Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 8221–8231
Tetrahedron

Enantioselective nucleophilic addition of organometallic reagents to quinoline: regio-, stereo- and enantioselectivity

Franck Amiot, Laure Cointeaux, Emmanuelle Jan Silve and Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, 30, Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

Received 31 March 2004; revised 9 June 2004; accepted 16 June 2004

Available online 8 July 2004

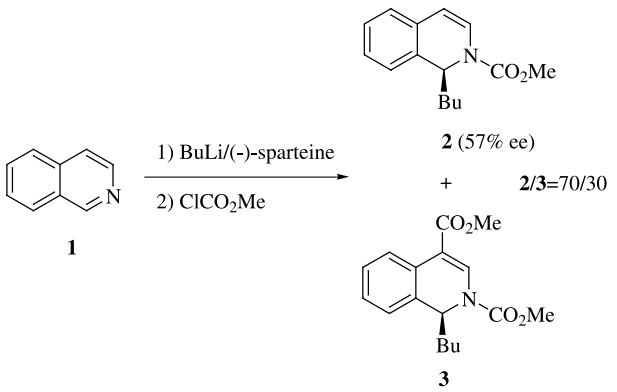
Abstract—Some 2-alkyl-1,2-dihydroquinoline and some 2-aryl-1,2-dihydroquinoline were obtained by enantioselective addition of methyl-, butyl-, phenyl- and 1-naphthyllithium on quinoline. Bisoxazolines were used as external chiral ligands, giving enantiomeric excess up to 79%. The ligand could be used in catalytic amounts without significant loss of enantioselectivity.

1. Introduction

The nucleophilic 1,2 addition of organometallic reagents on imines and related compounds is a well-known method to synthesise amines. The asymmetric version has extensively been studied, both with stoichiometric covalent auxiliaries[1] and with external chiral ligands, in stoichiometric or catalytic amounts.[2] In the particular case of azaaromatic compounds, the nucleophilic addition is more difficult because of the already poor reactivity of the C=N double bond and the aromatic nature of these systems.[3] Even fewer examples concern quinoline.

Quinoline derivatives are compounds of biological interest[4] and nucleophilic addition of an organometallic reagent, such as organolithiums and Grignards, is a good method to obtain a racemic 1,2- or 1,4-dihydroquinoline.[5] The use of quinolinium salts, to enhance the reactivity, often improves the results.[6] Nevertheless, not much is known about the synthesis of non-racemic alkylated 1,2-dihydroquinolines. Diastereoselective[4d,5h] and an enantioselective synthesis are known, using chiral aminals as auxiliary.[7] Excellent enantiomeric excess could be obtained with phenyl and naphthyl Grignard. To our knowledge, only the cyanation of the quinoline has been reported with catalytic amounts of chiral ligand to give the corresponding dihydroquinoline with 80% ee.[8] The enantioselective addition of organometallic reagents, as carbon nucleophiles, does not seem to have been explored with quinoline.

In our earlier work, we reported the first enantioselective addition of organolithium reagents on isoquinoline in the presence of (−)-sparteine.[9] Even a catalytic amount of ligand could be used. We have shown that a direct addition of butyllithium on isoquinoline gave a chiral 1,2-dihydroisoquinoline with an enantiomeric excess of 57% (Scheme 1).



Scheme 1. Enantioselective addition of butyllithium to isoquinoline.

The regioselectivity of this nucleophilic addition was complete at the benzylic position 1, but stabilisation of the adduct with methylchloroformate gave a mixture of N-acylated product **2** and bisacylated product **3**. The ratio of these two products was invariably 70/30 when temperature, solvent and amount of reagents were changed. Within the framework of our study on heteroaromatic compounds, we are now interested in enlarging the method previously described with isoquinoline, to quinoline as aromatic imine.

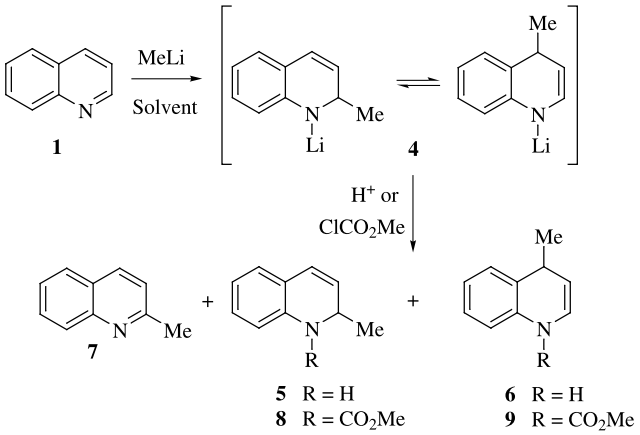
2. Results and discussion

The regioselectivity of the nucleophilic addition was studied with methyllithium, a relatively less reactive organolithium

Keywords: 1,2-Dihydroquinoline; Enantioselective addition; Chiral ligand; Organolithium reagents; Organometallics; Bioxazoline.
* Corresponding author. Tel.: +41-22-379-65-22; fax: +41-22-379-32-15; e-mail address: alexadre.alexakis@chiorg.unig.ch

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.088

Table 1. Regioselectivity of the addition of methyllithium to quinoline



Entries	Solvent	T [°C]	Time (min)	Ligand	Ratio **5/6** or **8**	Yield or conversion [%]
1	Toluene	−20	60	—	100/0	65[a]
2	Toluene	−20	60	DME (0.5 equiv)	100/0	100[a]
3	Toluene	−20	60	TMEDA (0.5 equiv)	100/0	100[a]
4	Et_2O	−40	10	—	100	0[b]
5	Et_2O	−20	10	—	100	18[b]
6	Et_2O	−20	10	DME (0.5 equiv)	100	81[b]

[a] Conversion estimated of crude NMR spectra.
[b] Yield of isolated product.

reagent. Table 1 shows that only the 1,2 addition was observed, giving the 2-methyl-1,2-dihydroquinoline **5** in 65% conversion after 1 h. No re-aromatised product **7** was observed in the crude mixture and the final dihydroquinoline **5** was stable enough to be studied by crude NMR analysis. However, this product could hardly be purified by flash chromatography on silicagel without a large part of re-aromatisation.

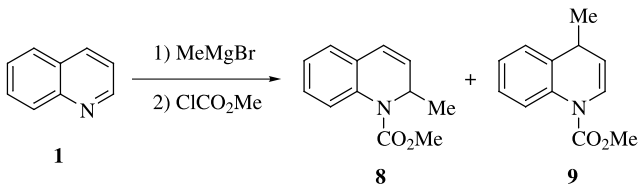
When dimethoxyethane (DME) was used as a non-chiral ligand (entry 2), the conversion was complete under the same conditions, indicating that the presence of a 1,2 diether enhanced the rate of the reaction. No change in the regioselectivity was observed and only the 1,2 adduct **5** was obtained. A similar behaviour was observed with a diamine, such as tetramethylethylenediamine (TMEDA) (entry 3).

Using the method previously explored with isoquinoline, the lithiated intermediate **4** was trapped, in Et_2O, with methylchloroformate after 10 min (Table 1). In this case, only the N-acylation was observed. The regioselectivity was not affected and the 1,2-dihydroquinoline **8** was the unique product. The influence of the temperature was determined and we can see that at −40 °C no reaction was observed after 10 min (entry 4). This also shows that methylchloroformate did not activate the imine moiety[6a] in the nucleophilic addition but only stabilises the adduct. When the temperature rose to −20 °C, the 1,2-dihydroquinoline **8** could be obtained in 18% yield (entry 5). However, the presence of sub-stoichiometric amounts of DME increased dramatically the yield up to 81% (entry 6).

These results show that the nucleophilic addition of an alkyllithium reagent on quinoline is completely regioselective and the 1,2-dihydroquinoline can be isolated in good yield without any by-product. Even more importantly, with asymmetric catalysis in view, the nucleophile can be activated by sub-stoichiometric amounts of an external ligand like DME or TMEDA in toluene or in Et_2O. These results had comforted us in the possibility of an enantioselective activation of this nucleophilic addition.

