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First asymmetric synthesis of (*R*)-desmethylsibutramine†

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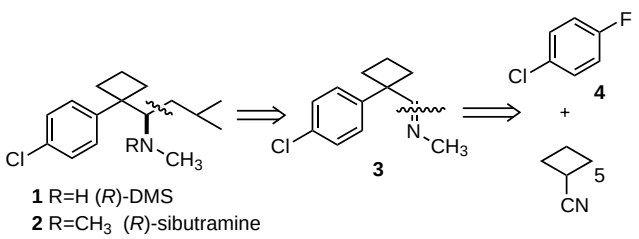
Abstract—A catalytic enantioselective addition of iBuLi to aldimine **3** derived from methyl amine and 1-(4-chlorophenyl) cyclobutanecarboxaldehyde is used as the key step in the asymmetric synthesis of (*R*)-desmethylsibutramine, a single enantiomer version of a pharmacologically active metabolite of anti-obesity drug sibutramine (Meridia®).

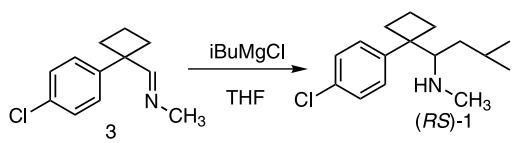
(*R*)-Desmethylsibutramine ((*R*)-DMS) **1** is a single enantiomeric version of a pharmacologically active metabolite of sibutramine **2**, a new class of compound for the treatment of obesity.[1] Preliminary preclinical studies indicate that (*R*)-DMS is a potent serotonin, norepinephrine, and dopamine reuptake inhibitor.[2] In order to evaluate this unique triple mechanism of action toward attention deficit hyperactivity disorder (ADHD) and major depression, process research efforts were directed toward the synthesis of optically pure (*R*)-DMS. In context with such studies, we recently reported the synthesis of optically pure (*R*)-DMS and (*S*)-DMS using two different resolution processes.[3,4] Although these resolution methods are effective in producing several kilo quantities of optically pure (*R*)-DMS, the overall yield for these multi-step processes are only in the range of 20–25%. In order to identify an efficient high yielding synthesis for (*R*)-DMS, we focused our research efforts toward catalytic asymmetric methods. Herein, we report the first asymmetric synthesis of (*R*)-DMS using a catalytic enantioselective addition of iBuLi to methyl imine **3** as the key step.[4]



Scheme 1.

The resolution process provides a scalable route for the production of optically pure DMS; however, a highly economical process will be needed to meet long-term goals. A short, convergent racemic and asymmetric synthesis for DMS was evaluated as a potential approach to economical processes. It was envisioned that the addition of isobutyl organometallics to the methyl imine would provide a direct access to DMS. Also, such methods in principle can be conveniently translated into a catalytic asymmetric synthesis by conducting imine addition reactions in the presence of chiral Lewis acids and/or chiral ligands.

Our retro synthetic analysis is based on the disconnection that eliminates the use of protection and deprotection steps as shown in Scheme 1. The enantioselective addition of an *iso*-butyl organometallic to aldimine **3** derived from methylamine, would provide optically active DMS. The required imine **3** can be readily obtained from commercially available 4-chloro-fluorobenzene **4** and cyclobutyl nitrile **5**.[5]



(1)

Thus, treatment of 4-chloro-fluorobenzene **4** with cyclobutyl nitrile in the presence of KHMDS in THF provided nitrile **6** in 90% yield. Nitrile **6** was converted

Keywords: asymmetric synthesis; desmethylsibutramine; chiral ligands.

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† This paper is dedicated to Professor Carl R. Johnson on the occasion of his retirement.

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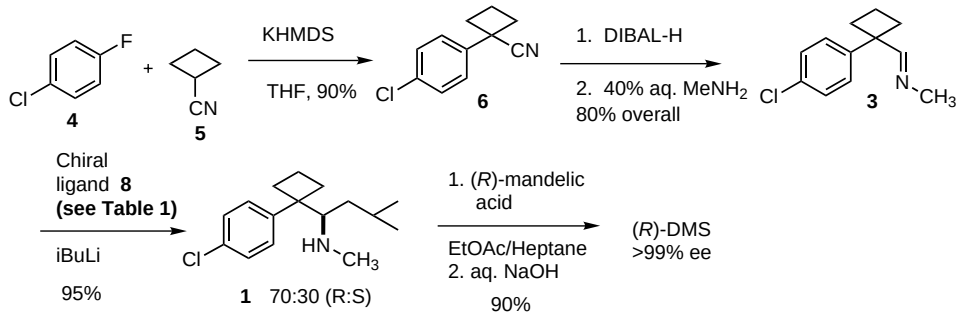
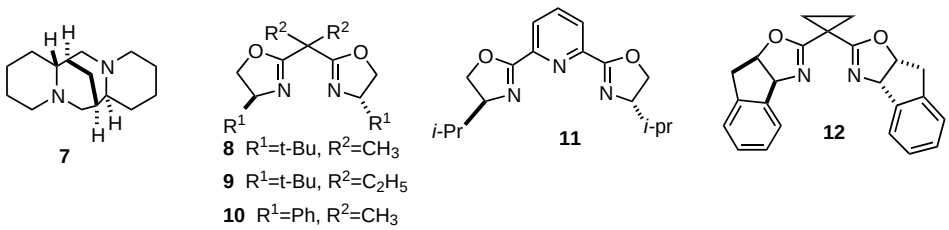


Scheme 2.



to methylimine **3** using a two-step sequence, as shown in Scheme 2. Reaction of nitrile **6** with DIBAL-H afforded an aldehyde, which upon treatment with the aqueous solution of methylamine provided the desired imine **3** in 80% overall yield.

