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Preparation of axially chiral quinolinium salts related to NAD^+ models: new investigations of these biomimetic models as 'chiral amide-transferring agents'

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Abstract—The general purpose of this work is to investigate the potential of biomimetic NAD^+ models as 'nucleophile-transferring agents' with the ultimate motivation to develop new synthetic tools. This first report focuses on the preparation of an axially chiral quinolinium salt **8**. A preliminary investigation of these NAD^+ analogues as 'chiral amide-transferring agents' is reported herein. The synthesis of the desired quinolinium salt **8** was first attempted via a Friedländer approach. Given the poor reproducibility of this first synthetic route, a second strategy making use of an intramolecular nickel-catalyzed coupling was developed with success, furnishing the quinolinium salt **8** in 12% overall yield. The potential of the quinolinium salt **8** as a 'chiral amide-transferring agent' was then investigated. Regioselective 1,4-addition of benzylamine and piperidine produced, respectively, adducts **18a** and **18b** with high diastereoselectivity (de >95%). The resulting 'chiral masked-amide' **18b** was reacted with various activated aryl esters affording the corresponding atropisomeric amide **20** with modest atropenantioselectivity (ee = 2–20%).

1. Introduction

In the course of these three decades, a large number of papers have been reported dealing with the NAD^+/NADH redox couple. Many research groups have focused their efforts on the design of chiral biomimetic NADH models,[1a–e] with the main goal to throw light on the high stereospecificity of the hydride transfer observed during biochemical processes. In parallel, this biomimetic approach led to the development of new synthetic tools, almost exclusively in the field of enantioselective reduction. To extend further the potential of these biomimetic tools, one can explore their aptitude for transferring groups other than 'hydride' to a substrate. Diverse nucleophiles such as cyanides,[2a–k] thiolates,[3] alcoholates,[4a–d] amides[5a–f] and enolates[6] have been reported to add to a variety of pyridinium salts related to NAD^+ models, yielding the corresponding 1,4-adducts (Fig. 1). These resulting 'masked nucleophiles' are expected to react with an electrophile, providing the desired products (Nu–E) along with the recovered pyridinium salt. The former may be considered in this process as a 'nucleophile shuttle'. These 'masked nucleophiles' might provide new synthetic tools in diverse areas of synthetic organic chemistry. In particular, in the field of asymmetric synthesis, chiral NAD^+ models should offer the opportunity to investigate the potential of 'chiral masked nucleophiles' in enantioselective transformations (Fig. 1).

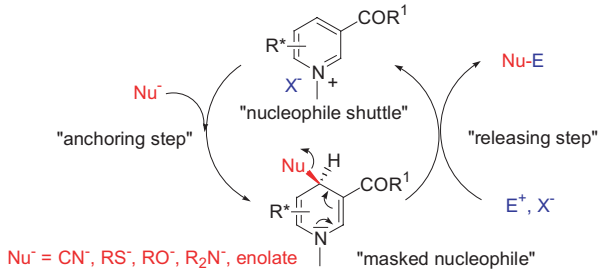

Figure 1. New investigations of NAD^+ models as 'nucleophile-transferring agents'.

One must briefly mention the pioneering work of Kellogg, reported some 20 years ago and related to the

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development of these NAD^+ models as 'nucleophile-transferring agents'.[7] Their first paper deals with the addition of thiolates to esters or amides via 1-methylpyridinium-3,5-dicarboxylic acid salts. The resulting 'masked thiolate' reacts with activated acid-derivatives to produce the thioesters in excellent yields, and this, under neutral conditions (Fig. 2a). Depending on the nature of the thiols, the authors noticed the formation of 1,2-adduct in addition to the expected 1,4-regioisomer. In a second paper, Kellogg reports attempts to use a chiral bridged pyridinium salt[6] as a chiral template to realize an enantioselective aldol condensation (Fig. 2b). Although the condensation occurs smoothly to produce the corresponding aldols in moderate to good yields, no enantioselectivity was observed (Fig. 2b). A second problem arises from the regioselectivity of the initial enolate addition. As observed with thiolates, significant amounts of 1,2-adduct are formed in many cases, which may complicate seriously the rational design of these pyridinium salts as new synthetic tools.

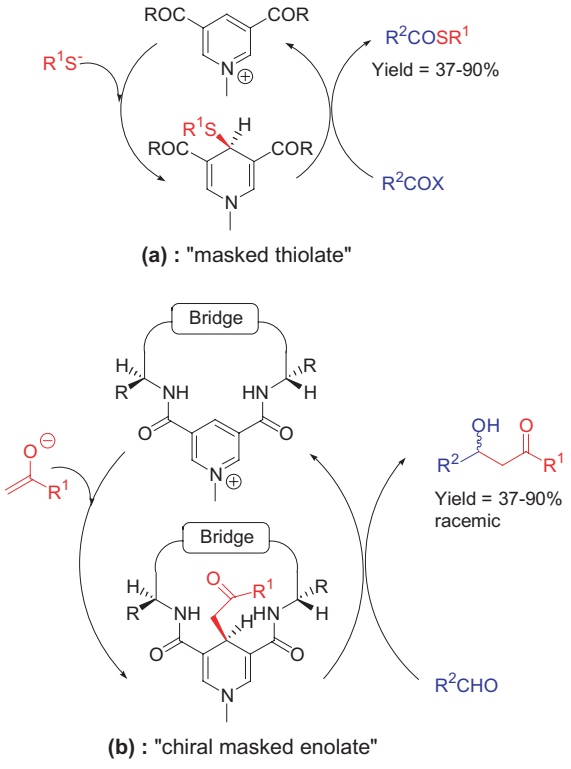


Figure 2. (a) Thiolate-transferring NAD^+ models used in the formation of thioesters. (b) Enolate-transferring NAD^+ models used in aldol condensation.

To the best of our knowledge, no steps forward have been accomplished in this area since this pioneering work. We report herein the use of quinolinium salts as 'amide-transferring agents'. We speculated that the use of quinolinium salts would be more appropriate to develop such applications by avoiding the formation of 1,2 adducts. We essentially concentrate here on the design and preparation of a new axially chiral quinolinium **8** (Fig. 3). Additionally, we demonstrated the diastereoselective 1,4-addition of amines with the perspective to develop these resulting 'chiral masked amides' as new tools in stereoselective synthesis. To this end, it appears attractive to evaluate their potential during atropenantioselective amidification of aryl esters (Fig. 3).

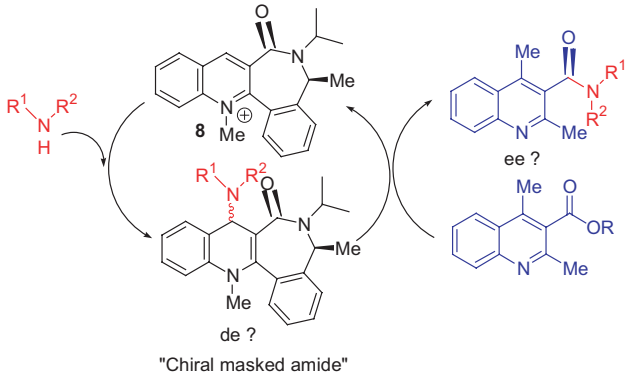


Figure 3. Design of a new axially chiral quinolinium salt as an 'amide-transferring agent'. Application to the atropenantioselective amidification of aryl esters.

