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Enantioselective addition of methyllithium to aromatic imines catalyzed by C_2 symmetric tertiary diamines

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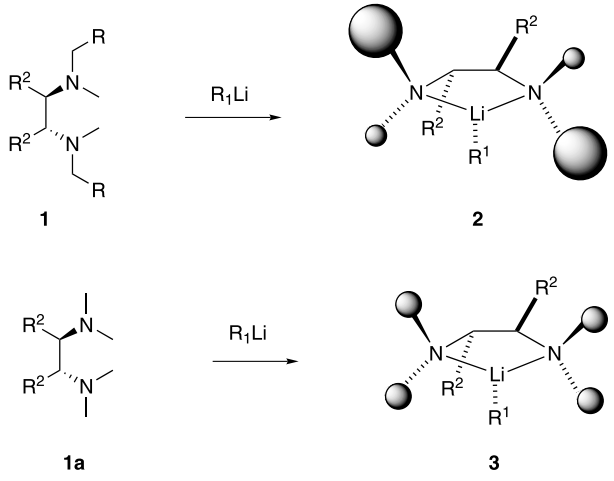
Abstract—Enantioselective addition of methyllithium to aromatic imines catalyzed by C_2 symmetric tertiary diamines is described. Eleven diamines have been tested, for which dramatic effect of the nitrogen substitution has been observed. Diamines bearing hindered group close to the nitrogen led to racemic product while homologous hindered diamines led to the best results. Enantiomeric excess up to 74% could be achieved. An explanation of the absolute configuration of the product obtained is given considering the mechanism of the reaction.

1. Introduction

The discovery of new ligands for enantioselective reactions is one of the major goals in asymmetric synthesis. Diamines have often been used as chiral inducers and have turned out to be a powerful tool in inducing high levels of enantioselectivity.[1] Their ability to be associated with several metals makes them even more attractive as a wide range of reactions can be performed in the presence of diamines.[2] We are interested in the continuing development of these ligands by modifying their structures and substituents to improve their selectivities and extend their application.[3] In that context, we recently reported conceptually new chiral tertiary diamines **1** capable to generate, when associated with organolithium reagents, reactive intermediates **2**, which contain a chiral nitrogen atom.[4] In the five membered ring formed with a metallic species, the more bulky nitrogen substituent adopts a trans relationship with the R^2 group of the carbon backbone (Scheme 1). Similar conceptually chiral diether ligands have been studied, for which stereogenic oxygen atoms are involved in the reactive intermediate.[5] Many ligands including (−)-sparteine have been used for the enantioselective addition of organometallic reagents to imines.[6]

In our preliminary study, concerning the catalytic enantioselective addition of methyllithium to aromatic imines, dramatic variations in selectivities have been observed depending on R substituent. On the contrary, in the case of diamine **1a**, both nitrogen atoms bearing four identical substituents cannot become stereogenic centers.[4] We would like to disclose in this article the complete study concerning the enantioselective addition of methyllithium to aromatic imines catalyzed by our diamines. Furthermore, mechanistic considerations will be discussed to explain the stereochemical outcome of the reaction.



Scheme 1.

Keywords: Asymmetry; Diamines; Organolithium; Imines; Catalysis.
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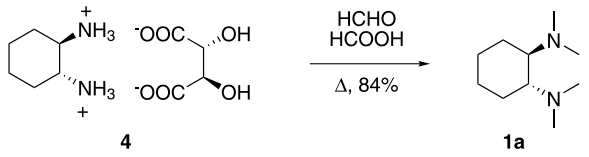
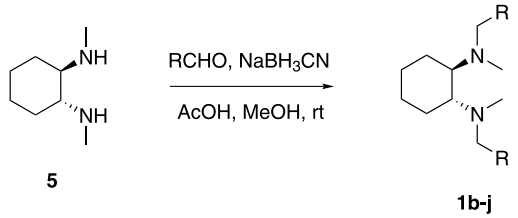


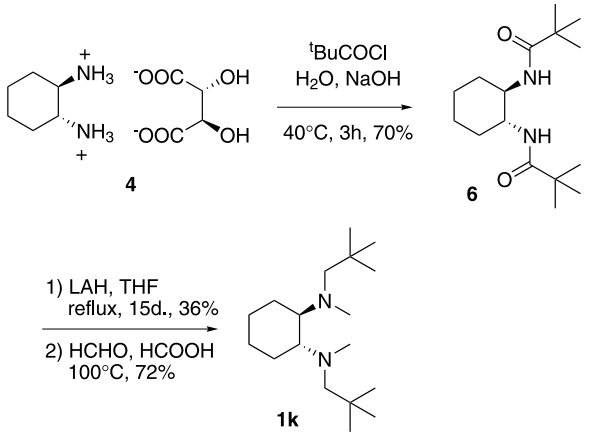
Scheme 2.

2. Synthesis of diamine ligands

Diamines **1a–j** have all been prepared in good yields from the same starting material **4** readily available on a large scale.[7] Ligand **1a** was obtained by an Eschweiler–Clark reaction directly performed on **4** (Scheme 2) while ligands **1b–j** have been obtained by reductive amination of *N*,*N*′-dimethyl-1,2-cyclohexanediamine **5** with the appropriate aldehyde (Scheme 3, Table 1). Diamine **5** can be prepared very easily on a large scale following the two steps procedure previously described.[8] Concerning the synthesis of bulkier ligand **1k**, reductive amination failed: only traces of the product were detected even after several days of reaction. Therefore, a three-step procedure was followed: bis-amide **6** was easily prepared from **4** and reduced with LAH to give the corresponding secondary diamine in moderate yield after 2 weeks. Finally, an Eschweiler–Clark methylation led to the desired ligand **1k** (Scheme 4, Table 1).



Scheme 3.



Scheme 4.

