Diastereoselective scalable synthesis of 2,6-*trans*-Piperidines using an *aza*-Michael reaction

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ABSTRACT

Highly efficient substrate and reagent controlled stereoselective synthesis of 2,6-*trans*-piperidine derivative (**1**) using an *aza*-Michael reaction is reported. This method was utilized to synthesize a variety of *trans*-piperidines on hundred-gram scales.

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Piperidines are extremely important core motif in a wide variety of natural products and active pharmaceutical ingredients [1]. Due to its intrinsic conformational preferences 2,6-disubstitued piperidine derivatives are broadly used in chemical synthesis to generate various compounds with therapeutic potential [2]. The nucleophilic and basic nitrogen in the piperidine framework offers numerous synthetic opportunities to tune SAR and explore a variety of biological and physicochemical properties. Therefore, understanding the combined structural and functional properties of piperidine derivatives plays a critical role in *de novo* drug design and development [3]. Although thermodynamically stable *cis*-2,6-disubstituted piperidines can be prepared relatively easily, constructing multigram-scale chiral 2,6-*trans*-piperidines is a daunting challenge. Herein, we report a highly efficient substrate and reagent controlled diastereoselective synthesis of 2,6-*trans*-piperidine derivatives **1** from easily available starting materials through an intramolecular *aza*-Michael reaction.

Although a number of synthetic methods are available to construct a wide variety of piperidine analogs, intramolecular Michael reaction is still the most popular route to generate 2,6-disubstitued analogs in a chiral fashion [4]. A plethora of organic and inorganic catalysts are known to promote this reaction, but none of these are applicable in large-scale synthesis. A recent example [4e] of a fully functionalized α,β-unsaturated carbonyl compound caught our

attention where the reaction has been catalyzed either by triflic acid or by a Pd (II) species. For our ongoing drug discovery program, we needed to prepare a large stock of compound **1** or an analog that contains an easily removable protecting group on the piperidine nitrogen to explore a variety of SAR. We planned to use an α,β-unsaturated ester as a starting material which eventually, after cyclization, can be further manipulated to a variety of functional groups to improve or tune properties of biologically active compounds. Although α,β-unsaturated esters are known to be poor Michael acceptors [4e], we wanted to use this substrate so that we can have better control in *trans/cis* selectivity during piperidine construction. Our investigation started from a suitable intermediate as shown in Scheme 1. The condensation of 4-bromo benzaldehyde with (S)-*tert*-butanesulfinamide gave sulfinimine **5a**, which was then treated with pent-4-enylmagnesium bromide at low temperature. Although the overall yield of this reaction was very good, we noticed moderate stereoselectivity where desired **6a** is the major product. Repeated attempts (Scheme 2) to achieve better selectivity failed. All the sulfinimines (**5a–c**) yielded similar diastereomeric mixtures of **6/7**.

At this point **6a** was purified from its diastereomer **7a** by traditional chromatography and its absolute stereochemistry was confirmed by NMR analysis of its Mosher amide. **6a** was converted to **8** (Scheme 1) which was reacted with ethyl acrylate in presence of Hoveyda-Grubbs catalyst to furnish intermediate **9**. The alkene **9** was a suitable precursor for *aza*-Michael reaction. A recent literature described the acid catalyzed *aza*-Michael cyclization using

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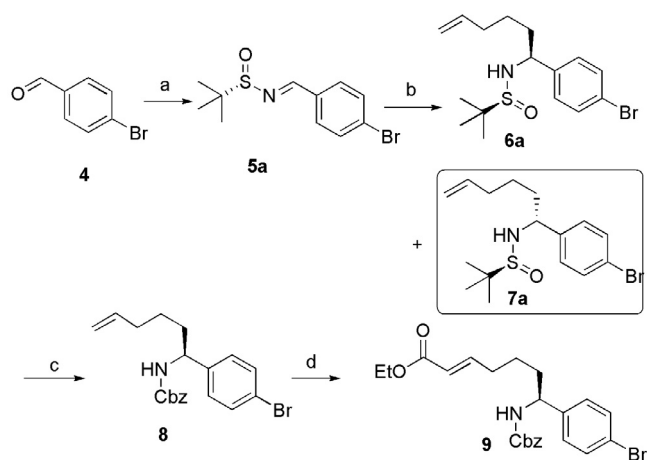
Scheme 1. Initial synthesis plan: (a) (S)-*tert*-Butanesulfinamide, Cs₂CO₃, CH₂Cl₂, 97% (b) Pent-4-enylmagnesium bromide, THF, −78 °C, 70% (c) (1) HCl, MeOH. (2) Na₂CO₃, CbzCl, THF/Water, 87%, (d) Ethyl acrylate, Hoveyda-Grubbs-II, CH₂Cl₂, 40 °C, 95%. Note: Then acid catalyzed cyclisation of **9** (Table 1) followed by reduction of ester using LAH.