The rate of the reaction was also studied with methyl Grignard as carbon nucleophile (Table 2). In the absence of methyl chloroformate, no reaction took place. Therefore, an activation of quinoline, as its quinolinium salt is needed.

Table 2. Regioselectivity of the addition of methyl Grignard to the quinoline

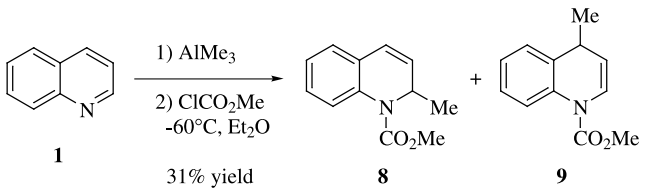


Entries	Solvent	T [°C]	Ligand	Yield [%]	**8/9**
1	Et_2O	−20	—	41	100/0
2	Et_2O	−20	DME 0.5 equiv	16	100/0
3	THF	−20	—	28	100/0
4	Toluene	−20	—	59	100/0
5	Toluene	−20	DME 0.5 equiv	34	100/0
6	CH_2Cl_2	−20	—	94	100/0
7	CH_2Cl_2	−20	DME 0.5 equiv	60	100/0

At −20 °C, methylchloroformate was added 10 min after the nucleophile in order to observe a significant rate of reaction. In Et_2O, without any ligand, the isolated yield of dihydroquinoline **8** was 41% (entry 1). Only the 1,2 adduct was observed. With 0.5 equiv. of dimethoxyethane, the isolated yield was only 16% (entry 2) but the

regioselectivity was complete. In tetrahydrofuran, the yield was worse than in Et_2O with 28% of isolated product (entry 3). In toluene, dihydroquinoline **8** was obtained in 59% yield (entry 4) but the presence of 0.5 equiv of dimethoxyethane decreased the yield down to 34% (entry 5). The best result was obtained in dichloromethane (entry 6) with 94% yield of the 1,2 adduct. Thus, in striking contrast to organolithium reagents, dimethoxyethane had a detrimental effect, the dihydroquinoline being obtained in only 60% yield. In all these experiments, the regioselectivity was complete at position 2 and no trace of 1,4 adduct **9** was observed. Unfortunately, the presence of a bidentate ligand such DME, dramatically decreased the yield of dihydroquinoline.

This regioselective 1,2 addition was also observed with trimethylaluminum (Scheme 2).

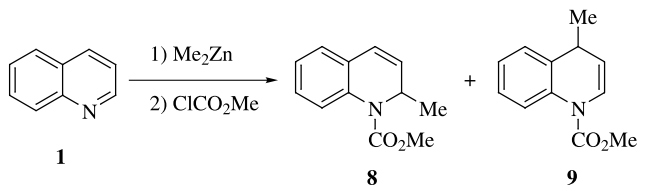


Scheme 2. Regioselectivity of the addition of $AlMe_3$ to quinoline.

Trimethylaluminum did not react after 12 h at room temperature. This nucleophile was not reactive enough with quinoline and activation as iminium salt with methylchloroformate was again required. In this case, the 1,2-dihydroquinoline **8** could be obtained in 31% yield at −60 °C. The regioselectivity was determined by NMR analysis of the crude and only the 1,2 adduct could be observed.

As for trimethylaluminum, dimethylzinc did not react with quinoline and methylchloroformate was used as an activating agent (Table 3).

Table 3. Regioselectivity of the addition of dimethylzinc to quinoline



Entries	Solvent	T [°C]	Ligand	Yield [%]	**8/9**
1	THF	−20	—	30	75/25
2	Et_2O	−20	—	18	>90/10
3	Et_2O	−20	DME 0.5 equiv	16	55/45

Methylchloroformate was added 10 min after the dimethylzinc. In tetrahydrofuran at −20 °C, a modest yield of 30% was observed and the ratio **8/9**, determined by NMR analysis, was found to be 75/25 (entry 1). In Et_2O, under the same conditions, the regioselectivity was better (entry 2) but the yield of isolated product was only 18%. The presence of a diether in the solution did not increase the yield and decreased dramatically the regioselectivity. In this case the ratio of 1,2- and 1,4-dihydroquinoline was 55/45 (entry 3).

2.1. Enantioselective additions with chiral diether 10

In summary, we can say that with organometallics such as alkyl Grignard, dimethylzinc and trimethylaluminum, quinoline has to be activated as a quinolinium salt. In all these cases, the yields were not as good as with organolithium reagents, which is able to add directly on the imine moiety. The presence of a diether decreased the yield, and the regioselectivity in the case of dimethylzinc. For these reasons, alkyllithium reagents appeared to us to be the best candidates for the 1,2 enantioselective nucleophilic addition to quinoline. So far, they were tested in the presence of three different ligands: the chiral 1,2 diether **10**,[10] developed by Tomioka, (−)-sparteine[11] **11** as a 1,2 diamine, and the bisoxazolines **12a**, **12b** and **12c** (Fig. 1).

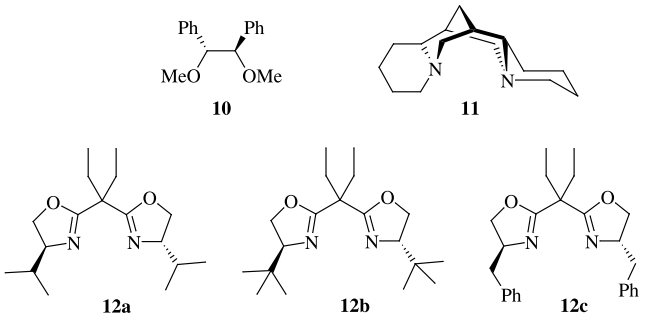


Figure 1. (*R*,*R*)-Dimethoxydiphenylethane **10**, (−)-sparteine **11**, bisoxazolines **12a**, **12b** and **12c**.

Firstly, methyllithium was used in the presence of 1 equiv of the chiral diether **10** (Table 4, entry 1). The desired dihydroquinoline was obtained in 67% isolated yield but the enantiomeric excess, determined by chiral GC analysis, was only 20%.

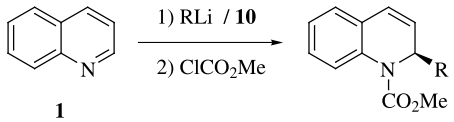
The catalytic version of this addition was tested with the more reactive *n*-butyllithium. Table 4 shows that conversion to the 2-butyl-1,2-dihydroquinoline **13** was good at low temperature in Et_2O or in toluene (entries 2–4). Unfortunately, the enantiomeric excess was very low. Phenyllithium (entries 5–9), as well as 1-naphthyllithium (entries 10 and 11), also showed very low enantioselectivity. However, it is striking to observe that, despite the very low yield, a moderate ee of 26% (although the best in this series!) could be obtained in toluene (entry 6). The yields were usually better with catalytic amount of ligand, indicating that the ligand might be destroyed by RLi, thus consuming most of this nucleophile.

2.2. Enantioselective additions with (−)-sparteine 11

The 1,2 diether **10** being rather inefficient, we have attempted to enhance the chiral induction by changing the nature of the chelating heteroatoms. (−)-Sparteine **11**, already known to be a good complexing chiral ligand for organolithium reagents,[11] appeared to us to be a good alternative. Using the same procedure as before, the organolithium reagent was firstly added to the mixture of (−)-sparteine **11** and quinoline **1** (Table 5).