2. Results and discussion

2.1. Design and preparation of the quinolinium salt 8

Quinolinium salt **8** was selected as the first candidate for these investigations. This choice was initially motivated by our previous work on the development of axially chiral NADH models.[8a–c] The guiding principle behind the design of these biomimetic models has been the configurational control of the chiral axis C3-C=O, insured by the presence of an additional configurational element (chiral inducer in Fig. 4) installed on the lactam moiety. In the course of this work, it was found that this chiral axis C3-C=O is the main configurational element responsible for the highly diastereoselective 1,4-reduction of these quinolinium salts. Accordingly, this configurational element is expected to play a key role, in terms of diastereoselectivity, during the 'anchoring step' of the amine on the quinolinium salt **8**. It is noteworthy that depending on the nature of the hydride, a complete opposite diastereofacial selectivity was previously observed during the reduction of these axially chiral quinolinium salts. One could ascribe this result to a pre-complexation of diborane on the carbonyl lactam, while sodium borohydride would react on the opposite face, as a result of a steric control (Fig. 4).

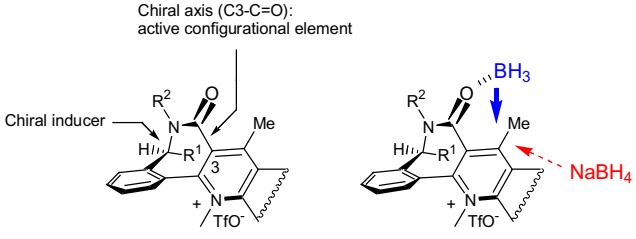
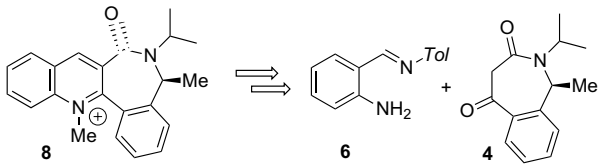


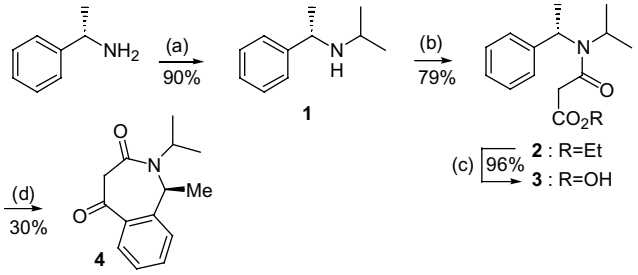
Figure 4. Diastereoselective 1,4-reduction of axially chiral quinolinium salt.

Our initial retrosynthetic analysis for the synthesis of **8** is inspired by our previous work.[8a–c] This approach is based on a Friedländer condensation between benzazepin-3,5-dione **4** and aniline **6** (Scheme 1).



Scheme 1. Retrosynthetic analysis of **8** via a Friedländer approach.

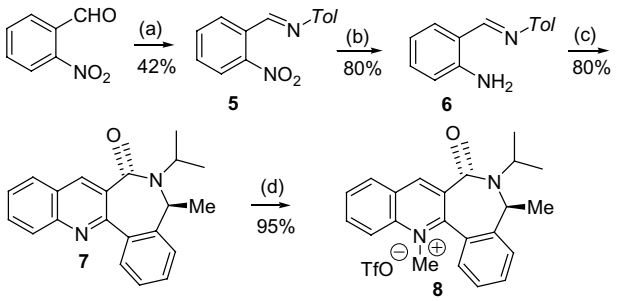
The key intermediate benzazepin-3,5-dione **4** was prepared within three steps from (*S*)-1-phenylethylamine. First reductive amination in the presence of acetone afforded **1** in 90% yield, which in turn was condensed with ethyl malonyl chloride to give β-amide ester **2** in 79% yield. Hydrolysis of **2** furnished carboxylic acid **3** in 96% yield, which was subsequently converted into its acid chloride, which was submitted to intramolecular Friedel–Crafts acylation to provide the desired benzazepin-3,5-dione **4**, however, in only 30% yield (Scheme 2).



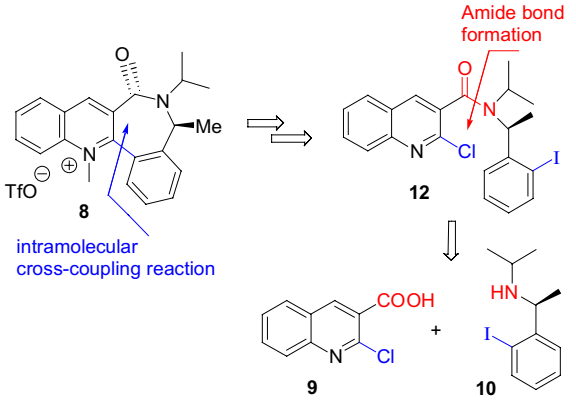
Scheme 2. Synthesis of benzazepin-3,5-dione **4**. Reagents and conditions: (a) acetone/reflux/12 h then $NaBH_4$/20 °C/2 h; (b) $ClCOCH_2CO_2Et/CH_2Cl_2/NEt_3$/12 h/20 °C; (c) KOH/EtOH/0 °C/5 h; (d) $(COCl)_2$/two drops of DMF/CH_2Cl_2 then $AlCl_3/CH_2Cl_2$/1h/20 °C.

The classical Friedländer conditions commonly make use of an *ortho*-aminobenzaldehyde.[9] Nevertheless, the poor stability of the former, which may severely limit the yield of the reaction, prompted us to undertake the Borsche modification.[10] The stable amino imine **6** was straightforwardly prepared in two steps on a multigram scale from 2-nitrobenzaldehyde (42% and 80% yields). Friedländer cyclization was carried out in EtOH in the presence of piperidine to produce the quinoline **7** in 80% yield. The later product was subsequently quaternized in a quantitative yield to give the final product **8** (Scheme 3). This first synthetic route suffers from a low overall yield and a lack of reproducibility in certain steps, making difficult to scale up this Friedländer approach.

An intramolecular metal-catalyzed coupling reaction of **12** was envisaged as an alternative route for the preparation of **8**. This new strategy required ready access to 2-chloro-3-quinolinecarboxylic acid **9** and (*S*)-2-iodo-α-methyl-*N*-isopropylbenzylamine **10** as key intermediates (Scheme 4).

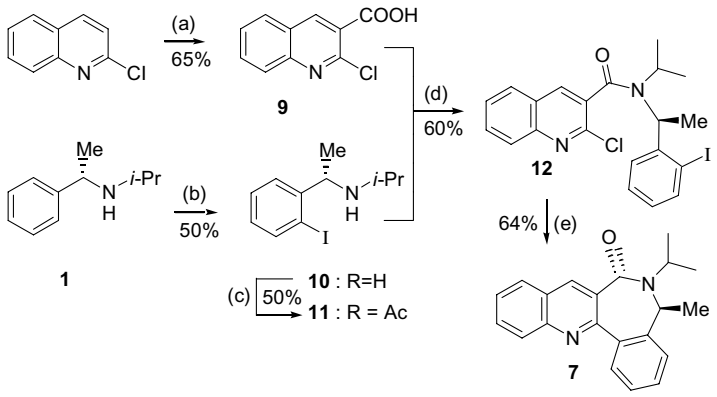


Scheme 3. Synthesis of **8** via Friedländer approach. Reagents and conditions: (a) *p*-toluidine/EtOH/reflux/2 h; (b) $Na_2S{\cdot}H_2O$/EtOH/reflux/10 min; (c) benzazepin-3,5-dione **4**/EtOH/piperidine/reflux/48 h; (d) TfOMe/CH_2Cl_2/20 °C/2 h.