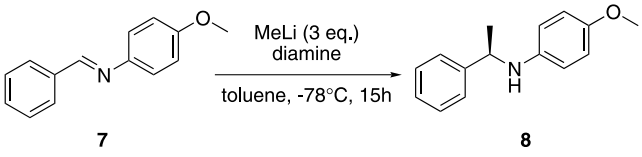
Table 1. Reductive amination of *N*,*N*′-dimethyl-1,2-cyclohexanediamine producing ligands **1b–j**

Entry	Product	R	Yield%
1	**1b**	Et	68
2	**1c**	*n*-Pr	89
3	**1d**	^{i}Pr	72
4	**1e**	^{i}Bu	82
5	**1f**	CH_2^tBu	83
6	**1g**	Ph	49
7	**1h**	CH_2Ph	82
8	**1i**	CH_2CH_2Ph	75
9	**1j**	2,4,6-Me_3–C_6H_2	87

3. Results and discussion

In a preliminary study, the efficiency of diamines were evaluated in the addition of methyllithium to imine **7**. We compared first diamines **1a** and **1g** under stoichiometric conditions and found that the adduct was formed in 20 and 48% ee, respectively, which validates our starting hypothesis.

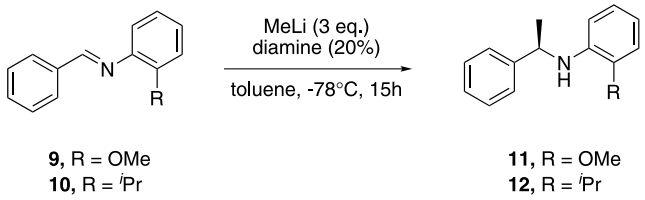
As methyllithium was reacting very slowly with imines at −78 °C without activation (6% yield after 120 min at −78 °C),[9] catalysis was thought to be possible and indeed we observed that 0.2 equiv of diamine was sufficient to maintain good yields without any loss of enantioselectivity. Therefore, all of the other diamines were tested in catalytic amount. A strong influence of the lateral chain was observed. By changing R from H to ethyl and *n*-propyl led to an increase of the ee. When bulkier substituents with ramified alkyl chains were placed close to the nitrogen atom, the products were obtained as a racemic mixture in good yields (Table 2, entries 4, 11, and 12). On the contrary, when the size of the bulky substituent increased in the β position to the nitrogen atom, an increase in ee was observed again. Indeed, the best selectivity was obtained with diamines **1f** and **1h** (Table 2, entries 6 and 9). Moving the bulky substituent another methylene unit away did not improve the selectivity but the corresponding ligand **1i** was still efficient as the product was obtained in 58% ee (Scheme 5).



Scheme 5.

Table 2. Enantioselective addition of MeLi to imine **7** with diamines **1a–k**

Entry	Ligand	Equivalent	Yield%	ee%
1	**1a**	2	78	20 (R)
2	**1b**	0.2	93	24 (R)
3	**1c**	0.2	93	34 (R)
4	**1d**	0.2	94	0
5	**1e**	0.2	94	53 (R)
6	**1f**	0.2	98	67 (R)
7	**1g**	0.2	78	48 (R)
8	**1g**	2	94	40 (R)
9	**1h**	0.2	98	68 (R)
10	**1i**	0.2	93	58 (R)
11	**1j**	0.2	95	0
12	**1k**	0.2	76	0



9, R = OMe
10, R = ^{i}Pr

11, R = OMe
12, R = ^{i}Pr

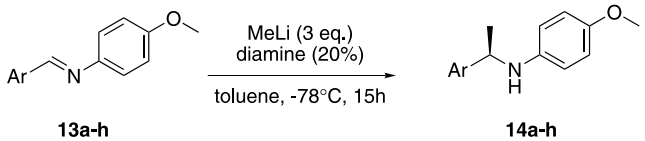
Scheme 6.

We have evaluated the efficiency of our best diamines on other imines. Initially, the *para*-methoxy phenyl moiety was selected because it is an easily removable protecting group of the nitrogen functionality. However, it appears to be more difficult in some cases.[9–11] Nevertheless, we have checked the influence of an *ortho* substituent such as in substrates **9** and **10** (Table 3). The *ortho*-methoxy substituent was found to accelerate considerably the rate of the addition, thus, allowing a fast addition of methyllithium through the non catalyzed process. Therefore, the selectivity obtained with diamine **1f** on imine **9** was very low. Imine **10** has improved the selectivity of the addition compared to the non *ortho*-substituted imines only when diamine **1a** was used (Table 3, entry 3). On the contrary, while **1f** led to 67% ee with **7**, the selectivity dropped to 20% ee with the *ortho* isopropyl substituted imine **10** (Table 3). This result is in sharp contrast with the result obtained with ligand **1a** and with the result reported by Tomioka.[9,10] We can explain these differences by the great sensitivity of our diamines to steric hindrance. However, this behavior had already been observed with (−)-sparteine[12] and when the fine tuning of our diamines **1a–1k** were made (Table 2). In the case of substrates as well, when steric hindrance was increased close to the reaction site, unfavored steric interactions appear with the hindered diamine **1f** (Scheme 6).

Table 3. Enantioselective addition of MeLi to imine **9–10** with diamines **1a** and **1f**

Entry	Substrate	Ligand	Yield%	ee%
1	**9**	**1a**	82	6
2	**9**	**1f**	77	2
3	**10**	**1a**	99	24
4	**10**	**1f**	93	20

The aldehyde part of the imines were changed with other aromatic substitution. Imines **13a–h** were tested under the same experimental conditions as **7** with diamines **1h** or **1f**. Although, both diamines **1f** and **1h** gave the same selectivity for imine **7**, diamine **1h** was usually found to be superior to **1f** with imines **13a–h** (Table 4). Similar levels of enantioselectivity were obtained with *para* substituted



13a-h

14a-h

a, Ar = *p*-Me-C_6H_4
b, Ar = *p*-Cl-C_6H_4
c, Ar = p-CF3-C6H4
d, Ar = 2-furyl
e, Ar = 2-thienyl
f, Ar = 2-pyridyl
g, Ar = 2-naphthyl
h, Ar = piperonyl

Scheme 7.