(a) R = Buᵗ; (b) R = adamantyl; (c) R = mesityl
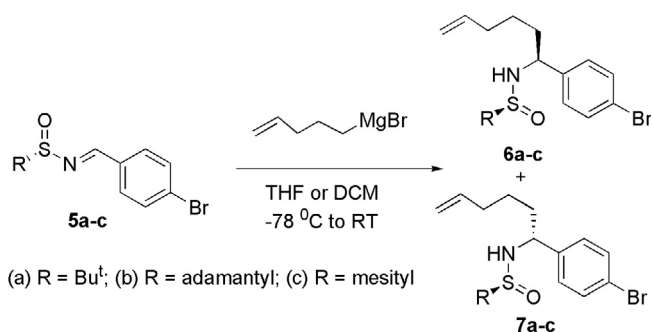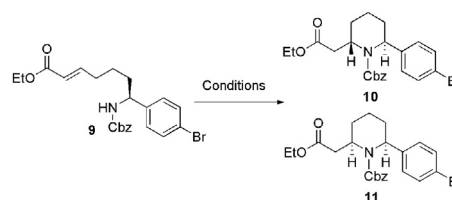
Scheme 2. Pent-4-enyl magnesium bromide addition.

triflic acid (TfOH) as catalyst to prepare *trans*-2,6-disubstituted piperidine [4e]. We attempted to use similar conditions to obtain *trans*-2,6-disubstituted piperidine but our substrates failed to yield any product (entry 1–4, Table 1).

Using slightly modified conditions (entry 5, 4 equiv. TfOH and 3.9 equiv. triethyl amine) resulted in loss of Cbz followed by cyclisation in favor of the *cis*-isomer. Recently [5] HCl was also used as catalyst for *aza*-Michael reactions. However, addition of 1 M HCl in Et₂O (0.6 mol%) (entry 6, Table 1) did not show any reaction for the starting material. At this point, we attempted base-catalyzed cyclization reactions. Use of potassium *tert*-butoxide (entry 7, Table 1) improved the selectivity (*trans*/*cis* = 60/40) but reduced the yield to 46%. Since a chiral *tert*-butyl sulfinyl group [6] is known to influence the stereochemical outcome of reactions, we envisioned that use of intermediate **12** (Table 2) instead of **9** (Scheme 1) as a possible starting material could provide better *trans*/*cis* selectivity. It would also eliminate protection-deprotection steps.

Pure diastereomer **6a** was treated with ethyl acrylate in the presence of Hoveyda-Grubbs catalyst to afford compound **12** in excellent yield. Since the *tert*-butyl sulfinyl group is acid sensitive, we planned to explore base catalyzed cyclization reactions. The results are summarized in Table 2.

We tried several conditions (entries 1–6), but failed to obtained promising results. However, to our surprise, use of Cs₂CO₃, CH₃CN, 80 °C, 16 h (entry 7) provided a good yield (>70%) with moderate selectivity, **13**/**14** (*trans*/*cis* = 60:40). After further optimization,

Table 1
Attempted *aza*-Michael reaction of Cbz protected amine **9**.