Scheme 4. Retrosynthetic analysis of **8** via an intramolecular coupling reaction.

The first key intermediate **9** was prepared by lithiation of 2-chloroquinoline with *n*-BuLi in the presence of TMEDA according to a known procedure.[11] The lithiated intermediate was trapped with carbon dioxide to afford acid **9** in 65% yield. The second key intermediate **10** was envisioned to arise from an *ortho*-lithiation of **1**. This approach was inspired by previous investigations on *ortho*-lithiation of benzylamine derivatives.[12] After many experimentations using various metallating agents (*n*-BuLi, *tert*-BuLi, *sec*-BuLi) and solvents (Et_2O, THF, cyclohexane/THF), *n*-BuLi in the presence of TMEDA in THF was found to offer the best conditions, affording after treatment of the lithiated intermediate with iodine, compound **10** in 50% yield. The latter compound was converted into its acetyl derivative **11** and subsequently subjected to chiral HPLC analysis, demonstrating that no significant racemization occurred during the lithiation of **1**. With both key intermediates in hand, quinoline **9** was converted into its acid chloride prior to reacting with the amine **10** to supply **12** in 60% yield. We next investigated the crucial intramolecular coupling reaction by using first the Ullmann coupling conditions. However, all attempts to cyclize **12** in the presence of copper powder in refluxing DMF failed, providing **7** in only 10% isolated yield. In search of more efficient conditions, we turned our attention to a nickel-catalyzed coupling reaction, which is reported to proceed under milder conditions as compared with the classical

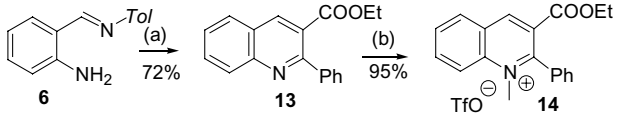


Scheme 5. Preparation of **7** via an intramolecular nickel-catalyzed coupling reaction. Reagents and conditions: (a) *n*-BuLi/TMEDA/THF/78 °C/20 min then CO_2; (b) *n*-BuLi/TMEDA/THF/−78 °C/2 h then I_2 in THF/12 h/20 °C; (c) MeCOCl/NEt_3/CH_2Cl_2/20 °C/2 h; (d) $(COCl)_2$/two drops of DMF/CH_2Cl_2 then **10**/12 h; (e) $NiBr_2(PPh_3)_2$/Zn/$Et_4N^+I^-$/THF/2 h/50 °C.

Ullmann conditions.[13a–d] The reductive coupling of **12** was carried out using $NiBr_2(PPh_3)_2$ and zinc in the presence of Et_4NI, affording **7** with a satisfactory yield (64%). This new approach presents significant advantages over the former Friedländer synthetic route, in particular it circumvents the poorly reproducible intramolecular Friedel–Crafts step (Scheme 5).

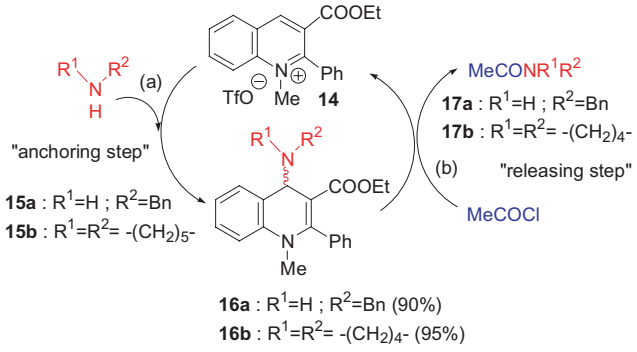
2.2. Investigation of the chiral quinolinium salt 8 as an 'amide-transferring agent'

We first focused our attention on the optimization of the two fundamental steps of this amide transfer process, that is the 'anchoring step' of the amine followed by the 'releasing step' of the resulting 'masked amide'. This optimization was achieved with the achiral quinolinium salt **14**, chosen as a model. It was prepared in two steps by condensation of **6** with ethyl benzoylacetate to give quinoline **13** in 72% yield. Quaternization of **13** afforded quinolinium salt **14** in 95% yield (Scheme 6).



Scheme 6. Preparation of the achiral quinolinium salt **14**. Reagents and conditions: (a) ethyl benzoylacetate/EtOH/piperidine/reflux/48 h; (b) TfOMe/CH_2Cl_2/20 °C/2 h.

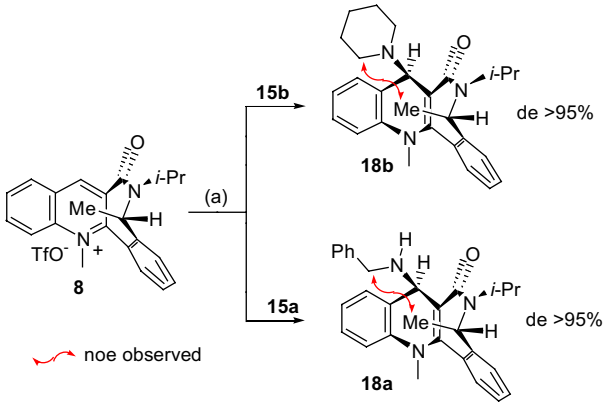
The 'anchoring step' of both benzylamine **15a** and piperidine **15b** on the quinolinium salt **14** was conducted under biphasic conditions (CH_2Cl_2/aqueous Na_2CO_3 solution). Under these conditions, adducts **16a** and **16b** could be isolated in 90% and 95% yields, respectively. As expected, and in contrast to what has been previously observed with pyridinium salts, addition of the nucleophile takes place exclusively at the C-4 position of the quinolinium salt **14**. These resulting 'masked amides' **16a** and **16b** could be released, under neutral reaction conditions, by treatment with acetyl chloride in CH_2Cl_2, to produce the corresponding carboxamides **17a** and **17b** in nearly quantitative yields. Importantly, the quinolinium salt **14** could be isolated in excellent yield and reused with success in a second experiment without erosion of the yield. This amide transfer may present a synthetic interest, as it results in the formation of an amide bond by means of an 'amide anion equivalent' under mild and neutral conditions (Scheme 7).



Scheme 7. Achiral quinolinium salt **14** as 'amide transferring-agent'. Reagents and conditions: (a) amines **15**/Na_2CO_3/H_2O/CH_2Cl_2/20 °C; (b) CH_2Cl_2/20 °C.

We finally evaluated the potential of these new 'amide transferring-agents' during the atropenantioselective amidification of aryl esters by means of the chiral quinolinium salt **8**. While a large amount of work deals with these atropoisomeric amides, only a few stereoselective methods have been investigated to have access to this class of atropisomers.[14] This new approach would supply a straightforward and elegant access to enantiomerically enriched atropisomeric benzamides. We first examined the diastereoselective addition of both amines **15a** and **15b**. Under the experimental conditions previously optimized, we were pleased to find out that adducts **18a** and **18b** were formed quantitatively as a single diastereoisomer in both cases. The relative configuration at C-4 was assigned with the aid of 2D-NOESY experiments, showing dipolar coupling between the methyl group of the lactam moiety and the methylene protons adjacent to the nitrogen of the amine (Scheme 8). This information clearly indicates that both amines **15a**,**b** react on the opposite face with respect to the

C=O lactam. The excellent diastereofacial selectivity observed is assumed to originate from a steric control exerted by the carbonyl lactam. This analysis is fully consistent with our previous explanation which accounts for the sense of the stereoselection observed during the reduction of these axially chiral NAD^+ models (Fig. 4). Finally, these results suggest that the chiral axis defined by the C3-C=O bond is the main configurational element governing the stereoselectivity of these additions, as already observed in the course of the reduction of these biomimetic models (Scheme 8).