Table 4. Enantioselective addition of MeLi to imines **7** and **13a–h** with diamines **1f** and **1h**

Entry	Substrate	Ligand	Yield%	ee%[a]
1	**7**	**1h**	98	68 (R)
2	**13a**	**1h**	50	74
3[b]	**13b**	**1f**	70	57 (+)
4	**13b**	**1h**	57	68 (+)
5	**13c**	**1f**	70	38 (−)
6	**13c**	**1h**	35	58 (−)
7	**13d**	**1f**	94	20
8	**13e**	**1f**	93	58
9	**13f**	**1f**	87	4
10[c]	**13g**	**1f**	78	42
11[c]	**13g**	**1h**	42	68
12	**13h**	**1h**	88	48 (+)

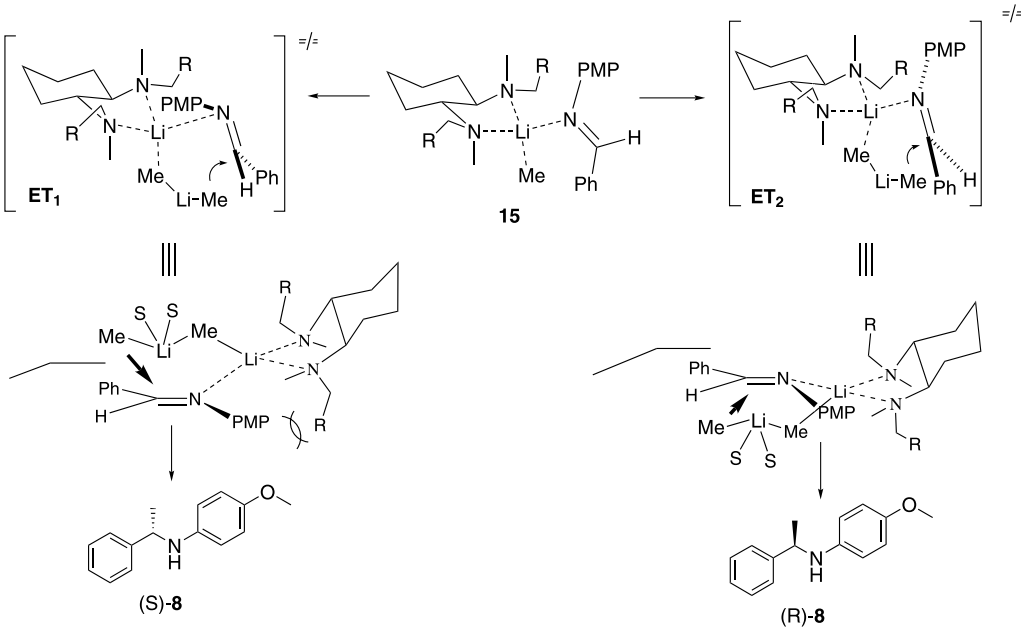
(a) Absolute configuration or sign of the optical rotation. (b) Reaction run at −65 °C. (c) Reaction run at −30 °C.

phenyl derivatives **13a–c** showing quite small electronic effects. On the other hand, the reactivity was found to be very different in some cases: for instance, poor yields were obtained with imines **13g** and **13h**, which reacted at −65 and −30 °C, respectively. Heteroaromatic substituted imines **13d–f** showed as well a very different behavior. Unlike imine **13e**, with the thienyl substitution, both imines **13d** and **13f** were not good substrates (Scheme 7).

This difference can be explained by the availability of the lone pair of the heteroatom in the aromatic ring system. As this lone pair is less engaged in the aromaticity of the heteroaromatic ring for pyridyl and furyl compared to thienyl, the corresponding imines **13d** and **13f** are much more activated than **13e** and react easily in a non-catalyzed process leading to the products with low selectivities.

The absolute configuration of product **8** has been already reported by Tomioka et al.[9] By using Tomioka's ligand, we have been able to assign by comparison the R absolute configuration for amine **8** when we have used our diamines. If the same stereochemical pathway is assumed for all imines employed, compounds **14a–h** should present the same R configuration as for product **8**. To explain these results, we think that a first complexation occurs between the diamine–MeLi complex and the nitrogen lone pair of the imine leading to the intermediate **15** close to the transition state (Scheme 8). The latter is reached after a small rotation of the imine double bond. If the imine turns to react with its Si face (ET_1, Scheme 8), an unfavorable interaction appears between the PMP nitrogen substituent and the R part of the ligand. On the contrary, if the imine turns to react with its Re face (ET_2, Scheme 8), a much more favored transition state is formed without destabilizing interactions. The addition occurs on the Re face of the imine leading to the product of R configuration.

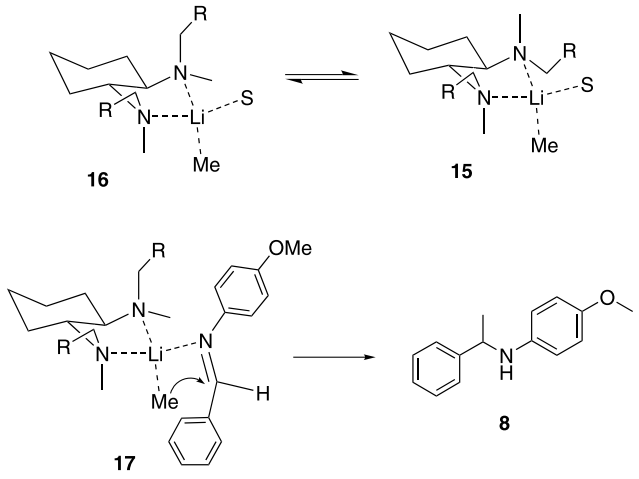
It has been noticed that increasing the amount of methyllithium accelerates the rate of the reaction. One reason for that has already been discussed by Tomioka et al.[9] by considering that the amide product can also be a ligand for the diamine. We envisioned a 6 centers transition state, in which two methyllithium aggregates to reach the most favored transition state ET_2 (Scheme 8). It then follows that with 1 equiv of methyllithium, much lower yields are obtained and it is very difficult for the reaction to



Scheme 8.

go to completion. In the catalytic process, we used only 20% of diamine with respect to substrate and 3 equiv of methyllithium, meaning that the ratio diamine–RLi is actually close to 7%. In that situation, and in a non polar solvent such as toluene, it can be reasonable to consider the methyllithium in a more aggregated state than the dimeric reactive intermediate. The second lithium of this species is likely complexed by diethylether present in the reaction medium (methyllithium is available as solution in diethylether). The theoretical studies dedicated to the aldehyde/alkyllithium condensation problem are relatively scarce[13] while no description of the addition pathway of organolithium reagents onto imines has been reported to our knowledge. Nevertheless, in the case of aldehydes, the formation of an open dimer intermediate, which converts into a six membered cyclic transition state has been preferred by theoretical studies.[13]