In toluene at −40 °C, butyllithium gave the desired dihydroquinoline **13** with 15% ee in the presence of

Table 4. Enantioselective addition of organolithium reagent to quinoline in the presence of (*R*,*R*)-dimethoxydiphenylethane **10**



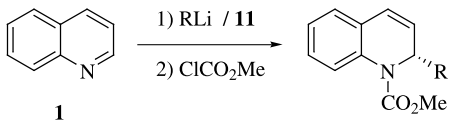
1

8 R = Me
13 R = Bu
14 R = Ph
15 R= Naphth

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yield [%]	ee [%]
1	Et_2O	Me	−20 1 h	1	67[a]	20
2	Et_2O	Bu	−60 1 h	0.2	86[a]	4
3	Toluene	Bu	−60 1 h	0.2	68[a]	0
4	Toluene	Bu	−78 1 h	0.2	53[a]	4
5	Et_2O	Ph[b]	−78 2 h	1	16	<2
6	Toluene	Ph[b]	−78 2 h	1	7	26
7	Toluene	Ph[b]	−78 2 h	0.2	54	<2
8	Toluene	Ph[b]	−60 2 h	1	20	12
9	Toluene	Ph[b]	−60 2 h	0.2	74	<2
10	Toluene	Naphth[b]	−50 2 h	1	57	<4
11	Toluene	Naphth[b]	−50 2 h	0.2	45	5

[a] Conversion determined by crude NMR analysis.
[b] PhLi and NaphthLi were prepared by halogen–metal exchange between PhI or NaphthI and *n*-BuLi.

Table 5. Enantioselective addition of butyllithium and methyllithium to quinoline in the presence of (−)-sparteine



1

8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	(−)-Sparteine [equiv]	Yield [%]	ee [%]
1	Toluene	Bu	−40 1 h	0.2	67	15
2	Toluene	Bu	−40 1 h	1	98	18
3	Toluene	Bu	−80 1 h	1	86	19
4	Et_2O	Bu	−40 1 h	1	98	16
5	Et_2O	Bu	−40 1 h	0.2	100	13
6	Et_2O	Bu	−60 1 h	1	99	18
7	Et_2O	Bu	−80 1 h	1	86	16
8[a]	Et_2O	Bu	−40 1 h	1	100	10
9[a]	Et_2O	Bu	−60 1 h	1	76	12
10	Et_2O	Me	−20 1 h	1	69	5

[a] By precomplexing the butyllithium and (−)-sparteine.

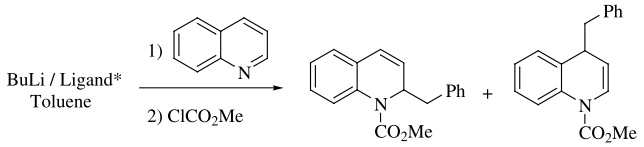
0.2 equiv of ligand (entry 1). Increasing the amount of ligand up to 1 equiv under the same conditions allowed to improve the yield up to 98% of isolated product, but the enantiomeric excess was only 18% (entry 2). This result could not be enhanced by cooling the temperature to −80 °C and enantiomeric excess was still 19% (entry 3). Using Et_2O instead of toluene gave lower enantiomeric excess with 1 equiv (entry 4), or 0.2 equiv of ligand (entry 5), even at lower temperatures (entries 6 and 7). Compared to diether **10**, (−)-sparteine **11** gave both higher yields and ee's. Finally, methyllithium was tested with stoichiometric amounts of ligand (entry 10). Both yield and enantiomeric excess of the dihydroquinoline **8** were comparable than before, with diphenyldimethoxyethane **10** as ligand.

Compared to isoquinoline, (−)-sparteine gave disappointingly low results with quinoline. So far, we have attempted to optimise the chiral induction by pre-complexing the ligand and the organolithium reagent before the reaction with quinoline. The precomplexation was done by stirring *n*-BuLi and (−)-sparteine at room temperature, for 30 min, then cooling this complex at the desired reaction temperature. Table 5 shows that 1 equiv of (−)-sparteine gave the dihydroquinoline **13** with 10% ee at −40 °C (entry 8), which was lower than without any pre-complexation (entry 4). At −60 °C, an enantiomeric excess of 12% could be observed (entry 9).

The same precomplexation procedure was repeated in toluene. However, we observed, this time, the nucleophilic addition of benzyl lithium, rather than of *n*-BuLi.

This organolithium reagent was formed by deprotonation of the solvent, toluene, in the presence of a diamine, such as

Table 6. Nucleophilic addition of benzyl lithium to quinoline by deprotonation of toluene in the presence of ligand



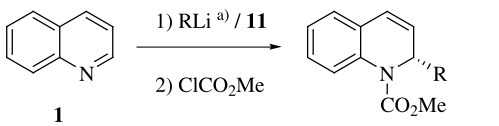
Entries	*T* [°C]	Ligand	Yield [%]	**16a/16b**[a]	ee [%] **16a/16b**
1	−60 1 h	**11** (1 equiv)	62	83/17	44/0
2	−60 1 h	TMCDA (1 equiv)	80	79/21	26/3

[a] Determined by NMR analysis.

(−)-sparteine **11**. In addition, the reaction was not regioselective and two products, the 2-benzyl-1,2-dihydroquinoline **16a** and the 4-benzyl-1,2-dihydroquinoline **16b**, were isolated, in a 83/17 ratio. The enantiomeric excess of the 1,2 adduct, **16a**, was 44%, while the 1,4 adduct, **16b**, was racemic (Table 6, entry 1). Similar results were obtained with (*R*,*R*) N,N′-tetramethyl cyclohexane-1,2-diamine (TMCDA) (entry 2), but with a lower enantioselectivity. Attempts were also made in the presence of diether **10** or bisoxazoline **12a**; toluene was not deprotonated by *n*-BuLi, a result which is consistent with the previous observations made in the presence of TMEDA or DABCO.[12] However, no nucleophilic addition at all was observed on quinoline, indicating that *n*-BuLi was consumed on reaction with diether **10** or bisoxazoline **12a**, at room temperature.

Phenyllithium generally affords better enantioselecttivities with (−)-sparteine than with other ligands.[13] The addition of phenyllithium to quinoline in stoichiometric amount of sparteine gave the 1,2-dihydroquinoline **14** in 82% yield and with 66% ee (Table 7, entry 1). These values were obtained in toluene at −78 °C after 1 h (entry 1), as well as in ether at −60 °C after 2 h (entry 5). When 2 equiv of ligand were added, the yield was stable and a slightly lower ee was obtained (entry 3). By increasing the temperature to −60 °C, an enantiomeric excess of 63% could be described (entry 4). Under the same conditions, whenever ether was used instead of toluene, the ee and the yield were similar (entries 5, 7 and 8). Therefore, with 1 equiv of sparteine, the enantiomeric excess was still up to 66%. In presence of 0.2 equiv of ligand, at −78 °C after 1 h, we found that the ee decreased dramatically. In toluene (entry 2), that value was 7% and rose up to 24% in ether (entry 6). In all cases, the enantiomeric excess was the best result observed thus far.

Table 7. Enantioseletive addition of aryllithium to quinoline in the presence of (−)-sparteine



1

14 R = Ph
15 R= Naphth

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yield [%]	ee [%]
1	Toluene	Ph	−78 1 h	1	82	66
2	Toluene	Ph	−78 1 h	0.2	38	7
3	Toluene	Ph	−78 1 h	2	88	57
4	Toluene	Ph	−60 2 h	1	91	63
5	Et_2O	Ph	−78 1 h	1	55	67
6	Et_2O	Ph	−78 1 h	0.2	60	24
7	Et_2O	Ph	−60 2 h	1	82	66
8	Et_2O	Ph	−20 2 h	1	70	57
9	Toluene	Naphth	−78 2 h	1	69	17
10	Toluene	Naphth	−78 2 h	0.2	24	9
11	Toluene	Naphth	−50 2 h	1	37	16
12	Toluene	Naphth	−50 2 h	0.2	66	6
13	Et_2O	Naphth	−78 2 h	1	86	28
14	Et_2O	Naphth	−78 2 h	0.2	64	12

RLi was prepared by halogen–metal exchange between RI and *n*-BuLi.

