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Non-Biaryl Atropisomers in Organocatalysis

Sebastian Brandes, Barbara Niess, Marco Bella, Auxiliadora Prieto, Jacob Overgaard, and Karl Anker Jørgensen*[a]

Abstract: A new class of 6′-hydroxy cinchona alkaloids, with a non-biaryl atropisomeric functionalisation at position 5′ of the quinoline core can be prepared by an easy amination procedure. These are the first derivatives for which the principle of atropisomerism is engrafted in the classical core of the cinchona alkaloids. The aminated cinchona alkaloids are effective organocatalysts for the Michael addition of β-keto esters to acrolein and methyl vinyl ketone, in up to 93% *ee* (*ee* = enantiomeric excess), as well as for the asymmetric Friedel–Crafts amination of a variety of 2-naphthols, permitting the preparation of the latter in up to 98% *ee*. The aminated 8-amino-2-naphthol itself is the first chiral organocatalyst based on non-biaryl atropisomerism. The two enantiomers of this chiral primary amine can be used for the direct α-fluorination of α-branched aldehydes. The fluorinated compounds can thereby be accessed in up to 90% *ee*.

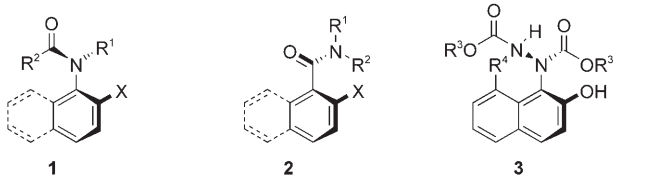
Keywords: amination · asymmetric catalysis · atropisomerism · fluorination · Michael addition

Introduction

Atropisomers are widely used in the field of asymmetric catalysis, as ligands, additives and also as catalysts themselves. The most famous structure by far being the 1,1′-binaphthyl core present in BINAP[1] and BINOL ligands,[2] which are nowadays not only used as ligands, but derivatives thereof finding applications in various fields of chemistry.[3]

The large majority of atropisomeric structures used in asymmetric catalysis belongs to the class of biaryl atropisomers bearing a chiral axis between the two aromatic moieties. Nonetheless, this is only a sub-class of atropisomers and in recent years several groups have focussed on another sub-class of atropisomers, the non-biaryl atropisomeric anilides **1** and aromatic amides **2**.[4–8]

What started out as a textbook curiosity[9] has been developed to be a prosperous field of organic chemistry with applications in enantioselective synthesis,[10] asymmetric catalysis,[11] medicinal chemistry[12] and a model system for allosteric interactions.[13]



While a variety of synthetic approaches are now available for the biaryl atropisomers,[14] ways to access enantiopure non-biaryl atropisomers are still limited. The enantioselective synthesis of non-biaryl atropisomers is often tedious; besides classical separation by chiral stationary phase chromatography,[15] kinetic[6a,16] and thermodynamic[17] resolutions, chiral pool approaches,[7,18] chiral auxiliary approaches[19] and enantioselective synthesis by desymmetrisation[8] have been reported. The enantiopurity achieved by these procedures varies from moderate to excellent; however, the downfall mostly lies in the length of the sequences. Recently, an elegant approach reported by Taguchi et al. provided, by means of catalytic asymmetric N-arylation, an easy and short access to atropisomeric anilides **1** (phenyl series; X = *t*Bu; R^1 = alkyl, alkenyl; R^2 = 4-$NO_2C_6H_4$).[20] In our own laboratories, we developed the first organocatalytic approach to non-biaryl atropisomeric structures of type **3**.[21]

[a] Dr. S. Brandes, Dr. B. Niess, Dr. M. Bella, Dr. A. Prieto, Dr. J. Overgaard, Prof. Dr. K. A. Jørgensen
The Danish National Research Foundation
Center for Catalysis, Department of Chemistry
Aarhus University, 8000 Aarhus C (Denmark)
Fax: (+45) 8619-6199
E-mail: kaj@chem.au.dk

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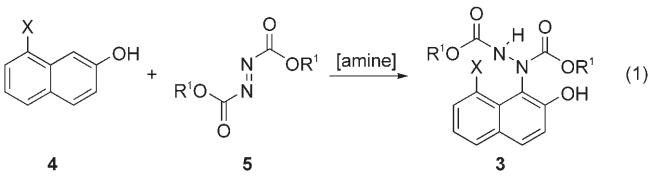
The latter structures were discovered during our investigation of an easy amination procedure for 2-naphthols **4**, utilising azodicarboxylates **5** as the nitrogen source [Eq. (1)]. It was found that a tertiary amine, such as DBU or Et_3N, can catalyse this Friedel–Crafts amination.

