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Enantioselective addition of organolithium reagents on isoquinoline

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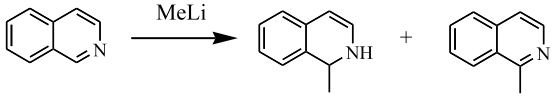
Abstract—1-Methyl-1,2-dihydroisoquinoline and 1-butyl-1,2-dihydroisoquinoline were obtained by enantioselective addition of organolithium reagents on the isoquinoline. (−)-Sparteine was used as an external catalytic chiral ligand and an enantiomeric excess of 57% could be obtained. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The nucleophilic 1,2-addition of organometallic reagents to a prochiral C=N double bond is a useful way to obtain optically active amines and some reviews have dealt with this subject.[1] The catalytic addition to an acyclic imine was reviewed by Kobayashi,[2] but the reaction with carbon nucleophiles is limited because of the poor reactivity of the imine. Hence, this reaction in the presence of catalytic amounts of chiral ligand is still not well developed. The addition of organolithium reagents to arylimines in the presence of a catalytic amount of a chiral amino ether gave the product amine with moderate enantioselectivity (ee = 47–67%).[3] (−)-Sparteine has been used successfully in such a reaction by Denmark et al.[4] and an ee of 91% was obtained with *n*-BuLi. The enantioselective addition of organolithium reagents to cyclic arylimines has been tested in the presence of a catalytic amount of (−)-sparteine.[5] The addition of *n*-butyllithium to 6,7-dimethoxy-3,4-dihydroisoquinoline in the presence of a stoichiometric amount of (−)-sparteine gave the corresponding amine with 46% ee but the enantiomeric excess decreased dramatically to 28% when 0.2 equiv. of the chiral ligand were used. To our knowledge, there is no example of enantioselective addition of a carbon nucleophile to aromatic imines such as isoquinoline.[6] Dihydro- or tetrahydroisoquinoline can be obtained by diastereoselective addition of a Grignard reagent to chiral iminium salts[7] or by diastereoselective cyclisation[8] with good enantiomeric excess. However, the direct addition of an organolithium reagent with an external chiral ligand has not been reported. We report herein a new methodology, which allows the synthesis of chiral 1,2-dihydroisoquinolines by the direct addition of alkyl- and aryllithium reagents to isoquinoline in the presence of (−)-sparteine. Dihydroisoquinoline derivatives are known to be useful intermediates for the synthesis of alkaloids and natural products of biological interests.

2. Results

Initially, methyllithium was added to isoquinoline without any activation of the imine moiety (Scheme 1). The results in Table 1 show that the reaction proceeded faster in ether than in toluene. At −30°C, no reaction was observed in toluene, whereas a conversion of 34%



1 2 3

Scheme 1.

Table 1.

Solvent	*T*, °C (time, h)	Ligand	Conversion (%)
Toluene	−30 (2)	–	0
Toluene	−20 (2)	–	60
Et_2O	−30 (2)	–	34
Et_2O	rt (24)	–	100

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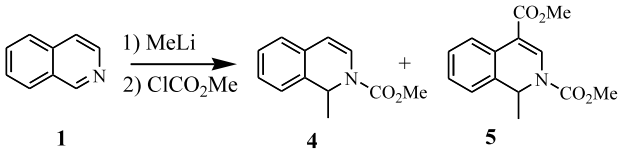
was possible in ether. The expected product, 1-methyl-1,2-dihydroisoquinoline **2** and the rearomatised product, 1-methylisoquinoline **3**, were obtained as a mixture. The unstable lithiated intermediate gave this rearomatised side product **3** by rapid loss of LiH.[9] Furthermore, our attempts to isolate the 1-methyl-1,2-dihydroisoquinoline **2** from the mixture by chromatography failed as **2** was unstable on silica gel and only the rearomatised product **3** could be retrieved.

For these reasons, the regioselectivity could not be ascertained by NMR analysis. In order to determine the regioselectivity of the addition of the organolithium reagent, the isoquinoline and methyllithium were stirred in toluene for 24 h. 1-Methylisoquinoline **3** was obtained as the exclusive product in 68% yield, indicating that only the benzylic position was involved in the 1,2-addition. To isolate the unstable amine, we decided to trap the lithiated intermediate in situ. Methyl chloroformate was added to the crude mixture before it rearomatised by loss of LiH (Scheme 2).