After completing the synthesis of the key intermediate methyl imine **3**, we focused our attention on the addition of organometallic reagents like iBuMgCl and iBuLi to aldimine **3**. Although a number of reports have been documented for the enantioselective addition of the organometallic addition to imines derived from aryl amines,[6,7] the addition to simple imines, such as methyl imines are relatively unknown.[8] Therefore, we began our studies with the addition of iBuMgCl to imine **3**.

Preliminary experiments with imine and iBuMgCl did not give the desired product when conducted at −20°C to ambient temperature. Attempts at heating the reaction mixture in THF led to decomposition. Subsequently, it was found that in the presence of $BF_3{\cdot}OEt_2$, the Grignard addition reaction proceeded at −20°C to give the desired product (Eq. (1)). Interestingly, the use of 2 equiv. of iBuMgCl with 1 equiv. of $BF_3{\cdot}OEt_2$ is required to provide a 60% yield. This route provided a short racemic synthesis of DMS. Application of the above racemic synthesis to the asymmetric process requires the identification of suitable chiral Lewis acids, or a chiral ligand that accelerates the formation of DMS from imine. Using chiral Lewis acids, or chiral ligands with iBuMgCl, gave disappointing results.

At this stage, we turned our attention to exploring the addition of iBuLi to imine **3** in the presence of chiral ligands. A variety of chiral ligands have been used in the asymmetric addition of organolithium reagents to imines.[6,7] Among them, sparteine **7** and bis-oxazolines derivatives represent the most widely used ligands for these types of asymmetric reactions.[9] Therefore, we began our studies with the addition of iBuLi to imine **3** with sparteine as a chiral ligand. Thus, using a stoichiometric amount of sparteine gave only 15% ee with sluggish conversion. At this point, we extended our investigation to include the bis-oxazoline type of ligands. As shown in Table 1, using 1 equiv. of **8** in toluene gave 35% ee with 95% conversion. Interestingly, decreasing the amount of **8** to 20 mol% increased the ee to 40%, without affecting the conversion. However, further reducing the amount of ligand did not increase ee, but rather decreased the ee to 20% with >95% conversion. Using 20 mol% of diethyl bis-oxazoline derivative **9** gave disappointing results with only 20% ee. When other C-2 symmetric bis-oxazolines, such as **10**–**12** were employed, no reaction occurred at any of the reaction conditions employed.[10]

Table 1. Asymmetric addition of iBuLi to methyl imine **3**

Entry	Chiral ligand (equiv.)	Solvent	Conversion[a] (%)	Ee[b]
1	7 (1.0)	Toluene	10	15
2	8 (1.0)	MTBE	0	–
3	8 (1.0)	Toluene	95	35
4	8 (0.2)	Toluene	95	40
5	8 (0.1)	Toluene	95	20
6	9 (0.2)	Toluene	95	20
7	10 (1.0)	Toluene	0	–
8	11 (1.0)	Toluene	0	–
9	12 (1.0)	Toluene	0	–

[a] Conversion is determined by HPLC A%.

[b] Ee is determined by chiral HPLC analysis using chirobiotic V column (4.6 mm×25 cm), and 20 mM ammonium acetate/IPA (65:35) as mobile phase with flow rate 0.7 mL/min (t_R for (*R*)-isomer 23.3 min and for (*S*)-isomer 28.5 min).

Thus, the optimum conditions for the addition of iBuLi to imine **3** involves the use of 20 mol% of **8** in toluene at –78 to –60°C, and provides 40% ee with 95% yield.[11] Although the asymmetric addition of iBuLi to imine **8** gave only 40% ee, it is important to note that the % ee can be enriched to >99% ee with >90% recovery by a single crystallization with (*R*)-mandelic acid ($[\alpha]_D^{20} = +5.3°$ (*c* 5.8, CH_3OH)). Utilizing this asymmetric synthesis (Scheme 2), the overall yield for (*R*)-DMS can be increased to 48%, compared to 20–25% for the resolution process.

In summary, we have demonstrated the first example of an asymmetric addition of iBuLi to methyl imine, and developed a tactile enantioselective synthesis of (*R*)-DMS. Identification of new chiral ligands to improve the enantioselectivity in the iBuLi addition to methyl imine **3** is currently being evaluated, and will be reported on shortly.

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11. Experimental procedure for asymmetric addition of iBuLi to imine **3** (entry 4, Table 1) is given below. To a −78°C cooled solution of **2** (58 mg, 0.2 mmol) in toluene (4 mL) was added iBuLi (1.3 mL, 1.5 M in hexane, 1.95 mmol) and stirred for 0.5 h. A solution of imine **3** (200 mg, 0.97 mmol) in toluene (1 mL) was added drop wise to the reaction mixture and stirred at –78 to –60°C for 3 h. The reaction was quenched with methanol (1 mL) and warmed to ambient temperature. The reaction mixture was diluted with EtOAc (10 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated. The product was purified by silica gel chromatography (eluting with 1% NEt_3 in EtOAc) to give 240 mg (95%) of amine as oil. NMR ($CDCl_3$): ^1H (δ), 0.85–1.1 (m, 6H), 1.24–1.5 (b, 2H), 1.65–2.14 (b, 4H), 2.2–2.5 (b, 4H), 2.5–2.7 (m, 2H), 3.4–3.6 (b, 1H), 7.3–7.5 (m, 4H), 9.0–9.5 (b, 2H). ^{13}C (δ): 15.5, 21.4, 23.5, 24.7, 31.4, 32.4, 33.2, 35.9, 49.1, 64.2, 128.5, 129.4, 133.0, 141.6.