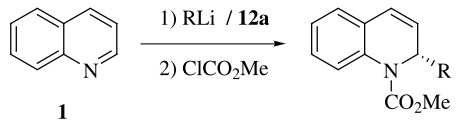
To extend this result, we also tested the addition of 1-naphthyllithium. The first observation was that the yield was satisfactory, but the enantiomeric excess was worse. In stoichiometric conditions, we have observed that in toluene at −78 °C (entry 9) or −50 °C (entry 11), the ee was the same with about 17%. Using Et_2O instead of toluene (entry 13), under the same conditions the enantiomeric excess increased to 28% and the yield was also better with 86%. Under catalytic conditions, in toluene (entries 10 and 12) or in ether (entry 14), the desired product **15** was obtained with a chiral induction, but the ee decreased, as before with phenyllitium.

2.3. Enantioselective additions with bisoxazolines 12a, 12b and 12c

The reactions with (−)-sparteine and alkyllithiums being a rather unselective, we have attempted to increase the enantiomeric excess of the 1,2-dihydroquinolines **8** and **13**, using more efficient ligands. Bisoxazolines were known to afford good results in enantioselective addition to acyclic imines.[13a] We therefore synthesised and tested bisoxazoline **12a** derived from L-valinol.

We have first tested the enantioselective addition with the bisoxazoline **12a** using methyllithium as carbon nucleophile (Table 8). The best result was obtained in toluene at −40 °C with one equiv of chiral ligand. An enantiomeric excess of 63% could be observed (entry 1). Catalytic amounts of this bisoxazoline under the same conditions gave the dihydroquinoline **8** in 43% isolated yield with an enantiomeric excess of 30% (entry 2). Decreasing the temperature to −60 °C did not allow a better enantiomeric excess (entry 3). Using Et_2O instead of toluene (entry 4) gave similar results in term of enantioselectivity. Nevertheless, bisoxazoline

Table 8. Enantioselective addition of alkyllithium to quinoline in the presence of bisoxazoline **12a**



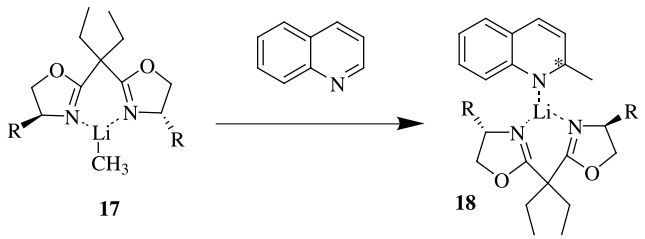
1

8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yied [%]	ee [%][a]
1	Toluene	Me	−40 2 h	1	47	63
2	Toluene	Me	−40 1 h	0.2	43	30
3	Toluene	Me	−60 2 h	0.2	40	32
4	Et_2O	Me	−60 2 h	0.2	31	31
5	Toluene	Me	−40 15 min	0.2	30[b]	62
6	Toluene	Me	−40 30 min	0.2	42[b]	57
7	Toluene	Me	−40 45 min	0.2	44[b]	59
8	Toluene	Me	−40 75 min	0.2	54[b]	54
9	Toluene	Bu	−60 1 h	1	63	72
10	Toluene	Bu	−70 1 h	1	85	79
11	Toluene	Bu	−60 1 h	0.2	75	66
12	Toluene	Bu	−70 1 h	0.2	63	67
13	Toluene	Bu	−80 1 h	0.2	55	67
14	Et_2O	Bu	−60 1 h	0.2	90	42
15	Et_2O	Bu	−70 1 h	0.2	79	45
16	Et_2O	Bu	−80 1 h	0.2	87	39

[a] Determined by chiral GC.
[b] Conversion determined by crude NMR analysis.

12a appeared to be the best chiral ligand for this reaction and we wanted to check what were the limitations of such an enantioselective nucleophilic addition in the presence of an external chiral ligand. Particularly, we wanted to know if the chiral ligand, associated to the organolithium reagent, was trapped by the lithiated amide intermediate produced by the nucleophilic addition, as indicated in Scheme 3.



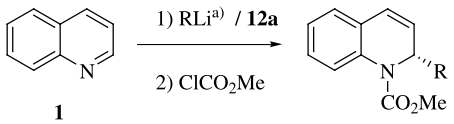
17 **18**

Scheme 3. Trapping of the chiral ligand by the lithiated intermediate.

The chiral ligand would then become inefficient for another catalytic cycle and the enantioselectivity would decrease during the reaction. In order to verify this hypothesis, the reaction was reproduced in toluene at −40 °C in the presence of catalytic amount of chiral bisoxazoline **12a**. Methylchloroformate was added after 15, 30, 45, or 75 min and in each reaction, the enantiomeric excess was compared to the conversion (Table 8). At 15 min, an enantiomeric excess of 62% was observed for a conversion of 30% (entry 5). This enantiomeric excess is higher than those observed in catalytic version, and it is closer to the stoichiometric version (entry 1). After 30 min, the conversion rose up to 42% but the enantiomeric excess decreased to 57% (entry 6). We observed that the reaction was slower than in the first 15 min, indicating that the acceleration of the reaction, due to the ligand, was not so well pronounced. After 75 min (entry 8), the decrease of the enantiomeric excess down to 54% was significant enough to be taken into consideration, and the conversion was only 54%. In regard to these two results: decrease of the enantiomeric excess and slow down the reaction rate, it appeared clear to us that the catalyst loses its efficiency during the reaction and this tends to prove the trapping of the ligand by the lithiated intermediate.

With butyllithium and a stoichiometric amount of ligand **12a** we obtained the 1,2-dihydroquinoline **13** in 63% isolated yield with 72% ee at −60 °C in toluene (Table 8, entry 9). By decreasing the temperature to −70 °C, an enantiomeric excess of 79% could be observed (entry 10). When catalytic amounts (0.2 equiv) of ligand were used under the same conditions, the enantiomeric excess was still up to 66% (entry 11). In this case, decreasing the temperature to −70 °C (entry 12) or −80 °C (entry 13) did not allow a better enantioselectivity, but rather decreased the yield of the reaction. Changing the solvent to Et_2O gave better yields but lower enantiomeric excess (entries 14–16). Thus, toluene appeared to be the best solvent in this reaction.

Table 9. Enantioselective addition of phenyl- and naphthyllithium to quinoline in the presence of bisoxazoline **12a**



1

14 R = Ph
15 R= Naphth

Entries	Solvent	R[a]	*T* [°C]	Ligand [equiv]	Yield [%]	ee [%]
1	Toluene	Ph	−78 1 h 00 min	1	6	<4
2	Toluene	Ph	−78 1 h 30 min	0.2	28	0
3	Toluene	Ph	−55 1 h 30 min	0.2	57	<4
4	Et_2O	Ph	−78 1 h 30 min	0.2	63	0
5	Et_2O	Ph	−55 1 h 30 min	0.2	82	0
6	Toluene	Naphth	−70 2 h	0.2	20	8
7	Toluene	Naphth	−50 2 h	0.2	55	0
8	Et_2O	Naphth	−78 2 h	0.2	36	0
9	Et_2O	Naphth	−50 2 h	0.2	65	0

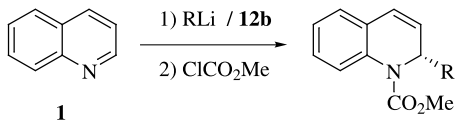
[a] RLi was prepared by halogen–metal exchange between RI and *n*-BuLi.

It was expected that phenyllithium would not behave favourably with bisoxazoline ligands.[13] This is indeed the case (Table 9).

Table 9, shows that only a trace amount of compounds **14**, with low ee, was obtained when the addition of phenyllithium to quinoline was carried out in toluene, at −78 °C and with 1 equiv of ligand (entry 1). Catalytic amounts of bisoxazoline **12a** gave the 2-phenyl- and 2-naphthyldihydroquinoline **14** and **15** with a better yield. The yields were better in ether than in toluene, but only racemates were obtained. Furthermore, the temperature influenced this value. In the case of the addition of phenyllithium, in toluene the yield was 28% at −78 °C (entry 2) and was enhanced to 57% at −55 °C (entry 3). In ether, the values were, respectively 63 and 82% (entries 4 and 5). Nevertheless, the increase of temperature did not change the enantiomeric excess.