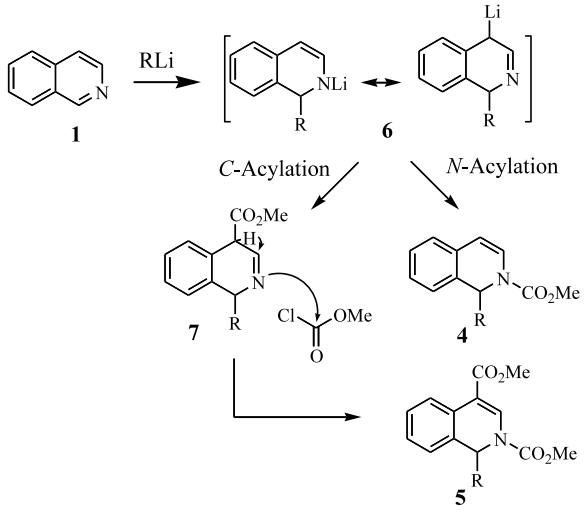
The nucleophilic addition was completely regioselective and no 3-alkylated product was detected. However, under these conditions both *C*- and *N*-acylation is possible, producing two inseparable dihydroisoquinolines (mono- and disubstituted **4** and **5**). Dimethoxyethane (DME) was then used as a non-chiral ligand and the reaction was carried out in both ether and toluene. The presence of 0.5 equiv. of DME enhanced the rate of the reaction and afforded the product in 74% isolated yield at −20°C in toluene, after 1.25 h (Table 2). The conversion was only 60% after 2 h without ligand (Table 1). However, irrespective of the conditions, products **4** and **5** were obtained in the same ratio of 70/30, indicating that *C*- or *N*-acylation was independent of the solvent, temperature and ligand.

This result has already been observed by Giam et al.[10] with pyridine. A mechanism can be proposed to explain this result (Scheme 3); the lithiated intermediate **6** gives the 1,2-dihydroisoquinoline **4** by direct *N*-acylation and the 1,4-diydroisoquinoline **7** by *C*-acylation. This product reacts immediately with the electrophile giving the bisacylated product **5**.



1 **4** **5**

Scheme 2.



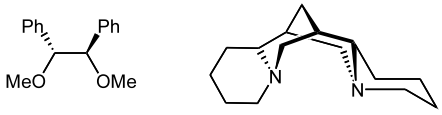
1 **6** **7** **4** **5**

Scheme 3.

In order to avoid formation of the bisacylated product we changed the experimental conditions (Table 3). With less than 1 equiv. of base a similar ratio of **4**:**5** was obtained, indicating that the proton is labile enough to allow the second acylation (entry 1). The presence of an excess or a deficiency of electrophile does not affect the product ratio, showing that sequential acylation of **4** to give **5** does not occur (entry 5). When the reaction was carried out without hydrolysis, no change was observed (entry 4).

These results show that it is possible to add an organolithium reagent to an aromatic imine such as isoquinoline. The nucleophilic addition was completely regioselective at the benzylic position and the reactivity was enhanced by the use of a diether.

With these results in hand, we were interested in the enantioselective nucleophilic addition in the presence of a chiral ligand. We have used the 1,2-diphenyldimethoxyethane **8** as a chiral diether and the (−)-sparteine **9** as a chiral diamine.



8 **9**

We first studied the enantioselective nucleophilic addition to isoquinoline with methyllithium (Scheme 4).

The chiral diether **8** was tested initially (Table 4). In this case, conversion was complete but the products and ligand could not be separated by chromatography

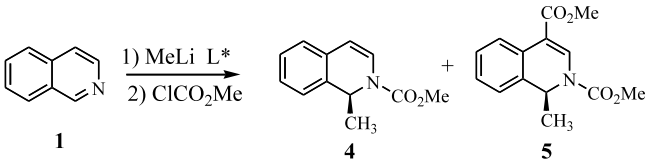
Table 2.

Solvent	*T*, °C (time, h)	Ligand (equiv.)	Conversion, % (yield, %)	Ratio **4**/**5**
Et_2O	rt (2)	DME (1)	100 (89)	70/30
Toluene	−20 (1.15)	DME (0.5)	100 (74)	70/30

Table 3.