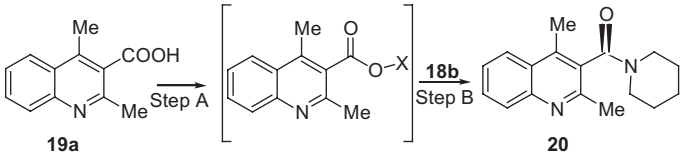
Scheme 8. Diastereoselective formation of 'chiral masked amides' **18a** and **18b**. Reagents and conditions: (a) $CH_2Cl_2/Na_2CO_3/20\,°C$.

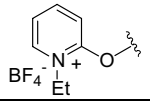
We next examined the reaction of the 'chiral masked amide' **18b** with various activated 2,4-dimethylquinoline-3-carboxylic esters, obtained from carboxylic acid **19a**.[17] The main results of this atropenantioselective amidification leading to the atropisomeric amide **20**[15] are summarized in Table 1. The racemic mixture of **20** was prepared in 80% yield from carboxylic acid **19a** under standard EDCI/HOBt/CH_2Cl_2 conditions. Both enantiomers of **20** could be separated by conventional chiral HPLC on chiracel OD. In a first experiment, substrate **19a** was converted into ester **19b** prior to reacting with the 'chiral masked amide' **18b** in CH_2Cl_2 at $-10\,°C$ (Table 1, entry 1). Under these conditions, no transfer of the piperidine occurred and only the starting materials were recovered. The same is true when the reaction is conducted at higher temperature (Table 1, entry 2). Assuming that the former ester is too poorly reactive, we envisaged to activate carboxylic acid **19a** using EDCI/HOBt coupling conditions. These new conditions provided the quinoline amide **20** in good yield, however, with insignificant enantioselectivity. (Table 1, entry 3). When the reaction is carried out at lower temperature, the yield is considerably affected, and this without observing any improvement of the enantioselectivity (Table 1, entry 4). Among the large variety of coupling reagents at our disposal, a 2-halopyridinium type coupling reagent was examined. Thus, 1-ethyl-2-fluoropyridinium salt (FEP)[18] was reacted with quinoline carboxylic acid **19a**, according to standard procedures, to furnish the presumed reactive (2-acyloxy)pyridinium salt. This resulting intermediate was then reacted with **18b** at various temperatures (Table 1, entries 5–7). A notable atropenantioselectivity was obtained at $-60\,°C$ (Table 1, entry 7). Although the degree of stereoselectivity remains moderate, this result constitutes the first atropenantioselective amidification of activated aryl esters providing a proof of concept of this approach.

3. Conclusion

In the course of this work, we have demonstrated that quinolinium salts, structurally related to NAD^+ models, may be used as 'amide-transferring agents'. Indeed, amines were found to add regioselectively at C4 of a biomimetic NAD^+ model **14** in quantitative yields. The resulting adducts **16a** and **16b** could react with acetyl chloride under neutral conditions to give the corresponding amides **17a** and **17b** and the recovered quinolinium salt **14** in excellent yields. We then turned our interest in the preparation of an axially chiral quinolinium salt **8** to investigate its potential as 'chiral amide-transferring agents'. This new chiral synthetic tool was assessed in an 'atropenantioselective amidification' of aryl esters with moderate success (ee = 2–20%). Although these preliminary results are presently modest in term of enantioselectivity, the atropenantioselectivity observed is encouraging and laid down the basis of future developments.

Table 1. Atropenantioselective amidification of quinoline carboxylic acid **19a**



Entry	Step A	X	Step B (°C)	Yield (%)	Ee (%)
1	$SOCl_2$ then	**19b**:PNP	−10	0	/
2	*p*-Nitrophenol	**19b**:PNP	25	0	/
3	EDCl/HOBt	Bt	25	85	3
4	EDCl/HOBt	Bt	−60	20	2
5	FEP		25	80	5
6	FEP		−10	85	12
7	FEP		−60	60	20

4. Experimental

4.1. General methods

Infrared spectra were recorded on a Beckmann IR 4250 spectrometer. ^{1}H and ^{13}C spectra were recorded on a 200 and 300 MHz Bruker apparatus and calibrated with the residual undeuterated solvent. Spectra were recorded in deuteriochloroform ($CDCl_3$), in hexadeuteriodimethylsulfoxide (DMSO-d_6) or pentadeuteriomethanol (MeOD-d_4). The following compounds were prepared according to literature procedures: ethyl malonyl chloride,[16] 2,4-dimethylquinoline-3-carboxylic acid **19a**,[17] FEP.[18] All other reagents were commercially available and, unless otherwise stated, were used without purification. Flash chromatography was performed with silica gel 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F_{254}).

4.2. Synthesis of the chiral quinolinium salt 8: Friedländer approach

4.2.1. (*S*)-*N*-(1-Phenylethyl)-1-methylethylamine 1. A solution of (*S*)-α-methylbenzylamine in acetone (400 mL) was refluxed 12 h. After evaporation of the solvent under vacuum, the residue was dissolved in methanol (300 mL) and sodium tetrahydroborate (1.5 g, 39.7 mmol) was slowly added at 0 °C. The solution was stirred 2 h at 20 °C. After evaporation of the solvent in vacuo, water (30 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The desired amine **1** was purified by distillation under reduced pressure to afford **1** in a 90% yield. Bp (20 mm Hg): 104 °C. IR (cm^{-1}, KBr): 3315, 2962, 1451, 1169, 761, 701. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (6H, t, J = 6.5 Hz), 1.35 (3H, d, J = 6.6 Hz), 2.63 (1H, sept, J = 6.2 Hz), 3.90 (1H, q, J = 6.6 Hz), 7.23–7.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.9, 24.7, 45.3, 54.9, 126.6, 126.5, 128.2, 145.9.

4.2.2. Ethyl 1-[*N*-(1(*S*)-phenylethyl)-*N*-isopropyl]-aminocarbonylacetate 2. A solution of amine **1** (1.08 g, 6.64 mmol) and triethylamine (0.8 g, 7.37 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of ethyl malonyl chloride (1.11 g, 7.37 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred 12 h at 20 °C followed by addition of water (10 mL). After phase separation, the organic layer was washed with a 10% aqueous solution of Na_2CO_3, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; cyclohexane/EtOAc: 90:10) to afford **2** as a yellow oil in 79% yield. The product consisted of a mixture of two isomers owing to the presence of the amide function. IR (cm^{-1}, KBr): 3454, 3060, 2977, 2937, 2360, 1736, 1647. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (1.8H, d, J = 6.7 Hz), 1.12 (1.2H, d, J = 6.7 Hz), 1.29 (6H, m), 1.65 (1.8H, d, J = 6.9 Hz), 1.71 (1.2H, d, J = 6.9 Hz), 3.48 (2.6H, m), 3.83 (0.4H, m), 4.21 (2H, q, J = 7.1 Hz), 4.10 (0.6H, q, J = 6.9 Hz), 5.04 (0.4H, m), 7.25–7.35 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 17.7, 18.0, 19.6, 20.5, 21.4, 21.9, 43.3, 47.7, 48.8, 51.8, 55.2, 61.2, 126.4, 126.7, 126.9, 127.5, 127.9, 141.4, 165.3, 167.9. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.45; H, 8.24; N, 4.95.