Entry	Condition[a,b]	Result[c]
1	Triflic acid (0.2 equiv.), CH₂Cl₂, −20 °C, up to 5 h.	No Reaction
2	Triflic acid (0.2 equiv.), CH₂Cl₂, 25 °C, up to 5 h.	No Reaction
3	Triflic acid (1 equiv.), CH₂Cl₂, −20 °C, up to 5 h.	No Reaction
4	Triflic acid (1 equiv.), CH₂Cl₂, 25 °C, up to 5 h.	Cbz group was partially cleaved. No cyclization occurred.
5	Triflic acid (4 equiv.), CH₂Cl₂, 25 °C 1 h then at 45 °C for 3 h. Cooled down to room temperature and 3.9 equiv. of Et₃N was added dropwise and stirred overnight (∼14 h).	Cbz group was cleaved at 45 °C. Upon addition of Et₃N, cyclization occurred. Yield: 81%; *trans*/*cis* = 44/56.
6	1 M HCl/Et₂O (0.6 mol%)	No reaction
7	*t*-BuOK (0.8 equiv.), THF, 25 °C, 30 min.	Yield: 46%; *trans*/*cis* = 60/40

[a] Reactions were run in 1 mmol scale.
[b] Volume of the solvent was 5 ml.
[c] Yields were defined as percentage peak area at 214 nm.

Table 2
Base-catalyzed cyclization of **12**.
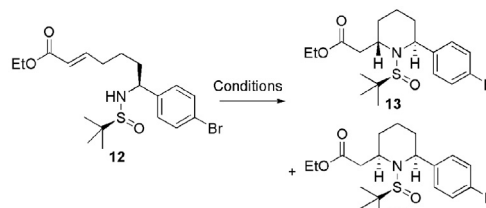
Entry	Condition[a,b]	Result[c]
1	*t*-BuOK (1.0 equiv.), THF, 25 °C, 30 min.	Traces of product. Complicated mixture
2	*t*-BuOK (1.05 equiv.), THF, −75 °C to 0 °C, 1 h.	Traces of product. Complicated mixture
3	Hunig's base (2.0 equiv.), ACN, 80 °C, 16 h	No product
4	TEA (2.0 equiv.), ACN, 80 °C, 16 h	No product
5	DBU (2.0 equiv.), ACN, 80 °C, 16 h	Yield: 56% *trans*/*cis* = 60/40
6	DBU (4.0 equiv.), DMA, 80 °C, 16 h	Yield: 56% *trans*/*cis* = 60/40
7	Cs₂CO₃(5 equiv.), ACN, 80 °C, 16 h	Yield: 70%, *trans*/*cis* = 60/40
8	Cs₂CO₃(5 equiv.), DMA, 40 °C, 4 h	Yield = 85%, *trans*/*cis* = 90/10

[a] Reactions were run in 1 mmol scale.
[b] Volume of the solvent was 5 ml.
[c] Yields were defined as percentage peak area at 214 nm.

Cs₂CO₃ (5 equiv.), DMA, 40 °C, 4 h (entry 8) provided more than 85% yield with good selectivity (*trans*/*cis* = 90/10).