So far, bisoxazoline **12a** gave an enantiomeric excess of 79% with *n*-BuLi, and the chiral induction with MeLi allowed an enantiomeric excess of around 63% in stoichiometric version or at the beginning of the catalytic reaction. The limitation of such a catalytic reaction is the trapping of the chiral ligand by the amine produced during the reaction. Bisoxazoline **12b**, having a tertiobutyl instead of an isopropyl group, is usually a better enantiodiscriminating ligand, due to the increased steric interactions. We therefore prepared and tested this new ligand (Table 10).

Table 10. Enantioselective addition of alkyllithium to quinoline in the presence of bisoxazoline **12b**



1

8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yied [%]	ee [%][a]
1	Toluene	Me	−40 2 h	0.2	<5	nd
2	Toluene	Bu	−70 1 h	1	80	32
3	Toluene	Bu	−70 1 h	0.2	70	37
4	Toluene	Bu	−40 1 h	0.2	69	7
5	Et_2O	Bu	−70 1 h	0.2	80	8

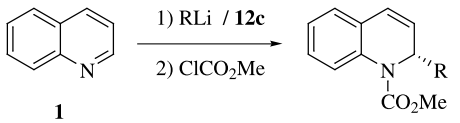
[a] Determined by chiral GC.

Methyllithium and catalytic amount of ligand **12b**, in toluene, did not afford significant addition product (entry 1). With the more reactive butyllithium, an enantiomeric excess of 37% was measured, with a good isolated yield (entry 3). Increasing the amount of ligand **12b** to 1 equiv, improved the yield to 80% but lowered the ee to 32%. Increasing the temperature or using ether instead of toluene, dramatically reduced the enantioselectivity (entries 4 and 5).

In a last attempt to optimise these results, we have used the benzylbisoxazoline **12c**, thinking that π-staking interactions with the substrate would have a favourable role.

With butyllithium as nucleophile, Table 11 shows that an enantiomeric excess of 69% could be obtained with 1 equiv of this ligand (entry 3), indicating that the bisoxazoline **12c**, with a benzyl group, gave a lower enantiomeric excess than the bisoxazoline **12a**, but a better than ligand **12b**. Nevertheless, catalytic amount of ligand can be used with a small loss of enantioselectivity (entries 4 and 5). Again, in ether, the ee are considerably lower than in toluene (entry 6). With ligand **12c**, methyllithium reacts normally, affording an ee of 21–22%, both in ether and toluene. Thus, bisoxazoline **12c** has an intermediate behaviour, compared to **12a** and **12b**. In view of the insignificant enantioselectivity observed with phenyllithium and bisoxazoline **12a**, no attempts were made with the other bisoxazolines.

Table 11. Enantioselective addition of alkyllithium to quinoline in the presence of bisoxazoline **12c**



1

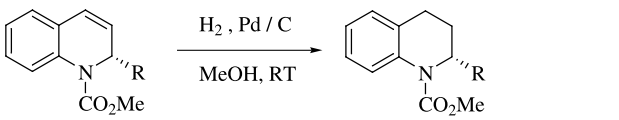
8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yied [%]	ee [%][a]
1	Toluene	Me	−40 1 h	0.2	69	21
2	Et_2O	Me	−40 2 h	0.2	86	22
3	Toluene	Bu	−70 2 h	1	57	69
4	Toluene	Bu	−70 2 h	0.2	79	41
5	Toluene	Bu	−40 2 h	0.2	89	40
6	Et_2O	Bu	−70 2 h	0.2	96	20

[a] Determined by chiral GC.

2.4. Determination of the absolute configuration

In order to determine the absolute configuration of the addition products, 1,2-dihydroquinolines **13** and **14** were converted to the known tetrahydroquinolines **19** and **20**.[14] Thus, **13** and **14** were hydrogenated with palladium on charcoal to afford tetrahydroquinolines **17** and **18**, in 98 and 81% yield respectively (Scheme 4).

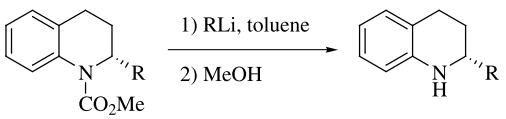


13 R = Bu
14 R = Ph

17 R = Bu (98% yield)
18 R = Ph (81% yield)

Scheme 4. Hydrogenation of 1,2-dihydroquinolines **13** and **14**.

Then, the carbamate functionality was removed by a Bouveault reaction with alkyllithium to provide the known products[14] **19** and **20** with the same enantiomeric excess as the starting 1,2-dihydroquinolines **13** and **14** and with a moderate non-optimised yield (31–35%) (Scheme 5).



17 R = Bu
18 R = Ph

19 R = Bu (31% yield)
20 R = Ph (35% yield)

Scheme 5. Removal of the carbamate of 1,2,3,4-tetrahydroquinolines **19** and **20**.

The specific rotation of 2-butyl-1,2,3,4-tetrahydroquinoline **19** gave a negative value of −39 for an enantiomeric excess of 41%, showing, by comparison with the literature data,[14] that the nucleophilic addition of *n*-butyllithium on quinoline, with bisoxazoline **12c** as ligand, gave (*S*)-2-butyl-1,2-dihydroquinoline **13**. For 2-phenyl-1,2,3,4-tetrahydroquinoline **20**, the sign of the specific rotation was negative with −31.4 for an enantiomeric excess of 64.6%. Thus, according to the literature data,[14] the nucleophilic addition of phenyllithium on quinoline, with sparteine as ligand, gave (*R*)-2-phenyl-1,2-dihydroquinolines **14**.

3. Conclusion

In conclusion, we have shown that it was possible to synthesise alkyl and aryl 1,2-dihydroquinolines from quinoline by direct addition of organometallic reagents. This reaction was completely regioselective with organolithium reagents, methyl Grignard and trimethylaluminum, and only the 1,2 addition was observed. Dimethylzinc gave a mixture of 1,2 and 1,4 adduct, depending on the experimental conditions. Organolithium reagents could react without any activation of the imine moiety. By this way, the N-acylation of the lithiated intermediate did not induced any by-product and allowed very good yields. With alkyllithium reagents, in the presence of a chiral ligand, an enantiomeric excess up to 79% could be obtained with butyllithium, using the bisoxazoline **12a** as an external ligand. The catalytic version gave lower enantiomeric excess due to the trapping of the ligand, but optimisation of these results will be done, using more efficient chiral ligands. With aryllithium reagents, (−)-sparteine **11** gave enantiomeric excess up to 66%, in stoichiometric conditions. So, in this case, the diamines as external ligands appeared to be good candidates to optimise this reaction.

4. Experimental

4.1. General remarks

All the reactions were carried out under argon atmosphere with magnetic stirring, unless otherwise specified. Two necked flasks were used with an internal thermometer. Solvents were dried by distillation from a drying agent as follow: Et_2O (Na/benzophenone), THF (Na/benzophenone), toluene (CaH_2), CH_2Cl_2 (CaH_2). Commercial MeLi Fluka in THF/Cumene 1/1, commercial *n*-BuLi Fluka in hexane, were used. Flash chromatography column: SiO_2 (Brunschwig 32–63, 60 Å). Gas chromatography: Hewlett Packard 5790A, integrator HP 3390A, HP-1 Capillary column, 10psi H_2. Chiral GC: Hewlett Packard, Lipodex E column 200034-32. Programs are written as follow: Initial temperature (°C)-initial time (min)-increasing temperature (°C/min)-final temperature (°C)-final time (min). Supercritical Fluid Chromatography (SFC): Berger, Column Chiralcel OJ and OD-H. Melting Point: Kofler hot stage. $[\alpha]_D^{20}$: Perkin–Elmer 241 polarimeter. ^1H NMR: Varian Gemini-200 at 200 MHz and Brucker DRX-400 at 400 MHz in $CDCl_3$, standard $CDCl_3$ (7.27 ppm). Coupling constants are expressed in Hz (multiplicity: singlet 's', doublet 'd', triplet 't', quadruplet 'q', multiplet 'm'). ^{13}C NMR: Varian Gemini-200 at 50 MHz and Brucker DRX-400 at 100 MHz in $CDCl_3$, standard $CDCl_3$ (77.0 ppm). Infra-red spectra (IR): FT-IR Perkin–Elmer 1600. The high-resolution mass spectra (HRMS) were recorded in the EI (70 eV) mode.