4.2.3. (*S*)-2-[*N*-(1-Phenylethyl)-*N*-isopropyl]amino carbonylacetic acid 3. A solution of KOH (930 mg, 16.6 mmol) in ethanol was slowly added to a solution of **2** (919 mg, 3.32 mmol) in ethanol (10 mL) at 0 °C. The resulting solution was stirred for 5 h and ethanol was removed in vacuo. The residue was treated with water (10 mL) and 1 N aqueous HCl (15 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). Drying ($MgSO_4$) and evaporation of CH_2Cl_2 under vacuum afforded acid **3** in 96% yield. The product consisted of a mixture of two isomers owing to the presence of the amide function IR (cm^{-1}, KBr): 3446, 3061, 3028, 2971, 2934, 2876, 1737, 1640. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (2.25H, d, J = 6.7 Hz), 1.19 (0.75H, d, J = 6.9 Hz), 1.40 (3H, J = 6.8 Hz), 1.69 (2.25H, d, J = 6.8 Hz), 1.71 (0.75H, d, J = 6.7 Hz), 3.30 (0.75H, d, J = 19.3 Hz), 3.45 (0.5H, s), 3.61 (0.75H, d, J = 19.3 Hz), 3.65 (0.75H, m), 3.91 (0.25H, m), 5.00 (0.75H, q, J = 6.9 Hz), 5.24 (0.25H, m), 7.30–7.40 (5H, m). HRMS (IE): calcd for $C_{14}H_{19}NO_3$ 249.1365; found: 249.1370.

4.2.4. (1*S*)-1,4-Dihydro-2-isopropyl-1-methyl-2-benzazepin-3,5-dione 4. Oxalyl chloride (1.8 mL, 11.9 mmol) was slowly added to a solution of acid **3** (2.69 g, 10.8 mmol) and DMF (100 μL) in CH_2Cl_2 (10 mL). After 1 h stirring at 20 °C, the organic solvent and oxalyl chloride in excess were removed in vacuo. The reddish liquid residue was dissolved in CH_2Cl_2 (15 mL) and aluminium chloride (3.33 g, 27.4 mmol) was added by small portions at 0 °C. The reaction mixture was stirred 1 h at room temperature and water (20 mL) was slowly added at 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were collected, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; cyclohexane/EtOAc: 50:50) to afford **4** as a white solid in 38% yield. Mp: 148 °C (cyclohexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.9 Hz), 1.80 (3H, J = 7.5 Hz), 3.78 (1H, d, J = 15.5 Hz), 4.48 (1H, d, J = 15.5 Hz), 4.67 (1H, q, J = 7.5 Hz), 5.00 (1H, m), 7.25 (1H, d, J = 7.54 Hz), 7.36 (1H, t, J = 7.54 Hz), 7.51 (1H, t, J = 7.5 Hz), 8.03 (1H, d, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.6, 24.3, 46.7, 53.2, 54.6, 128.6, 129.1, 130.8, 134.1, 144.9, 165.8, 191.3. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.75; H, 7.52; N, 5.97.

4.2.5. *N*-(2-Nitrobenzylidene)-*p*-toluidine 5. A solution of 2-nitrobenzaldehyde (10.0 g, 66 mmol) and *p*-toluidine (7.10 g, 66 mmol) in ethanol (250 mL) was refluxed for 2 h. After cooling to 0 °C, the orange precipitate was filtered and washed with cooled ethanol. After drying, the desired compound **5** was obtained as an orange solid in 42% yield. Mp: 70–71 °C (ethanol). IR (cm^{-1}, KBr): 3077, 3012, 2920, 1890, 1605.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.24 (d, 4H, J = 7.5 Hz), 7.61 (t, 1H, J = 7.5 Hz), 7.74 (t, 1H, J = 7.5 Hz), 8.07 (d, 1H, J = 7.9 Hz), 8.32 (d, 1H, J = 7.9 Hz), 8.96 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 121.6, 124.9, 130.0, 130.2, 131.3, 131.6, 133.8, 137.8, 148.8, 149.7, 155.2. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.95; H, 4.93; N, 11.86.

4.2.6. 2-(*p*-Tolylaminomethylidene)-aniline 6. Compound **5** (8.26 g, 22 mmol) was dissolved in ethanol (200 mL) the solution was heated to reflux and sodium sulfur monohydrate was added. The reflux was maintained 10 min after which the solution was cooled to 0 °C and the suspension was stirred for an additional 4 h at this temperature. During this time, a yellow precipitate was formed. This precipitate was filtered, washed with water and dried to give **6** in 80% yield. Mp: 101 °C. IR (cm^{-1}, KBr): 3447, 3257, 3018, 2890, 1624. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.4 (3H, s), 6.76 (2H, d, J = 7.5 Hz), 7.12–7.37 (6H, m), 8.56 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 116.1, 116.6, 118.1, 121.1, 130.1, 132.0, 134.6, 135.7, 149.1, 149.7, 162.8. Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.92; H, 6.86; N, 13.04.

4.2.7. (*S*)-1*H*-2-Isopropyl-1-methyl-2-benzazepino-[5,4-*b*]-quinolein-3-one 7. A solution of 2-(*p*-tolylaminoethylidene)-aniline **6** (1.5 g, 7.1 mmol), a few drops of triethylamine and 2-benzazepin-3,5-dione **4** (1.36 g, 7.1 mmol) in ethanol (200 mL) was refluxed 24 h, after which the solution was cooled and concentrated in vacuo. The residue was chromatographed on silica gel (cyclohexane/EtOAc: 90:10) to afford quinoline **7** as a yellow oil in 80% yield. $[\alpha]_D^{25}$ = +40 (c 0.13, CH_2Cl_2). IR (cm^{-1}, KBr): 1615, 1493, 1235, 1201. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, d, J = 7.15 Hz), 1.20 (3H, d, J = 7.16 Hz), 1.31 (3H, d, J = 6.8 Hz), 4.55 (1H, q, J = 7.2 Hz), 5.20 (1H, sept, J = 6.8 Hz), 7.20 (1H, d, J = 7.2 Hz), 7.35 (1H, t, J = 7.2 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.55 (1H, t, J = 7.9 Hz), 7.75 (1H, t, J = 7.2 Hz), 7.92 (1H, d, J = 8.3 Hz), 8.10 (1H, d, J = 8.6 Hz), 8.25 (1H, d, J = 7.2 Hz), 8.84 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.2, 21.8, 47.3, 53.0, 127.1, 127.4, 127.5, 128.9, 129.0, 129.8, 130.1, 130.7, 131.6, 131.8, 137.6, 140.7, 143.5, 148.9, 153.6, 166.5; HRMS (IE): calcd for $C_{21}H_{20}N_2O$: 316.1575; found: 316.1582.