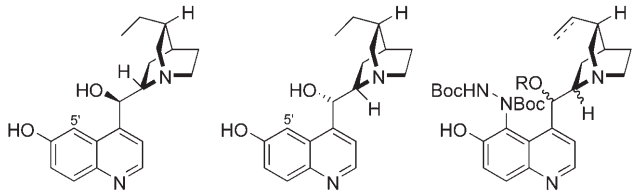


4 5 3 (1)

The initial results were intriguing, as the product (**3a**, $R^1 = Et$) of the reaction of 2-naphthol (**4a**, X = H) with diethyl azodicarboxylate (**5a**, $R^1 = Et$) showed diastereotopic behaviour with regard to the methylene groups of the carbamate moiety. An analysis of the product by chiral HPLC revealed that the product **3a** existed in two enantiomeric forms. This can only be attributed to a hindered rotation around the $N-C_{Aryl}$ bond, thereby creating atropisomers. Although aminated naphthalenes have been known for nearly a century, only now have they been recognised as chiral compounds.[22]

As the amination product of 2-naphthol **3a** racemised readily, 8-amino-2-naphthol (**4b**, $X = NH_2$) was chosen as a model system instead. Reaction with di-*tert*-butyl azodicarboxylate (**5b**, D*t*BuAD, $R^1 = t$Bu), indeed generated more stable atropisomers.

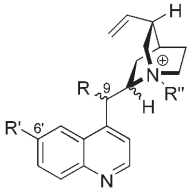
By screening a large variety of amines, and especially cinchona alkaloids as catalysts, the cinchona-derived quasi-enantiomers hydrocupreine (**6**) and hydrocupreidine (**7**) were found to give good enantioselection in the amination reaction.[21,23]



The use of cinchona alkaloids in the field of organocatalysis[24] has, in the last few years, led to an increasing number of derivatives, tailored to fit the need of the application. Their core has been identified as a "privileged structure",[25] catalysing a plethora of reactions.[26]

During the screening of the Friedel–Crafts amination, the structural similarity between the quinoline-6′-ol core and the naphthol motif became obvious to us, leading to the assumption that the cinchona alkaloid catalysts themselves might be transformed during the reaction. Under the given reaction conditions of the amination, only trace amounts of an aminated cinchona alkaloid catalyst were detected, but upon exposure of these cinchona alkaloids to a stoichiometric amount of D*t*BuAD (**5b**), the amination of position 5′ could be achieved quantitatively. Functionalisation of position 5′ of the cinchona alkaloids is found rarely, and so far only nitration,[27] diazotation[28] and bromination[29] of this position have been described.

Until now, the four major sites of derivatisation of the cinchona alkaloids have been: the 9-hydroxy function (R),[30] the 6′-hydroxy functionality (R′),[31] the quinuclidine nitrogen atom (R″)[32] and the vinyl side chain.[33]



R=OAlk, OAr, OSiR$_3$, NH$_2$, NHCSNHAlk
R'=OAlk, OCOR, NHCSNHAlk,
R''=Bn, Anthr, F, Cl

In the following, we will present a versatile method to functionalise position 5′ of the quinoline core and to concomitantly incorporate the principle of atropisomerism into the cinchona alkaloids. A series of these newly functionalised catalysts has been prepared and examined. Their performance in the addition of β-keto esters to α,β-unsaturated carbonyl compounds (Wynberg reaction)[34] and their performance in the Friedel–Crafts amination of naphthols will be outlined.