For less hindered diamines such as **1b**, **1c**, **1e** or **1h**, ET_1 can explain in part the lower selectivities obtained. But for hindered diamines with bulky substituents α to the nitrogen atom, the adduct was formed without any selectivity. As the chiral discrimination should have been much stronger with these diamines (**1d**, **1j**, **1k**), it seems reasonable to envision, for the diamine/RLi complex, the existence of the equilibrium of complexes **15** and **16** through the free diamine (Scheme 9). When R becomes too bulky, a competitive unfavored interaction between CH_2R and Me of methyllithium could lead to complex **16**, which is close to a *meso* situation. The reactive complex **17** would lead to a non selective process as little spatial discimination exists.



Scheme 9.

Further studies are under progress to obtain spectroscopic evidence about the real reactive species with the aim of establishing a more accurate mechanism.

In conclusion, new ligands have been developed for the catalytic asymmetric addition of methyllithium to imines. We have demonstrated that in this new ligand family, the asymmetric induction can be enhanced by a stereogenic nitrogen atom. These new diamines are of interest because they are easy to prepare on a large scale in enantiomerically pure form, stable on storage and recoverable after use. By choosing the appropriate nitrogen substituents, enantioselectivities up to 74% have been obtained. A model, which could explain the stereochemical outcome of the reaction has been proposed. Further studies are currently in progress in our laboratory to give experimental support to this mechanism and to find more efficient and more general diamines.

4. Experimental

4.1. General

Unless otherwise stated, all reagents were employed as received. Solvent were distilled on CaH_2 or Na/benzophenon. NMR spectrum were made on BRUCKER

400 MHz for proton and BRUCKER 100 MHz for carbon in $CDCl_3$.

4.1.1. *N,N,N′N′*-(1*R*,2*R*)-Tetramethylcyclohexane-1,2-diamine 1a. (*R,R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate salt **5** (24 g, 0.091 mol) was dissolved in formic acid 85% (36 mL) and formaldehyde 40% (44 mL) was added slowly at room temperature. The mixture was heated at reflux 2 h. After cooling, the reaction mixture was made basic until pH 14 and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was distilled (bp=50 °C/0.1 mmHg) to give a colorless liquid (11.35 g, 74%). ^{1}H NMR: δ(ppm) 1.05–1.15 (m, 4H), 1.68–1.74 (m, 2H), 1.78–1.90 (m, 2H), 2.26 (s, 12H), 2.35–2.40 (m, 2H). ^{13}C NMR: δ(ppm) 22.8, 25.6, 40.1, 63.8. $[\alpha]_D^{20}=-62.9$ (*c* 1.05, $CHCl_3$).

4.2. General procedure for reductive amination of 1b–j

To a solution of *N,N′*-dimethyl cyclohexanediamine (1 g, 7 mmol) in methanol (15 mL) was added aldehyde (21 mmol), sodium cyanoborohydride (28 mmol) and acetic acid (7 mmol). The mixture was stirred 24 h, methanol was then evaporated and the residue was diluted in ether (20 mL). The organic layer was washed with sodium hydroxide 10% (2×15 mL) and with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by distillation, acid–base extraction or column chromatography.

4.2.1. (1*R*,2*R*)-*N,N′*-Dipropyl-*N,N′*-dimethyl-cyclohexane-1,2-diamine 1b. The product was obtained according to the general procedure, purified by distillation (bp=80–90 °C/0.1 mmHg) and isolated as a colorless oil in 68% yield. ^{1}H NMR: δ(ppm) 0.86 (t, *J*=7.32 Hz, 6H), 1.0–1.2 (m, 4H), 1.4–1.5 (m, 4H), 1.65–1.71 (m, 2H), 1.73–1.80 (m, 2H), 2.23 (s, 6H), 2.35–2.50 (m, 6H). ^{13}C NMR: δ(ppm) 12.1, 21.6, 25.7, 25.9, 36.6, 56.5, 63.1. $[\alpha]_D^{20}=-27.7$ (*c* 1.0, $CHCl_3$). MS (*m/z*) 226, 211, 183, 154, 152, 126, 112, 86, 70, 57. HRMS calcd for $C_{14}H_{30}N_2$ 226.2409, found 226.2408.

4.2.2. (1*R*,2*R*)-*N,N′*-Dibutyl-*N,N′*-dimethyl-cyclohexane-1,2-diamine 1c. The product was obtained according to the general procedure, purified by distillation (bp=90–100 °C/0.1 mmHg) and isolated as a colorless oil in 89% yield. ^{1}H NMR: δ(ppm) 0.88 (t, *J*=7.2 Hz, 6H), 1.0–1.2 (m, 4H), 1.2–1.48 (m, 8H), 1.63–1.69 (m, 2H), 1.72–1.78 (m, 2H), 2.21 (s, 6H), 2.38–2.52 (m, 6H). ^{13}C NMR: δ(ppm) 14.1, 20.8, 25.6, 25.9, 30.8, 36.6, 54.2, 63.0. $[\alpha]_D^{20}=-21.6$ (*c* 0.99, $CHCl_3$). MS (*m/z*) 254, 239, 211, 197, 166, 139, 126, 100, 84, 56. HRMS calcd for $C_{16}H_{34}N_2$ 254.2722, found 254.2719.

4.2.3. (1*R*,2*R*)-*N,N′*-Diisobutyl-*N,N′*-dimethyl-cyclohexane-1,2-diamine 1d. The product was obtained according to the general procedure, purified by distillation (bp=80–90 °C/0.1 mmHg) and isolated as a colorless oil in 72% yield. ^{1}H NMR: δ(ppm) 0.88 (t, *J*=6.2 Hz, 12H), 1.03–1.25 (m, 4H), 1.63–1.80 (m, 6H), 2.12–2.21 (m, 2H), 2.19 (s, 6H), 2.35–2.45 (m, 4H). ^{13}C NMR: δ(ppm) 20.9, 21.1, 26.0, 26.4, 26.8, 36.1, 63.8, 64.9. $[\alpha]_D^{20}=+23.4$ (*c* 0.99, $CHCl_3$). MS (*m/z*) 254, 239, 211, 197, 166, 139, 126, 100, 84, 57. HRMS calcd for $C_{16}H_{34}N_2$ 254.2722, found 254.2719.