4.2.8. (1*S*)-1*H*-2-Isopropyl-1,9-dimethyl-3-oxo-2-benzazepino[5,4-*b*]quinolinium triflate 8. Methyl trifluoromethanesulfonate (0.38 mL, 3.3 mmol) and anhydrous Na_2CO_3 were added to a solution of quinoline **7** (870 mg, 2.8 mmol) in CH_2Cl_2 (15 mL) under nitrogen atmosphere. After being stirred at 20 °C for 2 h, the solution was filtrated to remove Na_2CO_3. The filtrate was concentrated in vacuo to afford the desired quinolinium **8** as a white solid in 100% yield. Mp: 136 °C (CH_2Cl_2/Et_2O). $[\alpha]_D^{25}$ = −32 (c 0.45, CH_2Cl_2). IR (cm^{-1}, KBr): 3505, 3069, 2983, 2937, 1630, 1588. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 6.8 Hz), 1.26 (3H, d, J = 7.5 Hz), 1.27 (3H, d, J = 6.8 Hz), 4.69 (3H, s), 4.73 (1H, q, J = 7.5 Hz), 5.06 (1H, sept, J = 6.8 Hz), 7.48 (1H, d, J = 7.5 Hz), 7.63 (2H, m), 7.76 (1H, d, J = 6.4 Hz), 7.96 (1H, t, J = 7.5 Hz), 8.23 (1H, d, J = 8.3 Hz), 8.30 (1H, t, J = 7.5 Hz), 8.31(1H, d, J = 9.0 Hz), 9.36 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.6, 21.4, 45.8, 48.8, 52.6, 120.6, 127.4, 128.3, 129.3, 129.4, 131.1, 131.5, 132.7, 134.2, 134.4, 138.8, 141.6, 145.4, 149.1, 156.1, 162.5. HRMS (FAB+): calcd for $C_{22}H_{23}N_2O$: 331.1810; found: 331.1829.

4.3. Preparation of the chiral quinoline 7: intramolecular coupling approach

4.3.1. 2-Chloroquinoline-3-carboxylic acid 9. To a solution of diisopropylamine (5.3 mL, 38 mmol) in dry THF (75 mL) cooled at −78 °C was added, under nitrogen, a solution of *n*-butyllithium in hexane (16.5 mL, 2.5 M, 41 mmol). After being stirred 20 min at −78 °C, a solution of 2-chloroquinoline (5 g, 30 mmol) in dry THF (30 mL) was slowly added. The reaction mixture was stirred for an additional 20 min and then poured into a large excess of dry ice. The solution was concentrated under vacuum before addition of water (25 mL). The aqueous solution was washed with Et_2O (3 × 10 mL) and acidified (pH = 4–5) with 1 N aqueous HCl. The precipitate formed was collected by filtration, washed with water (10 mL) and dried. The crude product was purified by recrystallization in ethanol to provide **9** as a white solid in 65% yield. Mp: 220 °C. IR (cm^{-1}, KBr): 3418, 3072, 2897, 2534, 2352, 1731. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.55 (1H, t, J = 7.5 Hz), 7.75 (1H, t, J = 7.5 Hz), 7.83 (1H, d, J = 8.3 Hz), 8.01 (1H, d, J = 8.3 Hz,), 8.75 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.1, 128.0, 128.2, 128.4, 129.3, 132.9, 138.1, 140.4, 148.2, 166.6. HRMS (FAB+): calcd for $C_{10}H_6ClNO_2$: 207.0087; found: 207.0082.

4.3.2. (*S*)-*N*-[1-(2-Iodophenyl)-ethyl]isopropylamine 10. To a solution of TMEDA (3.61 mL, 43 mmol) in dry THF (75 mL) was added at −78 °C *n*-butyllithium in hexane (17 mL, 2,5 M, 43 mmol). The solution was stirred for 20 min before adding (*S*)-*N*-isopropyl-α-methylbenzylamine **1** (3.6 g, 22 mmol). The reaction mixture was stirred at 20 °C for a further 2 h and then cooled to −78 °C prior to adding stepwise a solution of iodine (11 g, 43 mmol) in THF (75 mL). The reaction mixture was stirred at 20 °C for 12 h. The reaction was treated with a solution of sodium disulfite (10 g) in water (50 mL). After evaporation of the organic solvent under vacuum, the aqueous solution was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and CH_2Cl_2 evaporated in vacuo. Yield: 50% of **10** as a colourless oil after flash chromatography (SiO_2; cyclohexane/ethyl acetate: 65:35) $[\alpha]_D^{25}$ = −36.5 (c 0.0043, CH_2Cl_2). IR (cm^{-1}, KBr): 3325, 3057, 2962, 2925, 2865. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 6.4 Hz), 0.97 (3H, d, J = 6.0 Hz), 1.20 (3H, d, J = 6.8 Hz), 2.50 (1H, sept, J = 6.4 Hz), 4.10 (1H, q, J = 6.8 Hz), 6.85 (1H, t, J = 7.0 Hz), 7.28 (1H, d, J = 7.0 Hz), 7.32 (1H, t, J = 7.9 Hz), 7.73 (1H, d, J = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.9, 24.2, 46.4, 59.2, 100.0,

127.4, 129.0, 139.9, 147.2. HRMS (IE): calcd for $C_{11}H_{16}IN$ 289.0327; found: 289.0320.

4.3.3. (±)-*N*-[1-(2-Iodophenyl)-ethyl]-*N*-isopropyl acetamide 11. To a solution of (±)-**10** (290 mg, 1 mmol) and NEt_3 (210 μL, 2 mmol) in CH_2Cl_2 (15 mL) was added dropwise acetyl chloride (143 μL, 2 mmol). The solution was stirred at 20 °C for 2 h and then washed with water (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), evaporated and subjected to flash chromatography (SiO_2; cyclohexane/ethyl acetate: 80:20) to give **11** in 50% yield. The product consisted of a mixture of two isomers owing to the presence of the amide function. ^{1}H NMR (300 MHz, MeOD-d_4) δ 0.77 (3H, d, J = 6.5 Hz), 1.25 (3H, d, J = 6.5 Hz), 1.52 (3H, d, J = 6.5 Hz), 2.11 (0.5H, s), 2.32 (1.5H, s), 3.06 (0.7H, m), 3.71 (0.3H, br s), 4.84 (0.65H, q, J = 7.0 Hz), 5.07 (0.35H, br s), 6.90 (0.3H, m), 6.99 (0.66H, t, J = 7.0 Hz), 7.28–7.49 (2H, m), 7.78 (0.34H, d, J = 6.5 Hz), 7.85 (0.66H, d, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 19.9, 21.6, 24.9, 48.1, 61.1, 96.3, 128.7, 129.5, 130.0, 138.4, 140.8, 171.4. Anal Calcd for $C_{13}H_{18}INO$: C, 47.14; H, 5.48; N, 4.23. Found: C, 47.07; H, 5.38; N, 4.13. Both enantiomers of **11** were separated by HPLC (chiracel OJ, 1 mL/min, heptane/isopropanol: 90:10); retention time = 6.03 and 7.36 min.

