1379, 1116, 755, 699; *major diastereomer* : δ_H (400 MHz, $CDCl_3$) (ppm) 0.89 (3H, d, *J*=6.8), 1.12-1.22 (1H, m), 1.55-1.91 (4H, m), 2.39 (1H, t, *J*=11.2), 3.11 (1H, dq, *J*=2 and 11.6), 3.57 (1H, dd, *J*=2.4 and 11.2), 7.22-7.41 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 19.42, 30.88, 33.93, 34.29, 54.74, 61.71, 126.80, 127.27, 128.41 (two overlapped peaks); *minor diastereomer*: δ_H (400 MHz, $CDCl_3$) (ppm) 1.13 (3H, d, *J*=6.8), 1.55-1.91 (4H, m), 2.41 (1H, t, *J*=11.2), 2.82 (1H, dq, *J*=1.6 and 11.8), 2.97 (1H, dd, *J*=3.6 and 12.0), 3.67 (1H, dd, *J*=3.2 and 10.0), 7.22-7.41 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) (ppm) 17.25, 27.68, 29.13, 30.46, 51.82, 61.09, 126.70, 126.95, 128.35, 143.98; LC/MS Q-TOF (m/z): $[M+H]^+$ found 176.1442, $C_{12}H_{17}N$ requires 176.1439.

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