4.2.4. (1*R*,2*R*)-*N,N′*-Bis-(3-methylbutyl)-*N,N′*-dimethyl-cyclohexane-1,2-diamine 1e. The product was obtained according to the general procedure and purified by distillation (bp=130–140 °C/1 mmHg) and isolated as a colorless oil in 82% yield. ^{1}H NMR: δ(ppm) 0.87 (d, *J*=2.0 Hz, 6H), 0.89 (d, *J*=2.0 Hz, 6H), 1.03–1.22 (m, 4H), 1.26–1.40 (m, 4H), 1.57 (s, *J*=6.6 Hz, 2H), 1.65–1.72 (m, 2H), 1.74–1.82 (m, 2H), 2.23 (s, 6H), 2.42–2.56 (m, 6H). ^{13}C NMR: δ(ppm) 22.8, 23.0, 25.5, 25.9, 26.5, 36.7, 37.6, 52.6, 62.9. $[\alpha]_D^{20}=-27.2$ (*c* 1.02, $CHCl_3$). MS (*m/z*) 282, 267, 239, 211, 197, 180, 140, 126, 114, 84, 58. HRMS calcd for $C_{18}H_{38}N_2$ 282.3035, found 282.3026.

4.2.5. (1*R*,2*R*)-*N,N′*-Bis-(3,3-dimethyl-butyl)-*N,N′*-dimethyl-cyclohexane-1,2-diamine 1f. The product was obtained according to the general procedure, purified by distillation (bp=150 °C/1 mmHg) and isolated as a colorless oil in 83% yield. ^{1}H NMR: δ(ppm) 0.90 (s, 18H), 1.05–1.25 (m, 4H), 1.35–1.45 (m, 4H), 1.67–1.74 (m, 2H), 1.76–1.83 (m, 2H), 2.25 (s, 6H), 2.42–2.58 (m, 6H). ^{13}C NMR: δ(ppm) 22.3, 25.9, 29.6, 29.8, 37.0, 42.2, 50.1, 62.7. $[\alpha]_D^{20}=-31.1$ (*c* 1.02, $CHCl_3$). MS (*m/z*) 310, 295, 253, 225, 196, 180, 154, 128, 84, 57. HRMS calcd for $C_{20}H_{42}N_2$ 310.3348, found 310.3342.

4.2.6. (1*R*,2*R*)-*N,N′*-Dibenzyl-*N,N′*-dimethyl-cyclohexane-1,2-diamine 1g. The product was obtained according to the general procedure, purified by distillation (bp=170 °C/1 mmHg) and isolated as a colorless oil in 49% yield. ^{1}H NMR: δ(ppm) 1.05–1.35 (m, 4H), 1.7–1.8 (m, 2H), 1.9–2.0 (m, 2H), 2.24 (s, 6H), 2.6–2.7 (m, 2H), 3.68 (d, *J*=13.4 Hz, 2H), 3.76 (d, *J*=13.1 Hz, 2H), 7.2–7.35 (m, 6H), 7.38–7.45 (m, 4H). ^{13}C NMR: δ(ppm) 25.8, 25.9, 36.2, 58.6, 63.7, 126.5, 127.9, 128.8, 140.9. $[\alpha]_D^{20}=+7.22$ (*c* 1.02, $CHCl_3$). MS (*m/z*) 322, 257, 231, 200, 180, 160, 120, 91, 65. HRMS calcd for $C_{22}H_{30}N_2$ 322.2409, found 322.2418.

4.2.7. (1*R*,2*R*)-*N,N′*-Dimethyl-*N,N′*-diphenethyl-cyclohexane-1,2-diamine 1h. The product was obtained according to the general procedure, purified by distillation (bp=240 °C/1 mmHg) and isolated as a brown oil in 83% yield. ^{1}H NMR: δ(ppm) 1.05–1.30 (m, 4H), 1.65–1.75 (m, 2H), 1.78–1.88 (m, 2H), 2.35 (s, 6H), 2.52–2.62 (m, 2H), 2.70–2.85 (m, 8H), 7.15–7.25 (m, 6H), 7.28–7.40 (m, 4H). ^{13}C NMR: δ(ppm) 25.8, 25.9, 35.5, 36.6, 56.6, 63.5, 125.7, 128.1, 128.8, 141.1. $[\alpha]_D^{20}=-13.84$ (*c* 1.0, $CHCl_3$). MS (*m/z*) 350, 259, 214, 155, 112, 70. HRMS calcd for $C_{24}H_{34}N_2$ 350.2722, found 350.2737.

4.2.8. (1*R*,2*R*)-*N,N′*-Dimethyl-*N,N′*-bis-(3-phenyl-propyl)-cyclohexane-1,2-diamine 1i. The product was obtained according to the general procedure, purified by distillation (bp=190–210 °C/0.1 mmHg) and isolated as a yellow oil in 75% yield. ^{1}H NMR: δ(ppm) 1.05–1.25 (m, 4H), 1.68–1.75 (m, 2H), 1.76–1.90 (m, 6H), 2.28 (s, 6H), 2.50–2.72 (m, 10H), 7.18–7.25 (m, 6H), 7.28–7.33 (m, 4H). ^{13}C NMR: δ(ppm) 25.6, 25.7, 30.1, 33.8, 36.3, 54.1, 63.1, 125.5, 128.1, 128.3, 142.6. $[\alpha]_D^{20}=-6.7$ (*c* 1.44, $CHCl_3$). MS (*m/z*) 378, 287, 230, 188, 149, 91. HRMS calcd for $C_{26}H_{38}N_2$ 378.3035, found 378.3013.