4.3.4. *N*-[(1*S*)-1-(2-Iodophenyl)ethyl]-*N*-isopropyl-2-chloroquinoline-3-carboxamide 12. To a solution of 2-chloroquinoline-3-carboxylic acid (716 mg, 3.46 mmol) and DMF (50 μL) in CH_2Cl_2 (10 mL) was added oxalyl chloride (606 μL, 6.92 mmol). The reaction mixture was stirred at room temperature for 2 h. The organic solvent and oxalyl chloride in excess were evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and a solution of amine **10** (1 g, 3.5 mmol) and triethylamine (0.484 mL) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at 20 °C overnight. The solution was washed with water (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 85:15) to afford **12** in 60% yield. Mp: 94 °C (cyclohexane). $[\alpha]_D^{25}$ = +7.6 (c 0.25, CH_2Cl_2). IR (cm^{-1}, KBr): 3059, 2977, 2926, 2849, 1633. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 6.78 Hz), 1.04 (3H, d, J = 6.8 Hz), 1.88 (3H,d, J = 7.2 Hz), 3.67 (1H, sept, J = 6.8 Hz), 4.95 (1H, q, J = 7.2 Hz), 6.91 (1H, m), 7.34 (1H, s), 7.55 (1H, m), 7.72 (1H, m), 7.77–7.81 (2H, m), 7.98–8.01 (2H, m), 8.06 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 21.2, 21.5, 52.5, 59.2, 99.3, 128.9, 128.1, 128.2, 128.9, 129.0, 129.3, 129.6, 131.6, 132.6, 135.1, 139.9, 145.5, 147.0, 147.7, 167.7. Anal Calcd for $C_{21}H_{20}ClIN_2O$: C, 52.68; H, 4.21; N, 5.85. Found: C, 52.43; H, 4.52; N, 5.62.

4.3.5. (*S*)-1*H*-2-Isopropyl-1-methyl-2-benzazepino [5,4-*b*]-quinolein-3-one 7. A 250-mL, round-bottomed, three-necked flask was charged with $NiBr_2(PPh_3)_2$ (3.12 g, 4.2 mmol), $Et_4N^+I^-$ (1.86 g, 4.2 mmol) and zinc powder (2.75 g, 42 mmol) activated by acetic acid prior to use. After the material was evacuated and filled several times with nitrogen, dry THF (50 mL) was added and the solution became immediately reddish brown. A solution of quinoline **12** (2.1 g, 4.2 mmol) in dry THF (50 mL) was added dropwise. The resulting solution was stirred at 50 °C for 2 h under nitrogen atmosphere and then poured into 2 M aqueous ammoniac (50 mL). The aqueous solution was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 90:10) to afford **7** as a yellow oil in 64% yield. $[\alpha]_D^{25}$ = +40 (c 0.013, CH_2Cl_2). IR (cm^{-1}, KBr): 1615, 1493, 1235, 1201. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, d, J = 7.2 Hz), 1.20 (3H, d, J = 7.2 Hz), 1.31 (3H, d, J = 6.8 Hz), 4.55 (1H, q, J = 7.2 Hz), 5.20 (1H, sept, J = 6.8 Hz), 7.20 (1H, d, J = 7.2 Hz), 7.35 (1H, t, J = 7.2 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.55 (1H, t, J = 7.9 Hz), 7.75 (1H, t, J = 7.15 Hz), 7.92 (1H, d, J = 8.3 Hz), 8.10 (1H, d, J = 8.7 Hz), 8.25 (1H, d, J = 7.15 Hz), 8.84 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.2, 21.8, 47.3, 53.0, 127.1, 127.4, 127.5, 128.9, 129.0, 129.8, 130.1, 130.7, 131.6, 131.8, 137.6, 140.7, 143.5, 148.9, 153.6, 166.5. HRMS (IE): calcd for $C_{21}H_{20}N_2O$: 316.1575; found: 316.1582.

4.3.6. Ethyl 2-phenylquinoline-3-carboxylate 13. A solution of 2-(*p*-tolylaminoethylidene)-aniline **6** (1.5 g, 7.1 mmol), ethyl benzoyl acetate (1.36 g, 7.1 mmol) and a few drops of triethylamine in ethanol (200 mL) was refluxed 24 h. After cooling to room temperature, EtOH was evaporated under vacuum and the resulting residue was chromatographed on silica gel (cyclohexane/EtOAc: 90:10) affording **13** as a yellow oil in 72% yield. IR (cm^{-1}, KBr): 3423, 3059, 2981, 2936, 2902, 1721, 1619, 1594, 1555. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, J = 7.15 Hz), 4.10 (2H, q, J = 7.15 Hz), 7.4–7.3 (3H, m), 7.41 (1H, t, J = 7.9 Hz), 7.53 (2H, m), 7.65 (1H, t, J = 7.15 Hz), 7.75 (1H, d, J = 8.3 Hz), 8.06 (1H, d, J = 8.3 Hz), 8.50 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 61.9, 125.9, 126.2, 127.6, 128.5, 128.6, 128.9, 129.0, 129.9, 131.9, 139.4, 141.2, 148.7, 158.5, 168.4. Anal Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.13; H, 5.44; N, 5.23.

4.3.7. Ethyl 2-phenylquinolinium-3-carboxylate triflate 14. To a solution of quinoline **13** (332 mg, 1.2 mmol) in dry CH_2Cl_2 was added methyl triflate (164 mg, 1.7 mmol). The resulting solution was stirred at room temperature for 2 h. Addition of Et_2O (10 mL) furnished a white precipitate which was filtered to give the desired quinolinium salt **14** in a quantitative yield. IR (cm^{-1}, KBr): 3065, 2991, 2364, 1720, 1624, 1591. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, J = 7.15 Hz), 4.10 (2H, q, J = 7.15 Hz), 4.42 (3H, s), 7.63 (5H, m), 8.04 (1H, t, J = 7.5 Hz), 8.28 (2H, t, J = 7.5 Hz), 8.35 (1H, d, J = 2.3 Hz), 8.55 (1H, d, J = 9.05 Hz), 9.41 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 43.5, 63.3, 120.6, 128.1, 128.5, 128.7, 129.6, 131.4, 131.7, 131.8, 132.2, 138.8, 141.0, 148.4, 159.4, 136.4. Anal Calcd for $C_{20}H_{18}F_3NO_5S$: C, 54.42; H, 4.11; N, 3.17. Found: C, 54.22; H, 4.25; N, 3.12.

4.4. Preparation of the 'masked amides' 16a,b and 18a,b

4.4.1. General procedure

4.4.1.1. Ethyl 1-methyl-2-phenyl-4-benzylamino-1,4-dihydroquinoline-3-carboxylate 16a. To a solution of quinolinium salt **14** (44 mg, 0.104 mmol) and Na_2CO_3 (11.0 mg, 0.104 mmol) in CH_2Cl_2 (5 mL) was added benzylamine (12 μL, 0.114 mmol) at room temperature. The resulting biphasic solution was then stirred for 1.5 h at 20 °C after which 5 mL of water was added. The biphasic solution was stirred for an additional 15 min. The organic layer was collected, dried ($MgSO_4$) and concentrated in vacuo at room temperature. The adduct product **16a** was obtained in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, t, J = 7.0 Hz), 3.37 (2H, q, J = 7.0 Hz), 3.75 (5H, br s), 4.75 (1H, s), 7.12–7.30 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 15.5, 46.5, 66.0, 123.0, 127.5, 127.7, 128.5, 128.7, 128.9, 129.3, 131.0, 134.0, 142.5, 157.0, 169.5.