Moreover, the product of the amination reaction of 8-amino-2-naphthol **3b** ($X = NH_2$, $R^1 = t$Bu) displayed an interesting structure: the alignment of a primary amine and a phenol in close proximity to the chiral axis and the easy availability of both enantiomeric forms of this non-biaryl atropisomer inspired us to seek an application in organocatalysis.

It has been shown that primary amino acids catalyse aldol reactions with high enantioselectivity, especially with sterically encumbered substrates.[35] Moreover, calculations of aldol reactions catalysed by primary amines underscored the viability of enantioselection in this reaction.[36] In contrast to the widely used secondary amines in organocatalysis, a primary amine could offer the advantage of a less encumbered imine/enamine intermediate, which is, for example, of interest in the derivatisation of α-branched aldehydes.

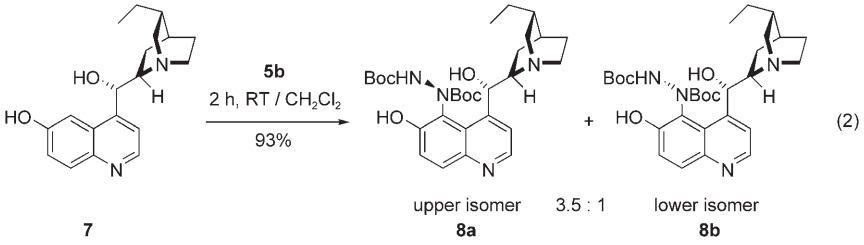
With the existing knowledge in our group about α-functionalisations of carbonyl compounds,[37] the fluorination of α-branched aldehydes appeared as a promising target to prove our idea. Although, the organocatalytic α-fluorination of carbonyl compounds has been investigated thoroughly in the last few years,[38] the fluorination of α-branched aldehydes still leaves room for improvement. We therefore investigated the possible use of the atropisomeric aminated 8-amino-2-naphthol **3b** as an organocatalyst in the fluorination of α-branched aldehydes.

In the following we will present our investigation of the aminination of cinchona alkaloids and present the properties of these aminated cinchona alkaloids, including the analysis of their X-ray structures, which help to explain their catalytic and physical properties. Furthermore, the catalytic properties of the atropisomeric aminated 8-amino-2-naphthol will be described.

Results and Discussion

Aminated 6′-hydroxy cinchona alkaloids: 6′-Hydroxy cinchona alkaloids were aminated by a simple protocol; the catalyst was stirred at RT in CH_2Cl_2 and 1.2 equivalents of D*t*BuAD (**5b**) were added. The reaction was monitored by TLC and during the reaction of hydrocupreidine (**7**) with **5b** two products **8a** and **b** were observed by TLC [Eq. (2)]. These products were easily separated by column chromatography and proved to be diastereomers, which were obtained in a ratio of **8a**/**8b** 3.5:1.

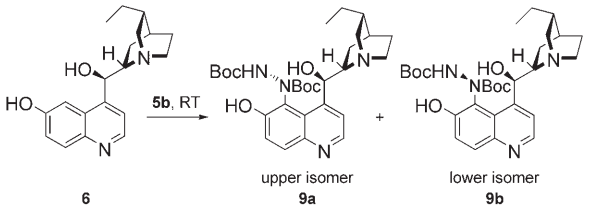
The two diastereomers showed an amazing difference in their polarity (see Experimental Section), and thus we named them upper (**8a**) and lower isomer (**8b**), according to their respective TLC R_f values (**8a**: $R_f = 0.67$, **8b**: $R_f = 0.29$; EtOAc/MeOH/aq NH_3 90:10:1).



We then investigated the influence of the solvent upon the diastereomeric ratio in the reaction of hydrocupreine (**6**) with D*t*BuAD (**5b**) (Table 1).

It appears from Table 1 that performing the reaction in polar solvents gave good chemical yields (entries 1, 2, and 8), while apolar solvents (entries 4 and 5) gave only traces of product, even after 24 h. The *dr* (*dr* = diastereomeric ratio) of **9a**/**9b** varied between 1:17 and 1:2, showing significant dependence upon the reaction time (entries 8 and 9). Upon prolonged stirring the lower isomer **9b** apparently started to isomerise, leading to a diminished diastereomeric ratio. The best diastereomeric ratio in favour of the lower diastereomer **9b** was obtained when the reaction was conducted in MeCN. Unfortunately, after column chromatography the **9a**/**9b** *dr* dropped from 1:17 to 1:12 (entry 8). However, in the solid state these diastereomers were bench stable and no isomerisation occurred even after months at room temperature.