4.2.9. (1*R*,2*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis-(2,4,6-trimethyl-benzyl)-cyclohexane-1,2-diamine 1j. The product was obtained according to the general procedure, purified by acid–base treatment and isolated as a solid in 87% yield. ^{1}H NMR: δ(ppm) 1.10–1.26 (m, 4H), 1.75–1.82 (m, 2H), 1.87 (s, 6H), 1.96–2.04 (m, 2H), 2.27 (s, 6H), 2.38 (s, 12H), 2.40–2.47 (m, 2H), 3.48 (d, J=12.6 Hz, 2H), 3.72 (d, J=12.9 Hz, 2H), 6.81 (s, 4H). ^{13}C NMR: δ(ppm) 20.0, 20.9, 24.6, 26.1, 34.0, 52.5, 61.1, 128.7, 133.6, 135.8, 138.2. $[\alpha]_D^{20}$= −16.7 (*c* 0.88, $CHCl_3$). MS (*m*/*z*) 406, 302, 273, 202, 163, 133, 91. HRMS calcd for $C_{28}H_{42}N_2$ 406.3348, found 406.3329.

4.2.10. Bis-(*tert*-butyl)-cyclohexane-1,2-diamide 6. (*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate salt (2 g, 7.6 mmol) was dissolved in water (5 mL) with sodium hydroxide (600 mg, 15.2 mmol) and pivaloyl chloride (9.3 mL, 76 mmol) was added while the mixture was heated at 40 °C. After stirring 3 h at this temperature, the solution was quenched with sodium hydroxide until basic pH and extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and solvent are evaporated. The solid was diluted in ether and insoluble impurities were filtered. After evaporation under reduced pressure, the bis-(*tert*-butyl)-cyclohexane diamide was isolated in 70% yield. ^{1}H NMR: δ(ppm) 1.17 (s, 18H), 1.20–1.45 (m, 4H), 1.68–1.82 (m, 2H), 2.0–2.11 (m, 2H), 3.60–6.38 (m, 2H), 6.17 (br s, 2H). ^{13}C NMR: δ(ppm) 24.7, 27.5, 32.4, 38.5, 53.6, 179.1.

4.2.11. (1*R*,2*R*)-*N*,*N*′-Bis-(2,2-dimethyl-propyl)-*N*,*N*′-dimethyl-cyclohexane-1,2-diamine 1k. To a suspension of LAH (4.8 g, 0.13 mmol) in THF (50 mL) was added bis-(*tert*-butyl)-cyclohexane diamide **6** (3.55 g, 0.013 mmol) and the mixture was refluxed 2 weeks. The solution was cooled to room temperature, poured into crushed ice and extracted with ether. The combined organic layer was dried over Na_2CO_3, filtered and concentrated to give the crude diamine as a solid, which was methylated without purification. The diamine (1.2 g, 4.7 mmol) was dissolved in formic acid 85% (2.3 mL), formaldehyde 40% (1.9 mL) was added and the mixture was refluxed 3 h. After basification and extraction with ether, the organic layer was dried over Na_2SO_4, filtered and concentrate. The residue was purified by bulb-to-bulb distillation (120 °C/1 mmHg) to give the product as a colorless oil in 72% yield. ^{1}H NMR: δ(ppm) 0.90 (s, 18H), 1.03–1.12 (m, 2H), 1.17–1.30 (m, 2H), 1.64–1.70 (m, 2H), 1.73–1.80 (m, 2H), 2.25–2.40 (m, 12H). ^{13}C NMR: δ(ppm) 26.1, 27.1, 28.6, 33.3, 38.7, 66.6, 70.0. $[\alpha]_D^{20}$= +6.3 (*c* 1.03, $CHCl_3$). MS (*m*/*z*) 282, 225, 169, 124, 114, 58. HRMS calcd for $C_{18}H_{38}N_2$ 282.3035, found 282.3024.

4.3. Asymmetric addition of MeLi to imines. General procedure

To a cooled (−78 °C) stirred solution of imine (0.48 mmol) and diamine ligand (0.096 or 0.96 mmol), in dry toluene (8 mL) under an inert atmosphere, was added an ether solution of MeLi (low halide, 1.6 M in ether, 1.44 mmol) over a period of 5 min. The mixture was stirred at −78 °C for the time indicated and quenched with methanol (1 mL) at deep temperature and with water (5 mL) at room temperature. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the pure product.

4.3.1. (4-Methoxy-phenyl)-(1-phenyl-ethyl)-amine 8. The mixture was stirred 15 h before the quench. The product was purified by silica gel chromatography to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 1.49 (d, J=6.8 Hz, 3H), 3.68 (s, 3H), 4.39 (q, J=6.8 Hz, 1H), 6.46 (d, J=9.0 Hz, 2H), 6.70 (d, J=9.0 Hz, 2H), 7.1–7.5 (m, 5H). ^{13}C NMR: δ(ppm) 25.2, 54.3, 55.8, 114.6, 114.8, 125.9, 126.9, 128.7, 141.6, 145.6, 151.9. Enantiomeric excess was determined by SFC Chiralcel OD-H, 200 bar, 2 mL min^{-1}, 2% MeOH in CO_2, 30 °C, R t_1=9.26 min, S t_2=9.84 min. Chiralcel OB-H, 200 bar, 2 mL min^{-1}, 15% MeOH in CO_2, 30 °C, S t_1=6.77 min, R t_2=12.31 min.

4.3.2. (2-Methoxy-phenyl)-(1-phenyl-ethyl)-amine 11. The mixture was stirred 2 h before the quench. The residue was purified by silica gel column chromatography (toluene) to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 1.61 (d, J=6.6 Hz, 3H), 3.93 (s, 3H), 4.53 (q, J=6.7 Hz, 1H), 4.6–4.85 (s, 1H), 6.41 (dd, J_1=7.8 Hz, J_2=1.5 Hz, 1H), 6.67 (dt, J_1=7.6 Hz, J_2=1.5 Hz, 1H), 6.76 (dt, J_1=7.6 Hz, J_2=1.5 Hz, 1H), 6.82 (dd, J_1=7.8 Hz, J_2=1.5 Hz, 1H), 7.25–7.30 (m, 1H), 7.37 (t, J=7.8 Hz, 1H), 7.41–7.45 (m, 1H). ^{13}C NMR: δ(ppm) 25.1, 53.3, 55.3, 109.2, 111.0, 116.3, 121.1, 125.8, 126.7, 128.5, 137.1, 145.4, 146.5. Enantiomeric excess was determined by SFC Chiralcel OD-H, 200 bar, 2 mL min^{-1}, 2% MeOH in CO_2, (2%, 6 min, 1% min^{-1}, 15%), 30 °C, t_1=5.58 min, t_2=7.90 min.