At this stage we have solved the problem of making *trans*-piperidine with excellent yield and selectivity. However, the poor selectivity of the first step (Scheme 1, from **5a** to **6a**) made this route
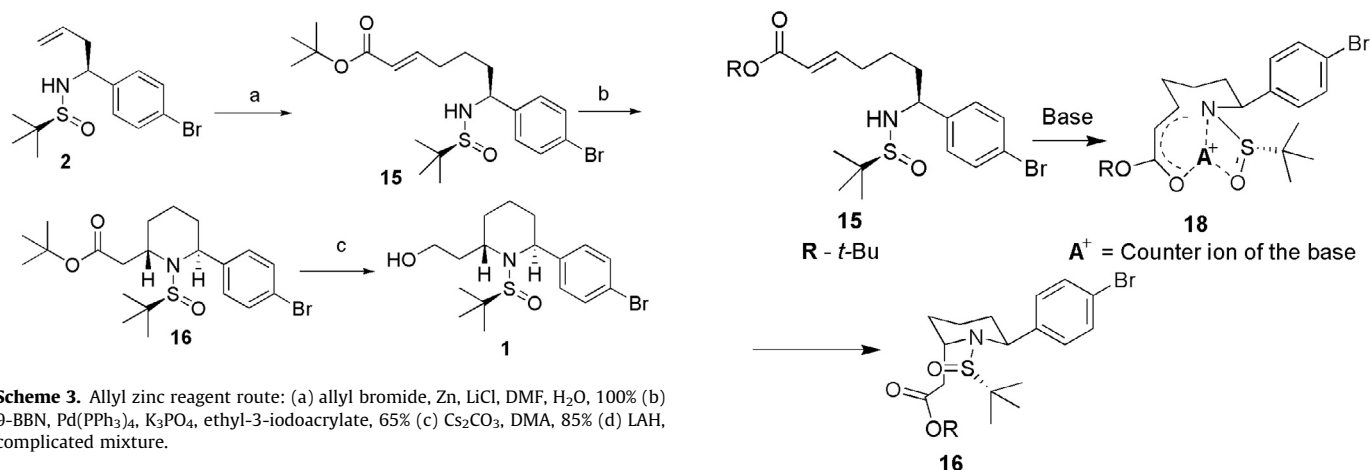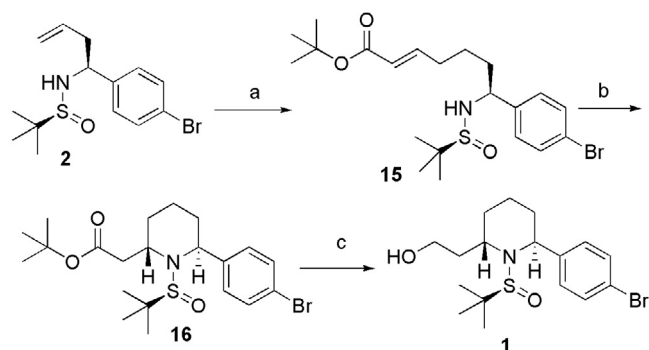
Scheme 3. Allyl zinc reagent route: (a) allyl bromide, Zn, LiCl, DMF, H_2O, 100% (b) 9-BBN, Pd(PPh$_3$)$_4$, K_3PO_4, ethyl-3-iodoacrylate, 65% (c) Cs_2CO_3, DMA, 85% (d) LAH, complicated mixture.

Fig. 1. Plausible mechanism for base mediated selectivity.

Scheme 4. Utilization of tert-butyl ester – the optimized synthesis: (a) 9-BBN, Pd (PPh$_3$)$_4$, K_3PO_4, tert-butyl-3-iodoacrylate, THF/Water, 82% (b) TBAF, THF, 82% (c) DIBAL, THF, 88%

unattractive for consideration in multigram-scale syntheses. To make this process more efficient we decided to use an allyl zinc reagent, which are well known [7] to afford better selectivity when added to sulfinimine. Accordingly, we revised the synthetic scheme as shown below (Scheme 3). Conversion of **5a** to **2** went smoothly to a single diastereomer. Compound **2** was reacted with 9-BBN [8]

and coupled with 3-iodo acrylate to form **12**. The stereochemical and spectroscopic data of **12** were identical as obtained from **6a**.

During the work-up and isolation process of **12**, we observed that the ethyl ester was partially hydrolyzed to the carboxylic acid. To avoid this hydrolysis, we planned to utilize a tert-butyl ester as a sterically hindered counterpart, which theoretically should retard the hydrolysis process as shown in Scheme 4. We prepared the tert-butyl acrylate **15** following the same procedure described for **12** (Scheme 3). Surprisingly, use of intermediate **15** not only eliminated the hydrolysis of the ester but also improved trans/cis selectivity (no cis isomer of **16** has been detected). Although high yield and selectivity have been achieved, we faced operational challenges (efficient stirring, work-up) during hundred-gram scale synthesis due to poor solubility of Cs_2CO_3. In our further optimization process, we discovered that the use of TBAF as a base [9] made the reaction mixture completely homogeneous and provided an excellent yield of **16** as a single diastereomer. After achieving high yield and selectivity, our next goal was to directly reduce ester **16** to alcohol **1**.