Entry	Nu^- (equiv.)	$ClCO_2Me$ (equiv.)	Solvent	*T*, °C (time, h)	Conversion, % (yield, %)	Ratio **4**/**5**
1	MeLi (0.8)	0.8	$PhCH_3$	−10 (2)	88 (45)	80/20
2	BuLi (1)	0.8	THF	−40 (1)	100 (73)	82/18
3	BuLi (0.8)	0.8	THF	−40 (1)	100 (53)	72/28
4	BuLi (1)	1	THF	−40 (1)	100 (53)	75/25[a]
5	BuLi (1)	2	THF	−40 (1)	100 (42)	80/20

[a] No hydrolysis.



Scheme 4.

and the isolated yield could not be determined. Nevertheless, the enantiomeric excess of the mono-acylated product **4** could be determined and was found to be 13% with 0.5 equiv. of ligand at −20°C (entry 1). In order to enhance the enantiomeric excess, (−)-sparteine was used. The presence of this ligand enhances the rate of the reaction and dihydroisoquinoline could be obtained in 89% yield in toluene at −40°C after 1 h (entry 3). This was not possible without activation (see Table 1). The inseparable dihydroisoquinolines **4** and **5** were obtained in the same ratio as above.

Both of the products could be analysed by super-critical fluid chromatography (SFC) on a chiral OJ column (using 1% methanol), but could not be separated by conventional chromatographic techniques. Indeed, all of the fractions containing both products were purified by SFC. Table 4 shows that the minor product **5** was obtained with almost the same enantiomeric excess as the product **4** at −40°C but kinetic resolution was observed at lower temperatures, increasing the ee of the side product **5** (entry 6). With 1 equiv. of ligand, product **4** was obtained with 42% ee (entry 2). With 0.25 equiv. of ligand under the same conditions the enantiomeric excess was still 36% (entry 3). The yield and enantioselectivity did not improve on completing the reactions at lower temperatures.

n-Butyllithium was also tested as an alkyl nucleophile (Scheme 5). The addition of butyllithium to isoquinoline followed by the addition of methyl chloroformate gave the 1,2-dihydroisoquinoline **10** with an ee of 57% when 1 equiv. of chiral ligand was used in toluene at −80°C. The enantiomeric excess in ether was only 37%. Only the ee of the 1,2-dihydroisoquinoline **10** could be determined by chiral GC, but as indicated in Table 5, the mono- and bisacylated products **10** and **11** were obtained in the same ratio of 70/30.

In order to determine the enantiomeric excess of the bisacylated dihydroisoquinoline, acetyl chloride was used instead of methyl chloroformate (Scheme 6).

In this case, both products **12** and **13** were obtained but they could be separated by flash chromatography. The enantiomeric excess of each of them has been determined by SFC analysis (Table 6). The best results were obtained in toluene at −70°C with 1 equiv. of (−)-sparteine (entry 7). 56% ee was observed on the major product **12** and 47% ee on the minor one. This result confirmed the first analysis in the former experiment. Under the same conditions with 0.2 equiv. of chiral ligand (entry 2), only the 1,2-dihydroisoquinoline **12** could be detected in 28% yield and with 40% ee. At −40°C an enantiomeric excess of 53% has been observed with 1 equiv. of ligand (entry 5) but when a catalytic amount of ligand was used at this temperature, the enantiomeric excess of product **12** decreased to 37% (entry 4). In ether, the yield was higher but the enantiomeric excess was significantly lower.

Finally, an aryl group was introduced using phenyllithium as nucleophile (Scheme 7). The two products of mono- and bisacylation **14** and **15** are still obtained but could not be separated. Only the enantiomeric excess of the 1-phenyl-*N*-methoxycarbonyl-1,2-dihydroisoquinoline **14** could be determined (Table 7).

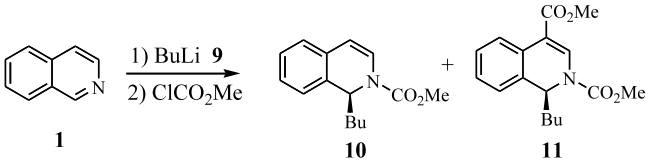
Using 1.2 equiv. of phenyllithium and 0.2 equiv. of (−)-sparteine, products **14** and **15** were obtained in moderate global yield of 34%. The enantiomeric excess of the product **14** was found to be 25% by SFC analysis (entry 1). At lower temperature, yield and enantiomeric excess were not better (entry 2). The use of 1 equiv. of (−)-sparteine afforded an enantiomeric excess of 38% with 27% yield (entry 3). Increasing the time of the reaction led to the rearomatisation of the amine. To enhance the yield, an excess of nucleophile was then used (entry 4) but in this case, the enantiomeric excess decreased dramatically to 15% in the presence of 0.2 equiv. of chiral ligand.