4.3.3. (2-Isopropyl-phenyl)-(1-phenyl-ethyl)-amine 12. The mixture was stirred 2 h before the quench. The residue was purified by silica gel column chromatography (toluene) to give the product as a yellow oil. R_F=0.61 (cyclohexane/ether=95:5). ^{1}H NMR: δ(ppm) 1.47 (d, J=6.8 Hz, 6H), 1.69 (d, J=6.8 Hz, 3H), 3.12 (sept, J=6.8 Hz, 1H), 4.0–4.3 (br s, 1H), 4.67 (q, J=6.8 Hz, 1H), 6.55 (dd, J_1=1.0 Hz, J_2=8.3 Hz, 1H), 6.83 (dt, J_1=1.0 Hz, J_2=7.6 Hz, 1H), 7.09 (dt, J_1=1.8 Hz, J_2=7.6 Hz, 1H), 7.26–7.55 (m, 6H). ^{13}C NMR: δ(ppm) 22.2, 22.3, 25.25, 27.3, 53.35, 111.6, 117.1, 124.7, 125.7, 126.5, 126.75, 128.6, 131.6, 143.7, 145.3. Enantiomeric excess was determined by SFC Chiralcel OJ, 200 bar, 2 mL min^{-1}, 2% MeOH in CO_2, (2%, 6 min, 1% min^{-1}, 15%), 30 °C, t_1=5.12 min, t_2=6.00 min. $[\alpha]_D^{20}$= −29.5 (*c* 1.25, $CHCl_3$, ee=20% with **1f**). MS (*m*/*z*) 239, 224, 182, 134, 105, 91, 51. HRMS calcd for $C_{17}H_{21}N$ 239.1674, found 239.1686.

4.3.4. (4-Methoxy-phenyl)-(1-*p*-tolyl-ethyl)-amine 13a. The mixture was stirred 12 h before the quench. The residue was purified by silica gel column chromatography (pentane/ether=10:1) to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 7.17 (d, 2H, J=7.8 Hz), 7.04 (d, 2H, J=7.8 Hz), 6.61 (d, 2H, J=9.0 Hz), 6.39 (d, 2H, J=9.0 Hz), 4.30 (q, 1H, J=6.6 Hz), 3.80–3.62 (br s, 1H), 3.61 (s, 3H), 2.24 (s, 3H), 1.40 (d, 3H, J=6.6 Hz). ^{13}C NMR: δ(ppm) 151.8, 142.5, 141.7, 136.3, 129.3, 125.8, 114.5, 55.7, 53.9, 25.2, 21.1. Enantiomeric excess was determined by SFC Chiralpak AS-H, 200 bar, 2 mL min^{-1}, 5% MeOH in CO_2, (5%, 5 min, 1% min^{-1}, 20%), 30 °C, t_1=3.34 min, t_2=4.47 min. MS (*m*/*z*) 241, 226, 119, 108, 91, 65. HRMS calcd for $C_{16}H_{19}NO$ 241.1466, found 241.1462.

4.3.5. [1-(4-Chloro-phenyl)-ethyl]-(4-methoxy-phenyl)-amine 13b. The mixture was stirred 12 h before the quench. The residue was purified by silica gel column chromatography (pentane/ether=10:1) to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 7.35–7.30 (m, 4H), 6.74 (d, 2H, J=9.1 Hz), 6.48 (d, 2H, J=9.1 Hz), 4.42 (q, 1H, J=6.8 Hz), 3.83–3.74 (br s, 1H), 3.74 (s, 3H), 1.51 (d, 3H, J=6.8 Hz). ^{13}C NMR: δ(ppm) 152.3, 132.5, 129.8, 128.8, 127.4, 114.9, 114.8, 114.0, 55.7, 54.1, 25.0. Enantiomeric excess was determined by SFC Chiralpak AD, 200 bar, 2 mL min^{-1}, 5% MeOH in CO_2, (5%, 5 min, 1% min^{-1}, 20%), 30 °C, t_1=7.56 min, t_2=8.61 min, and Chiralpak AS-H, 200 bar, 2 mL min^{-1}, 5% MeOH in CO_2, (5%, 5 min, 1% min^{-1}, 20%), 30 °C, t_1=4.65 min, t_2=5.86 min. $[\alpha]_D^{20}$= +15.0 (c 0.93, $CHCl_3$, ee=68% with **1h**). MS (m/z) 261, 246, 139, 123, 108, 77, 52. HRMS calcd for $C_{15}H_{16}^{35}ClNO$ 261.0920, found 261.0921. HRMS calcd for $C_{15}H_{16}^{37}ClNO$ 263.0890, found 263.0902.

4.3.6. (4-Methoxy-phenyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amine 13c. The mixture was stirred 12 h before the quench. The residue was purified by silica gel column chromatography (pentane/ether=10:1) to give the product as a yellow oil. RF=0.22 (eluent:pentane/ether=10:1). ^{1}H NMR: δ(ppm) 7.49 (d, 2H, J=8.2 Hz), 7.40 (d, 2H, J=8.2 Hz), 6.61 (d, 2H, J=8.8 Hz), 6.34 (d, 2H, J=8.8 Hz), 4.37 (q, 1H, J=6.7 Hz), 3.78–3.75 (br s, 1H), 3.60 (s, 3H), 1.42 (d, 3H, J=6.7 Hz). ^{13}C NMR: δ(ppm) 152.3, 149.8, 141.0, 126.2, 125.7, 125.6, 125.6, 114.9, 114.6, 55.7, 54.1, 25.1. Enantiomeric excess was determined by SFC Chiralpak AD, 200 bar, 2 mL min^{-1}, 5% MeOH in CO_2, (5%, 5 min, 1% min^{-1}, 20%), 30 °C, t_1=3.27 min, t_2=3.64 min. $[\alpha]_D^{20}$= −4.3 (c 0.91, $CHCl_3$, ee=58% with **1h**). MS (m/z) 295, 280, 173, 122, 95, 77. HRMS calcd for $C_{16}H_{16}F_3NO$ 295.1184, found 295.1186.