Attempted reduction of **16** with LAH gave a complicated mixture including de-brominated product. Use of both LiBH$_4$ or a mixture of LiBH$_4$/LiEt$_3$BH cleanly reduces the ester albeit at a very slow pace. Finally DIBAL [10] was found to be the reagent of choice for

17, X-ray crystal structure
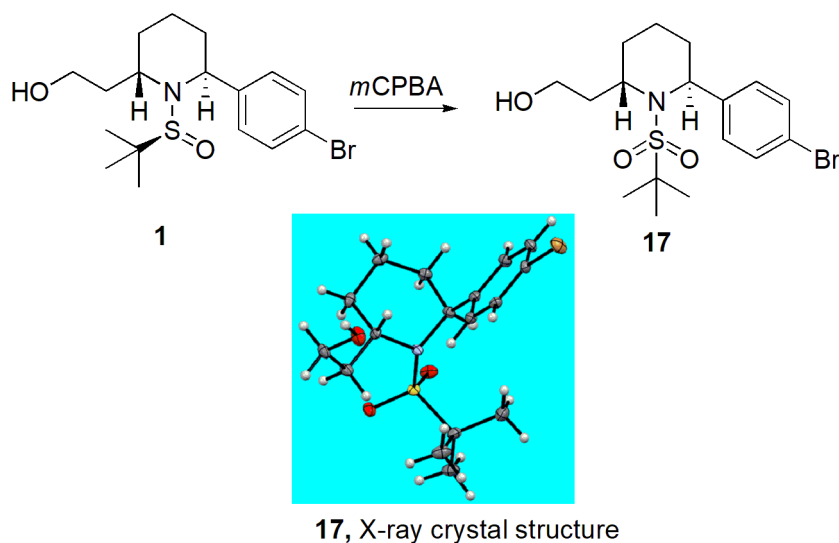
Scheme 5. Oxidation of sulfinamide to sulfonamide.
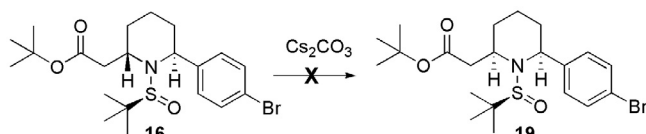
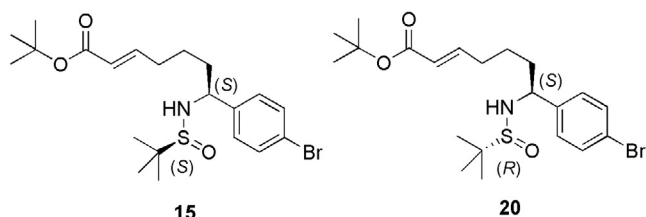**Scheme 6.** *Trans-cis* isomerization does not occur.

Fig. 2. "Matched (*SS*)" and "mismatched (*SR*)" systems.

the reduction in large scale. After reduction, the desired *trans*-piperidine **1** was isolated by crystallization. NMR spectra of both the ester and the alcohol were not conclusive for structural assignment. So, **1** was oxidized to **17** (Scheme 5). The X-ray structure of **17** confirmed the desired stereochemistry.

After completion of the synthesis of **1**, we also successfully extended this methodology to other analogs (see SI for **16b-16e**). This unique feature of the intra-molecular *aza*-Michael reaction with high stereoselectivity can plausibly be explained as shown in Fig. 1. Both the size of the acrylate and stereochemistry of the sulfinyl group help to bind the counter ion effectively (**18**) to generate the *trans*-ring system (**16**). Further mechanistic detail will be published elsewhere.

Treatment of **16** with base (Cs$_2$CO$_3$, 1–10 equiv., DMA, 40 °C, 4 h) did not show any isomerization to the thermodynamically more stable *cis*-form **19** (Scheme 6).

We also observed (Fig. 2) that only compound **15** [11] (matched stereochemistry) and its enantiomer delivered desired products with high yield and selectivity, whereas compound **20** (mismatched stereochemistry) and its enantiomer showed poor tendency towards cyclization.

This is the first example of hitherto unknown large-scale synthesis of 2,6-*trans*-piperidine analogs from an extremely poor Michael acceptor. Further application of this methodology to other systems is in progress. The important product **1** was utilized to prepare a novel class of anti-infective agents.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.12.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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[11] Compound **15** is an interesting intermediate. It can be easily converted to *trans*-alcohol **21** or *cis*-alcohol **23** using simple chemical manipulation as shown below.

Reagent: (a) TBAF, THF. (b) (i) LiBH$_4$, (ii) HCl, MeOH (c) (i) HCl, MeOH (ii) Et$_3$N (d) LiBH$_4$.