4.4.1.2. Ethyl 1-methyl-2-phenyl-4-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylate 16b. According to the general procedure from **14** (44 mg, 0.104 mmol) and piperidine (10 μL, 0.117 mmol) affording **16b** in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, d, J = 7.0 Hz), 1.25 (2H, br s), 1.40 (2H, br s), 2.20 (2H, br s), 2.41 (2H, br s), 2.99 (3H, s), 3.75 (2H, q, J = 7 Hz), 4.90 (1H, s), 6.95–7.40 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 25.0, 26.7, 36.8, 49.0, 59.5, 60.3, 98.0, 113.7, 123.4, 123.5, 127.7, 128.5, 128.9, 130.5, 130.8, 137.7, 141.7, 154.4, 168.5.

4.4.1.3. (1*S*,4*R*)-4-Benzylamino-4,9-dihydro-1,9-dimethylbenzazepino[5,4-*b*]quinolin-3-one 18a. According to the general procedure from **8** (50 mg, 0.104 mmol) and benzylamine (12 μL, 0.114 mmol) affording **18a** in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 7.0 Hz), 1.24 (3H, d, J = 7.0 Hz), 1.55 (1H, s), 1.76 (3H, d, J = 7.15 Hz), 3.17 (3H, s), 3.69 (2H, s), 4.56 (1H, q, J = 7.15 Hz), 5.13 (1H, m), 5.35 (1H, s), 7.0–7.3 (13H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 20.8, 21.1, 39.2, 46.4, 51.0, 53.1, 55.4, 90.4, 114.4, 115.6, 122.3, 126.7, 127.1, 127.4, 127.8, 127.9, 128.4, 128.6, 128.9, 129.7, 130.7, 131.8, 141.4, 142.6, 142.9, 143.0, 168.0.

4.4.1.4. (1*S*,4*R*)-4,9-Dihydro-1,9-dimethyl-4-(piperidin-1-yl)benzazepino[5,4-*b*]quinolin-3-one 18b. According to the general procedure from **8** (50 mg, 0.104 mmol) and piperidine (10 μL, 0.107 mmol) affording **18b** in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.8 Hz), 1.22 (3H, d, J = 6.8 Hz), 1.35 (6H, s large), 1.71 (3H, d, J = 7.15 Hz), 2.15 (2H, br s), 2.38 (2H, br s), 3.12 (3H, s), 4.53 (1H, q, J = 7.15 Hz), 5.11 (1H, m), 5.37 (1H, s), 7.0–7.3 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 20.8, 21.1, 24.9, 26.8, 39.2, 46.5, 50.3, 52.8, 61.9, 90.4, 113.9, 115.4, 121.7, 122.5, 127.4, 127.9, 129.6, 130.3, 130.7, 131.8, 143.1, 143.5, 144.7, 167.9.

4.5. Atropenantioselective amidification of 2,4-dimethylquinoline-3-carboxylic acid 19a

4.5.1. 4-Nitrophenyl 2,4-dimethylquinoline-3-carboxylate 19b. To a solution of 2,4-dimethylquinoline-3-carboxylic acid **19a** (0.201 g, 1 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.18 mL, 1.19 mmol) and DMF (25 μL). The resulting solution was stirred at 20 °C for 1 h. The solvent was evaporated under vacuum and the residue dissolved in CH_2Cl_2 (10 mL). A solution a 4-nitrophenol in CH_2Cl_2 (10 mL) was added at 0 °C and the solution was allowed to stir for an additional 12 h at 20 °C. After adding water (20 mL) and separation phase, the aqueous layer was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under vacuum to afford ester **19b** in 84%, as a yellow oil, after flash chromatography (SiO_2; cyclohexane/ethyl acetate: 90:10) IR (cm^{-1}, KBr): 3111, 3071, 2930, 1926, 1730, 1615, 1581, 1568, 1524. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (3H, s), 2.79 (3H, s), 7.43 (2H, d, J = 8.5 Hz), 7.54 (1H, t, J = 7.7 Hz), 7.72 (1H, t, J = 7.7 Hz), 7.99 (2H, d, J = 8.3 Hz), 8.31 (1H, d, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 24.6, 122.7, 124.5, 125.9, 126.4, 127.2, 129.8, 131.2, 143.1, 146.1, 149.9, 154.3, 155.4, 158.9, 167.0. Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.50; N, 8.71.

4.5.2. *rac*-3-(Piperidinylcarbonyl)-2,4-dimethylquinoline 20. A solution of 2,4-dimethylquinoline-3-carboxylic acid **19a** (0.201 g, 1.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (0.191 g, 1.0 mmol), 1-hydroxy-1*H*-benzotriazol (0.135 g, 1.0 mmol) and diisopropylethylamine (0.174 mL, 1.0 mmol) in dichloromethane (10 mL) was stirred for 15 min. Piperidine (0.99 mL, 1.0 mmol) was added and the resulting solution was stirred for a further 2 h at 20 °C. The solvent was evaporated under vacuum and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 80:20). Yield = 80%. IR (cm^{-1}, KBr): 3436, 3066, 2925, 2854, 1628, 1588, 1566. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.44 (2H, m), 1.61–1.65 (6H, m), 2.55 (3H, s), 2.60 (3H, s), 3.65–3.85 (2H, m), 7.48 (1H, t, J = 7.15 Hz), 7.63 (1H, t, J = 8.3 Hz), 7.90 (1H, d, J = 7.5 Hz), 7.94 (1H, d, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 22.4, 23.4, 24.7, 25.5, 41.2, 46.3, 122.7, 125.0, 125.2, 128.2, 128.6, 129.0, 138.8, 145.9, 153.4, 166.9. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.95; H, 7.44; N, 10.28. Both enantiomers of **20** were separated by HPLC (chiracel OD, 1 mL/min, heptane/isopropanol: 90:10); retention time = 7.43 and 9.06 min.

4.5.3. 3-(Piperidinylcarbonyl)-2,4-dimethylquinoline 20 (EDCI/HOBt activation). A solution of 2,4-dimethylquinoline-3-carboxylic acid **19a** (100 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (95 mg, 0.5 mmol), 1-hydroxy-1*H*-benzotriazol (70 mg, 0.5 mmol) and diisopropylethylamine (87 μL, 0.5 mmol) in dichloromethane (3 mL) was stirred for 15 min. A solution of **18b** (207.8 mg, 0.5 mmol) in CH_2Cl_2 was then added at 20 °C and the resulting solution was

stirred for 12 h. After evaporation of the solvent, the residue was purified by flash chromatography (SiO_2; cyclohexane/ethyl acetate: 80/20) affording 20 in 80% yield. The enantiomeric excess was determined by chiral HPLC in the same conditions than those reported in Section 4.5.2.

4.5.4. 3-(Piperidinylcarbonyl)-2,4-dimethylquinoline 20 (FEP activation). To a solution of **18b** (41.5 mg, 0,1 mmol) in CH_2Cl_2 (1 mL) was slowly added a solution of 2,4-dimethylquinoline-3-carboxylic acid **19a** (20.0 mg, 0.1 mmol), *N*-ethylpyridinium trifluoroborate (21 mg, 0.1 mmol) and diisopropylethylamine (18 μL, 0.1 mmol) in dichloromethane (3 mL). The mixture was stirred overnight at −60 °C and then slowly warmed to room temperature. The solvent was removed in vacuo and the resulting residue was chromatographed on preparative TLC plate (SiO_2; cyclohexane/ethyl acetate: 65:35). The enantiomeric excess was determined by HPLC as reported in Section 4.5.2.

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