4.3.7. (1-Furan-2-yl-ethyl)-(4-methoxy-phenyl)-amine 13d. The mixture was stirred 15 h before the quench. The residue was purified by silica gel column chromatography (pentane/ether=10:1) to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 1.54 (d, J=6.6 Hz, 3H), 3.74 (s, 3H), 4.55 (q, J=6.6 Hz, 1H), 6.14 (d, J=3.3 Hz, 1H), 6.28 (dd, J_1=1.7 Hz, J_2=3.0 Hz, 1H), 6.61 (d, J=8.8 Hz, 2H), 6.76 (d, J=8.8 Hz, 2H), 7.33 (dd, J_1=0.8 Hz, J_2=1.8 Hz, 1H). ^{13}C NMR: δ(ppm) 20.9, 48.3, 55.7, 105.0, 110.0, 114.7, 115.1, 141.1, 141.35, 152.4, 157.4. Enantiomeric excess was determined by SFC Chiralcel OD-H, 200 bar, 2 mL min^{-1}, 2% MeOH in CO_2, (2%, 6 min, 1% min^{-1}, 10%), 30 °C, t_1=5.82 min, t_2=6.24 min.

4.3.8. (4-Methoxy-phenyl)-(1-thiophen-2-yl-ethyl)-amine 13e. The mixture was stirred 15 h before the quench. The residue was purified by silica gel column chromatography to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 1.64 (d, J=6.6 Hz, 3H), 3.76 (s, 3H), 4.78 (q, J=6.6 Hz, 1H), 6.63 (d, J=9.1 Hz, 2H), 6.79 (d, J=9.1 Hz, 2H), 6.96–7.02 (m, 2H), 7.20 (dd, J_1=1.4 Hz, J_2=4.9 Hz, 1H). ^{13}C NMR: δ(ppm) 24.6, 50.4, 55.6, 114.7, 115.0, 122.8, 123.5, 126.6, 141.0, 150.4, 152.3. Enantiomeric excess was determined by SFC Chiralcel OD-H, 200 bar, 2 mL min^{-1}, 2% MeOH in CO_2, (2%, 20 min), 30 °C, t_1=9.48 min, t_2=10.06 min.

4.3.9. (4-Methoxy-phenyl)-(1-pyridin-2-yl-ethyl)-amine 13f. The mixture was stirred 15 h before the quench. The residue was purified by silica gel column chromatography to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 1.53 (d, J=6.6 Hz, 3H), 3.69 (s, 3H), 4.1 (br s, 1H), 4.55 (q, J=6.8 Hz, 1H), 6.53 (d, J=8.8 Hz, 2H), 6.71 (d, J=9.1 Hz, 2H), 7.12 (m, 1H), 7.34 (d, J=7.8 Hz, 1H), 7.59 (dt, J_1=1.8 Hz, J_2=7.6 Hz, 1H), 8.57 (d, J=4.8 Hz, 1H). ^{13}C NMR: δ(ppm) 23.3, 55.6, 55.7, 114.75, 114.8, 120.4, 121.9, 136.8, 141.4, 149.3, 152.0, 164.2. Enantiomeric excess was determined by SFC Chiralcel OJ, 200 bar, 2 mL min^{-1}, 5% MeOH in CO_2, (5%, 6 min, 1% min^{-1}, 15%), 30 °C, t_1=8.58 min, t_2=10.45 min.

4.3.10. (4-Methoxy-phenyl)-(2-naphtalen-2-yl-ethyl)-amine 13g. The mixture was stirred 35 h before the quench. The residue was purified by silica gel column chromatography (pentane/ether=10:1) to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 7.73–7.70 (m, 4H), 7.42 (d, J=8.6 Hz, 1H), 7.39–7.32 (m, 2H), 6.59 (d, J=8.8 Hz, 2H), 6.43 (d, J=8.8 Hz, 2H), 4.48 (q, 1H, J=6.6 Hz), 4.35–3.65 (br s, 1H), 3.58 (s, 3H), 1.49 (d, 3H, J=6.6 Hz). ^{13}C NMR: δ(ppm) 152.0, 142.9, 141.4, 133.6, 132.7, 129.1, 128.4, 127.8, 127.7, 126.0, 125.5, 124.5, 124.4, 114.8, 55.7, 54.6, 25.1. Enantiomeric excess was determined by SFC Chiracel OD-H, 175 bar, 2 mL min^{-1}, 2% MeOH in CO_2, (2%, 20 min), 30 °C, t_1=8.36 min, t_2=8.72 min.

4.3.11. (1-Benzo[1,3]dioxol-5-yl-ethyl)-(4-methoxy-phenyl)-amine 13h. The mixture was stirred 14 h at −30 °C before the quench. The residue was purified by silica gel column chromatography (pentane/ether=10:1) to give the product as a yellow oil. ^{1}H NMR: δ(ppm) 6.79–6.74 (m, 2H), 6.68–6.61 (m, 3H), 6.40 (d, J=8.8 Hz, 2H), 5.84 (d, J=5.3 Hz, 2H), 4.25 (q, J=6.6 Hz, 1H), 3.80–3.50 (br s, 1H), 3.62 (s, 3H), 1.38 (d, J=6.6 Hz, 3H). ^{13}C NMR: δ(ppm) 151.9, 147.9, 146.3, 141.5, 139.7, 118.9, 114.7, 114.5, 108.3, 106.3, 100.9, 55.7, 54.1, 25.4. Enantiomeric excess was determined by SFC Chiralcel OD-H, 200 bar, 2 mL min^{-1}, 5% MeOH in CO_2, (5%, 5 min, 1% min^{-1}, 20%), 30 °C, t_1=6.76 min, t_2=7.28 min, and Chiralcel OJ, 200 bar, 2 mL min^{-1}, 5%, 5 min, 1% min^{-1}, 20%), 30 °C, t_1=11.5 min, t_2=12.4 min. $[\alpha]_D^{20}$= +12.7 (c 1.1, $CHCl_3$, ee=48% with **1h**). MS (m/z) 271, 149, 123, 108, 91, 65. HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1202.

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