4.1.1. 2-Methyl-1,2-dihydroquinoline (5). To a stirred solution of quinoline (0.3 mL; 2.5 mmol) in dry toluene (10 mL) was added DME (1.3 mL; 1.25 mmol) under an argon atmosphere at −20 °C. Then methyllithium (3.1 mL; 5 mmol) was added. After 1 h, the solution was hydrolysed with water, extracted with Et_2O (3×20 mL), dried with $MgSO_4$, and filtered. The solvent was evaporated. The crude product was purified by flash chromatography on silicagel with cyclohexane/Et_2O (80/20) and the dihydroquinoline **5** was obtained in 57% yield as yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.0–6.35 (m, 4H); 6.30 (m, 1H); 5.50 (m, 1H); 4.42 (m, 1H); 3.70 (s, 1H); 1.30 (d, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 144.4; 129; 127.6; 127.2; 125.6; 120.9; 117.9; 113.1; 48.8; 24.7. IR: 3388; 3033; 2963; 1639; 1602; 1487; 1453; 1318; 1277; 1122; 1038 cm^{-1}.

4.1.2. 2-Methyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (8). *With MeMgBr.* To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) in dry dichloromethane (20 mL) was added methylmagnesium bromide (1 mL, 3 mmol as a 3 M solution in Et_2O) at −20 °C under an argon atmosphere. After 10 min at −20 °C, methylchloroformate (2.2 mL, 3 mmol) was added dropwise. After 15 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with dichloromethane (3×20 mL), dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography with cyclohexane/Et_2O (90/10) as eluent and the desired 1,2-dihydroquinoline **8** was obtained in 94% yield.

With Me_2Zn. To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) in dry tetrahydrofuran (10 mL) was added Me_2Zn (1.2 mL, 3 mmol as a 2 M solution in toluene) at −20 °C under an argon atmosphere. After 10 min, methylchloroformate (2.2 mL, 3 mmol) was added dropwise. After 15 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (3×20 mL), dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel using cyclohexane/Et_2O (95/5) as eluent. A mixture of inseparable 1,2-dihydroquinoline **8** and 1,4-dihydroquinoline **9** was obtained in 30% yield.

With Me_3Al. To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) Et_2O was added Me_3Al (2 mL, 4 mmol as a 2 M solution in toluene) under an argon atmosphere at −20 °C. Methylchloroformate (2.2 mL, 3 mmol) was then added dropwise. After 1 h 30 min at −20 °C, the solution was hydrolysed with water, extracted with Et_2O (3×20 mL), dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel using cyclohexane/Et_2O (95/5). The 1,2-dihydroquinoline **8** was obtained in 31% yield.

4.1.3. *(S)*−2-Methyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (8). To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) and bisoxazoline **12a**

(747 mg, 0.5 mmol) in dry toluene (20 mL) was added methyllithium (3 mL, 3 mmol as a 1 M solution in THF/cumene 1/1) at −60 °C. After 2 h methylchloroformate (0.23 mL, 3 mmol) was added. After 10 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (2×20 mL) and dichloromethane (2×20 mL), dried with $MgSO_4$ and filtered. The crude solution was purified by flash chromatography on silicagel with cyclohexane/Et_2O (80/20) as eluent and the dihydroquinoline **8** was obtained in 47% yield as pale pink oil. The enantiomeric excess was found to be 63% by chiral GC. TLC: R_f=0.42 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.6–7.0 (m, 4H); 6.4 (d, 1H, J=9.5 Hz); 6.0 (dd, 1H, J_1=5.9 Hz, J_2=9.7 Hz); 5.10 (q, 1H, J=6.3 Hz); 3.79 (s, 3H); 1.10 (d, 3H, J=6.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.1; 134; 130; 131.1; 127.8; 127.4; 124.9; 126.6; 124.6. IR: 2955; 1710; 1491; 1439; 1316; 1129; 765 cm^{-1}. MS-EI: *m/z* (relative intensity) 203 (19); 188 (100); 144 (89); 129 (18); 115 (10); 102 (9); 77 (11); 59 (15). Anal. calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89. Found: C, 69.46; H, 6.63; N, 6.52. Program of GC analysis: 90-1-170. $[\alpha]_D^{20}$=+22.9 (c=1.2 in $CHCl_3$) for an ee of 63%.

4.1.4. (*S*)-2-Butyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (13). To a solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) and bisoxazoline **12a** (735 mg, 2.5 mmol) in dry toluene (20 mL) was added *n*-BuLi (1.8 mL, 3 mmol as a 1.6 M solution in hexane) at −70 °C under an argon atmosphere. After 1 h, methylchloroformate (0.23 mL, 3 mmol) was added. After 10 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (2×20 mL) and dichloromethane (2×20 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel with cyclohexane/Et_2O (80/20) as eluent and gave the 1,2-dihydroquinoline **13** in 80% yield as yellow oil. The enantiomeric excess of 79% was determined by chiral GC analysis using the Lipodex E column. TLC: R_f=0.50 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.23–7.08 (m, 4H); 6.46 (d, 1H, J=8 Hz); 6.09 (m, 1H); 5.00 (m, 1H); 3.81 (s, 3H); 1.45–1.27 (m, 6H); 0.88 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9; 134.3; 130.1; 127.4; 127.1; 126; 124.7; 124.4; 124.2; 52.8; 32.5; 27.3; 22.3; 13.9. IR: 2931; 1699; 1490; 1438; 1325; 1250; 1131; 764 cm^{-1}. MS-EI: *m/z* (relative intensity) 245 (3); 188 (100); 144 (68); 129 (16); 102 (6); 77 (6); 59 (11). Anal. calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.89; N, 5.48. Program of chiral GC: 90-1-170-20. $[\alpha]_D^{20}$=+35.7 (c=1.02 in $CHCl_3$) for an ee of 79%.

4.1.5. (*R*)-2-Phenyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (14). To a solution of iodobenzene (0.34 mL, 3 mmol, 1.2 equiv) and (−)-sparteine (0.57 mL, 2.5 mmol, 1 equiv) in dry toluene (10 mL) was added dropwise *n*-BuLi (1.88 mL, 3 mmol, as a 1.6 M solution in hexane) at −78 °C under an argon atmosphere. The solution was stirred during 1 h at −78 °C, and was diluted with 11 mL of toluene. Then quinoline (0.29 mL, 2.5 mmol, 1 equiv) was added, and the yellow reaction turned orange, with time. After 1 h at −78 °C, methylchloroformate (0.23 mL, 3 mmol, 1.2 equiv) was added and the solution became yellow. After 10 min, the solution was quenched with a solution of NH_4Cl, extracted with ether (2×20 mL) and dichloromethane (2×20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **14** was obtained in 82% yield as yellow oil. An enantiomeric excess of 66% was determined by chiral SFC analysis, using the column chiralcel OD-H. TLC: R_f=0.30 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s br, 1H); 7.43–7.37 (m, 2H); 7.37–7.24 (m, 4H); 7.21 (dd, 1H, J_1=7.6 Hz, J_2=1.8 Hz); 7.15 (t, 1H, J=7.3 Hz); 6.74 (m, 1H); 6.35–6.24 (m, 2H); 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3; 139.7; 134.7; 128.6; 128.3; 127.9; 127.2; 127.1; 126.4; 125.4; 124.7; 124.4; 55.7; 53.3. IR: 2953, 1694; 1488; 1436; 1377; 1324; 1270; 1125; 1028; 844; 760; 695 cm^{-1}. MS-EI: *m/z* (relative intensity) 265 (41); 188 (100); 144 (66); 129 (19); 102 (11); 77 (17); 59 (15). HRMS: calcd for $C_{17}H_{15}NO_2$ ($M^{+\cdot}$) 265.1103. Found: 265.1087. Program of chiral SFC: OD-H 6%-6-1-15%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{25}$=−438.2 (c=3.1 in $CHCl_3$) for an ee of 66%.