In order to determine the absolute configuration of the dihydroisoquinoline **4**, generated in the presence of (−)-sparteine, it was hydrogenated with palladium on charcoal to give the tetrahydroisoquinoline **16** in 80% yield (Scheme 8).

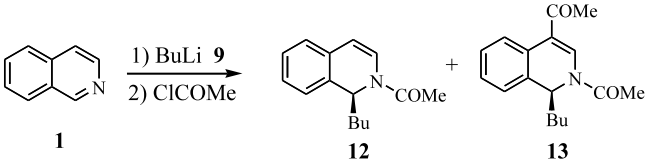
The carbamate moiety **16** was then reduced with $LiAlH_4$ to give the known product **17**.[11] Measurement of the specific rotation gave a negative value of −2.1, which indicates that the nucleophilic addition of an alkyllithium reagent on the isoquinoline with (−)-sparteine gave (*S*)-methyl-1,2-dihydroisoquinoline. The

Table 4.

Entry	Solvent	T, °C (time, h)	Ligand (equiv.)	Yield (%)	Ratio **4**/**5**	ee (%) **4**/**5**
1	Toluene	−20 (1.5)	**8** (0.5)	–	–	13/–
2	Toluene	−40 (1)	**9** (1)	77	75/25	42/48
3	Toluene	−40 (1)	**9** (0.25)	89	70/30	36/38
4	Et_2O	−40 (1)	**9** (0.2)	76	70/30	23/30
5	Et_2O	−78 (3)	**9** (0.2)	7	70/30	21/37
6	Toluene	−78 (3)	**9** (0.2)	54	70/30	29/53



Scheme 5.



Scheme 6.

same mode of facial attack was observed when alkyllithium reagents such as methyllithium and butyllithium were added to 6,7-dimethoxy-3,4-dihydroisoquinoline.[5]

3. Conclusion

We have shown through this work that the nucleophilic addition of organolithium reagents could be performed on an aromatic imine. This reaction represents a good way to add an alkyl or an aryl group to such a system without activation of the nitrogen atom, as is usually described.[7] The regioselectivity of this 1,2-addition was complete and allowed the direct synthesis of a 1,2-dihydroisoquinoline from the isoquinoline in good yields. Furthermore, this method maintains the intracyclic double bond free for further transformations. The undesired bisacylated side product can be isolated and involved in further functional transformations. We have noted that the presence of a diether or a diamine enhances the rate of the reaction and such activation also allows chiral induction. So far, the enantioselective addition of organolithium reagents on isoquinoline has been performed in the presence of (–)-sparteine. This external chiral ligand could be used in catalytic amounts without drastic loss of enantioselectivity. The best results were obtained using *n*-butyllithium in toluene, giving the 1,2-dihydroisoquinoline **10** with 56% ee and improvements may be sought by the use of other chiral ligands. The enantioselective addition of alkyllithium reagents to aromatic imines is of great interest in the synthesis of natural alkaloids.

4. Experimental

4.1. General remarks

All ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 200 and 50 MHz respectively. Chiral separations on super-critical fluid chromatography (SFC) were carried out using a Chiralcel OJ column with 1% MeOH as eluent. All solvents were dry and reactions were carried out under an atmosphere of argon.

4.2. General procedure

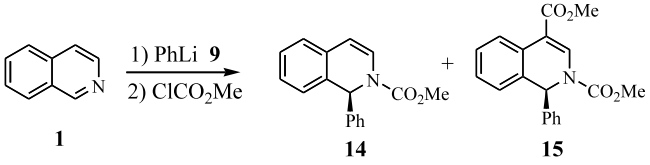
In a 50 ml two-necked flask, equipped with a thermometer, charged with isoquinoline (200 mg, 1.55 mmol), was added anhydrous solvent (20 ml). (–)-Sparteine was then added via syringe at room temperature with stirring. The solution was then cooled down to the desired temperature and the organolithium reagent (1.2 equiv.) was added. After stirring for 1 h at this temperature methyl chloroformate (0.14 ml, 1.2 equiv.) or acetyl chloride (0.13 ml, 1.2 equiv.) was added. The solution was stirred for a further 10 min at low temperature and then hydrolysed with a semi-saturated solution of NH_4Cl. The solution was then extracted with ether (2×20 ml) and dichloromethane (2×20 ml). The organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was then purified by chromatography on silica gel with cyclohexane/ether 80/20 as eluent.