4.1.6. (*R*)-2-Naphthyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (15). To a solution of 1-iodonaphthalene (1.8 mL, 1.2 mmol, 1.2 equiv) and (−)-sparteine (0.23 mL, 1 mmol, 1 equiv) in dry Et_2O (3.5 mL) was added dropwise *n*-BuLi (0.75 mL, 1.2 mmol, as a 1.6 M solution in hexane) at −78 °C under an argon atmosphere. The solution was stirred during 1 h at −78 °C, and was diluted with 3.5 mL of Et_2O. Then quinoline (0.12 mL, 1 mmol, 1 equiv) was added, and the yellow reaction turned orange, with time. After 2 h at −78 °C, methylchloroformate (0.09 mL, 1.2 mmol, 1.2 equiv) was added and the solution became yellow. After 10 min, the solution was quenched with a solution of NH_4Cl, extracted with ether (2×7 mL) and dichloromethane (2×7 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **15** was obtained in 85.6% yield as yellow oil. An enantiomeric excess of 27.5% was determined by chiral SFC analysis, using the column chiralcel OJ. TLC: R_f=0.31 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (d, 1H, J=7.8 Hz); 7.92 (d, 1H, J=8.1 Hz); 7.79 (d, 1H, J=8.1 Hz); 7.71 (t, 1H, J=7.7 Hz); 7.59 (t, 1H, J=7.6 Hz); 7.40 (d, 1H, J=7.1 Hz); 7.33–7.24 (m, 2H); 7.24–7.14 (m, 3H); 7.09 (d, 1H, J=5.8 Hz); 6.73 (d, 1H, J=9.6 Hz); 6.38 (dd, 1H, J_1=9.6 Hz, J_2=6.1 Hz); 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4; 135.3; 135.2; 134.1; 130.4; 129.0; 128.9; 128.6; 127.8; 127.3; 126.6; 126.3; 125.7; 125.4; 125.2; 124.8; 123.7; 52.9; 53.4. IR: 2953; 1697; 1489; 1437; 1300; 1265; 1123; 1040; 754 cm^{-1}. MS-EI: *m/z* (relative intensity) 315 (51); 256 (62); 188 (100); 128 (17); 101 (5); 77 (9); 59 (10). HRMS: calcd for $C_{21}H_{17}NO_2$ ($M^{+\cdot}$) 315.1259. Found: 315.1247. Program of chiral SFC: OJ 10%-2-1-25%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{25}$=−169.5 (c=1.305 in $CHCl_3$) for an ee of 27.5%.

4.1.7. 2-Benzyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (16a) and 4-benzyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (16b). To a solution of (−)-sparteine (0.23 mL, 1 mmol, 1 equiv) in dry toluene (8 mL) was

added *n*-BuLi (0.75 mL, 1.2 mmol as a 1.6 M in hexane) at 25 °C under an argon atmosphere. The solution was stirred for 30 min. The temperature was then cooled to −60 °C and quinoline (0.12 mL, 1 mmol) was added. After 1 h at −60 °C, methylchloroformate (0.09 mL, 1.2 mmol) was added. After 10 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (2×10 mL) and dichloromethane (2×10 mL). The organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel with cyclohexane/Et_2O (95/5) as eluent and the products **16a** and **16b** were obtained in 62% global yield as yellow oil. Enantiomerics excess of 44% for **16a** and 0% for **16b** were determined by chiral SFC analysis, using the column chiralcel OD-H.

Product **16a**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.71 (s br, 1H); 7.35–7.13 (m, 9H); 6.55 (d, 1H, J=9.6 Hz); 6.00 (dd, 1H, J_1=5.8 Hz, J_2=9.6 Hz); 5.27 (s br, 1H); 3.66 (s, 3H); 2.75 (dd, 1H, J_1=2.8 Hz, J_2=7.5 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.0; 138.9; 137.8; 131.4; 129.9; 129.0; 128.8; 128.7; 126.8; 125.7; 124.8; 121.9; 113.1; 54.6; 53.3; 40.7. Program of chiral SFC: OD-H 2%-2-1-20%; MeOH; 200 Bar; 2 mL/min; 30 °C. $[\alpha]_D^{20}$=−162.3 (c=1.1 in $CHCl_3$) for an ee of 44%.

Product **16b**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.93 (d, 1H, J=8.4 Hz); 7.28–7.18 (m, 4H); 7.10 (t, 1H, J=7.3 Hz); 7.04–6.93 (m, 4H); 5.28 (dd, 1H, J_1=5.8 Hz, J_2=7.6 Hz); 3.82 (s, 3H); 3.62 (q, 1H, J=6.4 Hz); 2.85 (d, 2H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.8; 138.4; 136.5; 130.8; 129.5; 128.3; 127.9; 126.5; 126.3; 126.0; 124.7; 121.3; 112.6; 53.1; 44.4; 40.1. Program of chiral SFC: OD-H 2%-2-1-20%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C.

4.1.8. (*S*)-2-Butyl-1,2,3,4-tetrahydro-[N-methoxy carbonyl]-quinoline (17). To a solution of **13** of 40.4% ee (181.5 mg, 0.74 mmol, 1 equiv) in methanol (15 mL) was added 2 mol% of palladium on activated charcoal. The hydrogenation was performed at room temperature under H_2 (1 atm) for 3 h. The crude product was then filtered through Celite and the solvent was evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **17** was obtained in 98% yield as yellow oil. TLC: R_f=0.23 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 1H, J=7.8 Hz); 7.21–7.14 (m, 1H); 7.13–7.08 (m, 1H); 7.04 (t, 1H, J=7.3 Hz); 4.61–4.52 (m, 1H); 3.78 (s, 3H); 2.77–2.63 (m, 2H); 2.26–2.14 (m, 1H); 1.70–1.60 (m, 1H); 1.59–1.50 (m, 1H); 1.42–1.20 (m, 5H); 0.95–0.79 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4; 136.6; 131.2; 127.9; 125.8; 125.5; 124.0; 52.8; 52.6; 32.3; 28.8; 28.0; 24.4; 22.4; 13.9. IR: 2930; 1697; 1492; 1438; 1388; 1323; 1213; 1128; 1057; 911; 765; 716 cm^{-1}. MS-EI: m/z (relative intensity) 247 (19); 190 (100); 130 (14); 118 (16); 91 (7); 77 (6); 59 (7). $[\alpha]_D^{25}$=+36.7 (c=1.145 in $CHCl_3$). The enantiomeric excess was not determined.