Table 5.

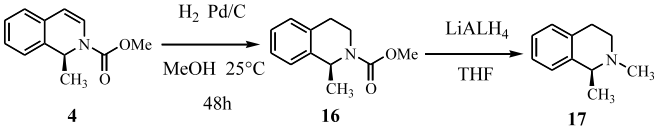
Solvent	T (°C)	Ligand (equiv.)	Yield (%)	Ratio **10**/**11**	ee (%) **10**
Toluene	−80	**9** (1)	85	70/30	57
Et_2O	−80	**9** (1)	86	70/30	37

Table 6.

Entry	Solvent	*T*, °C (time, h)	Ligand (equiv.)	Yield (%) **12**/**13**	ee (%) **12**/**13**
1	Et_2O	−70 (2)	**9** (0.2)	17/0	16/–
2	Toluene	−70 (1)	**9** (0.2)	28/0	40/–
3	Et_2O	−40 (1)	**9** (0.2)	51/25	20/30
4	Toluene	−40 (1)	**9** (0.2)	48/31	37/30
5	Toluene	−40 (1)	**9** (1)	48/20	53/36
6	Et_2O	−40 (1)	**9** (1)	67/12	37/42
7	Toluene	−70 (1)	**9** (1)	45/34	56/47



Scheme 7.



Scheme 8.

4.3. 1-Methyl-1,2-dihydro-[*N*-methoxycarbonyl]-isoquinoline, 4

The product was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.3–7 (m, 4H), 6.90 (d, 0.4H, $J=7.54$ Hz), 6.75 (d, 0.6H, $J=7.9$ Hz), 5.87 (d, 0.4H, $J=7.6$ Hz), 5.79 (d, 0.6H, $J=7.7$ Hz), 5.44 (q, 0.6H, $J=6.4$ Hz), 5.32 (q, 0.4H, $J=6.5$ Hz), 3.90 (s, 1.2H), 3.85 (s, 1.8H), 1.25 (d, 3H, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 153.2, 134.2, 129.6, 127.4, 127.1, 126.9, 125.6, 125.5, 125.4, 124.7, 124.6, 123.9, 108.1, 107.9, 53.2, 52.1, 51.7, 21.8, 21.2. MS: 203, 188, 144, 129; $[\alpha]_D^{20}=+18.5$ (*c* 0.87, $CHCl_3$) for ee = 36%.

4.4. 1-Methyl-4-methoxycarbonyl-1,2-dihydro-[*N*-methoxycarbonyl]-isoquinoline, 5

The product was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, $J=7.5$ Hz), 8.02 (s, 1H), 7.24 (m, 2H), 7.05 (m, 1H), 5.3 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 1.29 (d, 3H, $J=6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 212.4, 166.1, 135.2, 133.6, 127.7, 127.5, 127.1, 125.6, 124.9, 109, 53.9, 52.7, 51.5, 21.8; MS: 261, 246, 202, 187.

4.5. 1-Butyl-1,2-dihydro-[*N*-methoxycarbonyl]-isoquinoline, 10 and 1-butyl-4-methoxycarbonyl-1,2-dihydro-[*N*-methoxycarbonyl]-isoquinoline, 11

These two products could not be separated. ^{1}H NMR ($CDCl_3$): δ 7.2–7.06 (m, 4H), 6.79 (d, 1H, $J=0.8$ Hz), 5.84 (m, 1H), 5.33 (m, 1H), 3.85 (m, 3H), 1.64 (m, 4H), 1.27 (m, 2H), 0.85 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 166, 154.1, 153.4, 132.9, 132.1, 130, 127.6, 127.4, 127.3, 126.4, 126.3, 125.2, 124.4, 108.9, 108.7, 56, 55.53, 54.5, 53.8, 51.4, 34.9, 34.6, 27.3, 26.8, 22.5, 13.8; MS: 245, 188, 144, 129; MS: 303, 246, 202, 128.