4.1.9. (*R*)-2-Phenyl-1,2,3,4-tetrahydro-[N-methoxy carbonyl]-quinoline (18). To a solution of **14** of 65.5% ee (132.8 mg, 0.5 mmol, 1 equiv) in methanol (10 mL) was added 2 mol% of palladium on activated charcoal. The hydrogenation was performed at room temperature under H_2 (1 atm) for 3 h. The crude product was then filtered through Celite and the solvent was evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **18** was obtained in 81% yield as yellow oil. TLC: R_f=0.20 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, 1H, J=7.8 Hz); 7.34–7.19 (m, 6H); 7.16–7.06 (m, 2H); 5.52 (t, 1H, J=7.7 Hz); 3.74 (s, 3H); 2.75–2.61 (m, 2H); 2.57–2.48 (m, 1H); 1.98–1.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5; 143.3; 137.6; 132.6; 128.3; 127.5; 126.7; 126.4; 125.9; 124.8; 124.0; 58.2; 52.8; 33.1; 26.0. IR: 2952; 1698; 1491; 1438; 1380; 1323; 1236; 1133; 1056; 908; 727; 647 cm^{-1}. MS-EI: m/z (relative intensity) 267 (100); 235 (15); 208 (68); 176 (20); 144 (6); 130 (24); 91 (45); 77 (25); 51 (9). Anal. calcd for $C_{17}H_{17}NO_2$ (267.33): C, 76.38; H, 6.41; N, 5.24. Found: C, 75.32; H, 6.52; N, 4.96. $[\alpha]_D^{25}$=−76.3 (c=1.355 in $CHCl_3$). The enantiomeric excess was not determined.

4.1.10. (*S*)-2-Butyl-1,2,3,4-tetrahydroquinoline (19). To a solution of **17** (125.2 mg, 0.51 mmol, 1 equiv) in dry ether (5 mL) was added dropwise *n*-BuLi (1.25 mL, 2 mmol, as a 1.6 M solution in hexane) at −20 °C under an argon atmosphere. The mixture was stirred and the temperature was allowed to rise to room temperature. After 3 h, the solution was quenched with methanol, and the solvents were evaporated. The crude product was purified by chromatography on silica gel with cyclohexane/ether (98/2) as eluent, and the product **19** was obtained in 31% yield as yellow oil. An enantiomeric excess of 40.8% was determined by chiral SFC analysis, using the column chiralcel AD. TLC: R_f=0.63 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01–6.95 (m, 2H); 6.62 (t, 1H, J=7.6 Hz); 6.50 (d, 1H, J=7.3 Hz); 3.85 (s br, 1H); 3.30–3.20 (m, 1H); 2.88–2.69 (m, 2H); 2.03–1.93 (m, 1H); 1.67–1.55 (m, 1H); 1.55–1.47 (m, 2H); 1.46–1.33 (m, 4H); 0.95 (t, 1H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6; 129.2; 126.7; 121.5; 117.0; 114.1; 51.6; 36.3; 28.1; 27.9; 26.4; 22.8; 14.1. IR: 2927; 1608; 1485; 1352; 1310; 1276; 1214; 745 cm^{-1}. MS-EI: m/z (relative intensity) 189 (17); 144 (2); 132 (100); 117 (8); 77 (5); 51 (1). Program of chiral SFC: AD 5%-2-1-15%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{26}$=−38.7 (c=0.54 in $CHCl_3$) for an ee of 40.8%. The absolute configuration was assigned as (*S*) by analogy to the lit. data. (Lit.[14] $[\alpha]_D^{25}$=+79.9 (c=1 in $CHCl_3$) for an ee of 92% for *(R)* stereochemistry).

4.1.11. (*R*)-2-Phenyl-1,2,3,4-tetrahydroquinoline (20). To a solution of **18** (144.8 mg, 0.55 mmol, 1 equiv) in dry toluene (4 mL) was added dropwise MeLi (2.2 mL, 2.2 mmol, as a 1 M solution in THF/cumene: 1/1) at −20 °C under an argon atmosphere. The mixture was stirred and the temperature was allowed to rise to room temperature. After 1 h, the solution solution was quenched with methanol, and the solvents were evaporated. The crude product was purified by chromatography on silica gel with cyclohexane/ether (98/2) as eluent, and the product **20** was obtained in 35% yield as yellow oil. An enantiomeric excess of 64.6% was determined by chiral SFC analysis, using the column chiralcel AS. TLC: R_f=0.62 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.34 (m, 4H);

7.32–7.27 (m, 1H); 7.06–7.6.99 (m, 2H); 6.67 (t, 1H, J=7.4 Hz); 6.56 (d, 1H, J=7.6 Hz); 4.46 (dd, 1H, J=9.3, 3.4 Hz); 4.16 (s br, 1H); 2.99–2.89 (m, 1H); 7.15 (dt, 1H, J=16.3, 4.7 Hz); 2.17–2.10 (m, 1H); 2.06–1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7; 129.3; 128.8; 128.6; 127.4; 126.9; 126.5; 121.0; 117.3; 114.1; 56.3; 30.9; 26.4. IR: 3396; 2924; 1598; 1491; 1310; 1273; 831; 747; 698 cm^{-1}. MS-EI: m/z (relative intensity) 209 (92); 194 (15); 132 (100); 118 (17); 104 (13); 91 (25); 77 (24); 51 (10). Anal. calcd for $C_{15}H_{15}N$ (209.29): C, 86.08; H, 7.22; N, 6.69. Found: C, 84.90; H, 7.38; N, 5.44. Program of chiral SFC: AS 10%-2-1-25%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{27}=-31.4$ (c=1.26 in $CHCl_3$) for an ee of 64.6%. The absolute configuration was assigned as *(R)* by analogy to the lit. data. (Lit.[14] $[\alpha]_D^{25}=+69.9$ (c=1 in $CHCl_3$) for an ee of 72% for *(S)* stereochemistry).

Acknowledgements

The Swiss National Science Foundation, grant N° 2000-68095.02, is acknowledged for the financial support.

References and notes

1. (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
2. (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. (b) Tomioka, K. *Synthesis* **1990**, 541–550.
3. *The Chemistry of Heterocyclic Compounds*, Jones G. Ed., Wiley, Bristol, Vol. 32 (part I, 1977 and part II, 1982).
4. (a) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 77–89, and 465–475. (b) Goldstein, S. W.; Dambek, P. J. *Synthesis* **1989**, 221. (c) Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fakasawa, Y. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1345–1348. (d) Riva, R.; Guanti, G. *Chem. Commun.* **2000**, 1171–1172.
5. (a) Oldham, W.; Johns, I. B. *J. Am. Chem. Soc.* **1939**, *61*, 3289–3291. (b) Eisch, J. J.; Comfort, D. R. *J. Organomet. Chem.* **1972**, *38*, 209–215. (c) Otsuji, Y.; Yutani, K.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 520–524. (d) Eisch, J. J.; Comfort, D. R. *J. Organomet. Chem.* **1972**, *43*, C17–C19. (e) Crawforth, C. E.; Meth-Cohn, O.; Russell, C. A. *J. Chem. Soc., Chem. Commun.* **1972**, 259–260. (f) Crawforth, C. E.; Meth-Cohn, O.; Russell, C. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2807–2810. (g) Goldstein, S. W.; Dambek, P. J. *Synthesis* **1989**, 221–222. (h) Guanti, G.; Perrozzi, S.; Riva, R. *Tetrahedron: Asymmetry* **1998**, *9*, 3923–3927.
6. (a) Fraenkel, G.; Cooper, J. W.; Fink, C. M. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 523–525. (b) For reviews on the chemistry of N-acyliminium ions see: Speckamp, W. N.; Hiemstra, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. Koning, H.; Speckamp, W. N. *Stereoselective synthesis, (Houben-Weyl)*; Helmchen, G., Hoffman, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1996; Vol. E21, p 1953. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Pilli, R. A.; Maldaner, A. O. *Tetrahedron Lett.* **2000**, *41*, 7843–7846.
7. Alexakis, A.; Mangeney, P.; Rezgui, F. *Tetrahedron Lett.* **1999**, *40*, 6241–6244.
8. Shibasaki, M.; Takamura, M.; Funabashi, K.; Kanai, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328.
9. Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117–2122.
10. Tomioka, K.; Koga, K.; Shindo, M. *J. Org. Chem.* **1998**, *63*, 9351–9357.
11. (a) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560.
12. (a) Eisch, J. J. *Organomet. Synth.* **1981**, *2*, 95. (b) Eberhardt, G. G.; Butte, W. A. *J. Org. Chem.* **1964**, *29*, 2928–2932.
13. (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C. *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798. (b) Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett* **1998**, 1165.
14. Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.