4.6. 1-Butyl-1,2-dihydro-[*N*-methylcarbonyl]-isoquinoline, 12

The product was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.2–7.06 (m, 4H), 6.6 (dd, 1H, $J_1=1.2$, $J_2=7.6$ Hz), 5.9 (d, 1H, $J=7.6$ Hz), 5.65 (t, 1H, $J=7$ Hz), 2.2 (s, 3H), 1.6 (m, 2H), 1.2 (m, 4H), 0.82 (t, 3H, $J=6.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 168.4, 133.7, 129.8, 127.4, 127, 126.6, 124.9, 124.7, 110.5, 53.4, 34.5, 27.6, 22.6, 21.6, 13.9; MS: 229, 172, 130; $[\alpha]_D^{20}=+20.3$ (*c* 1.02, $CHCl_3$) for ee = 56%.

4.7. 1-Butyl-4-methylcarbonyl-1,2-dihydro-[*N*-methylcarbonyl]-isoquinoline, 13

^{1}H NMR ($CDCl_3$): δ 7.63 (s, 1H), 7.3–7 (m, 4H), 5.57, (m, 1H), 2.50 (s, 3H), 2.37 (s, 3H), 1.55 (m, 2H), 1.20 (m, 4H), 0.82 (t, 3H, $J=6.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 193, 164.5, 136.1, 128.2, 127.8, 127.3, 126.8, 126.4, 122, 120.7, 54.8, 35.1, 28.0, 27.5, 22.9, 22.1, 14.4; MS: 271, 214, 172, 129; $[\alpha]_D^{20}=+20$ (*c* 1.18, $CHCl_3$) for ee = 47%;

4.8. (*S*)-1-Methyl-1,2,3,4-tetrahydro-[*N*-methoxycarbonyl]-isoquinoline, 16

To a solution of **4** (150 mg, 0.74 mmol) in methanol (20 ml) was added a small amount of palladium on activated

Table 7.

Entry	Solvent	*T*, °C (time, h)	**9** (equiv.)	Yield (%)	ee (%) **14**
1	Toluene	−40 (1)	0.2	34	25
2	Toluene	−70 (1)	0.2	34	23
3	Toluene	−40 (1)	1	27	38
4	Toluene	−40 (1)	0.2	73	15[a]

[a] 4 equiv. of phenyllithium.

charcoal. The mixture was stirred under 1 atmosphere of hydrogen at room temperature during 48 h. The crude product was then filtered through Celite and the solvent was evaporated. The product was purified by flash chromatography on silica gel with ether and recovered as a colourless oil in 80% yield. The enantiomeric excess could not be determined by SFC or chiral GC analysis. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15 (m, 4H, H_{7-10}), 5.2 (m, 1H, H_1), 3.8 (m, 1H, H_{3a}), 3.74 (s, 3H, H_{12}), 3.25 (m, 1H, H_{3b}), 2.5 (m, 2H, H_4), 1.45 (d, 3H, J=6.7 Hz, H_{13}); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 150 (C_{11}), 129.3, 128, 127.8, 127.3, 126.8, 126.7 (C_{5-10}), 53 (C_{12}), 50.9 (C_1), 37.9 (C_3), 29.3 (C_4), 22.5 (C_{13}); IR: 3458, 2954, 1697, 1453, 1411, 1330, 1237, 1126, 1058, 979, 759, 735 cm^{-1}; $[\alpha]_D^{20}$=+5.9 (c 1.07, $CHCl_3$).

4.9. (*S*)-1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline, 17

To a stirred solution of (*S*)-1-methyl-1,2,3,4-tetrahydroisoquinoline-*N*-methoxycarbonyl **16** (100 mg, 0.48 mmol) in dry THF (20 ml) was added $LiAlH_4$ (63 mg, 1.53 mmol) at 0°C under an argon atmosphere. The temperature was allowed to rise to room temperature. After stirring for 24 h, the solution was slowly hydrolysed with water and the solid residue was filtered. The liquid mixture was then extracted with ether (2×20 ml) and dichloromethane (2×20 ml), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel with ether and the (*S*)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline **17** was obtained in 65% yield as a yellow oil. The enantiomeric excess could not be determined by SFC or chiral GC analysis. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15 (m, 4H), 4.1–2.7 (m, 5H), 2.56 (s, 3H), 1.48 (d, 3H, J=6.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 129.2, 128.7, 127.3, 127, 126.8, 126.6 (C_{5-10}), 59.6 (C_{12}), 48.8 (C_3), 42.5 (C_1), 27.4 (C_4), 20 (C_{11}); IR: 2927, 2793, 1602, 1494, 1448, 1371, 1328, 1289, 1222, 1105, 1036, 757, 732 cm^{-1}; $[\alpha]_D^{20}$=−2.1 (c 0.7, $CHCl_3$).

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