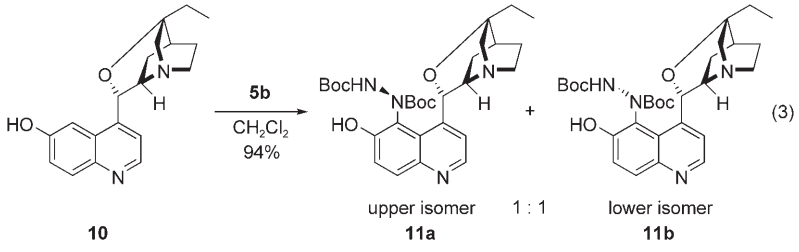
Table 1. Investigation of the parameters governing the reaction of hydrocupreine (**6**) with di-*tert*-butyl azodicarboxylate (**5b**).[a]

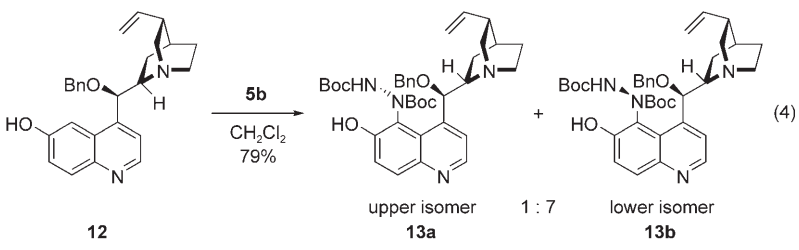


Entry	Solvent	*t* [h]	Yield [%][b]	*dr* **9a**/**9b**[c] (*dr* **9a**/**9b**)[d]
1	MeOH	2.5	87	1:12
2	CH_2Cl_2	2.0	80	(1:2.3)
3	THF	24.0	n.d.[e]	1:2
4	hexane	24.0	traces	n.d.
5	toluene	24.0	traces	n.d.
6	DMF	4.0	n.d.	1:12
7	DMSO	4.0	n.d.	1:4.8
8	MeCN	1.5	92	1:17 (1:12)
9	MeCN	24.0	n.d.	1:4

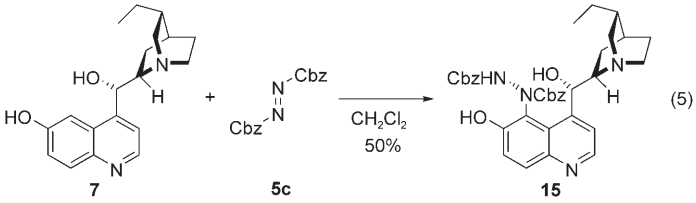
[a] Reactions were stopped after TLC control showed full consumption of the starting material. [b] Yields after flash chromatography. [c] *dr* was estimated by integration of the NMR spectra of the raw product. [d] *dr* after separation by column chromatography. [e] n.d. = not determined.

β-Isocupreidine[39] (**10**) and 9-benzyloxy-6′-hydroxyquinine[40] (**12**) were also submitted to the same reaction conditions, yielding the 5′-aminated products **11** and **13**, each as a set of diastereomers [Eq. (3) and (4)].





Other azodicarboxylates did not react as well as the *tert*-butyl derivative **5b**. From the reaction of dibenzyl azodicarboxylate (**5c**, $R^1 = Bn$) with hydrocupreidine **7**, only the lower diastereomer **15** could be isolated [Eq. (5)].



(5)

Fortunately, the upper diastereomers **8a**[41] and **9a**,[42] as well as the lower diastereomer **9b**[43] crystallised nicely, making single crystal X-ray analysis possible (Figure 1). These structures helped to elucidate the origin of the different physical properties of the cinchona alkaloid diastereomers, and as will be shown later, also their different chemical properties. In the structures of **8a** and **9a** the distance between the quinuclidine nitrogen atom and the hydrogen atom bound to the hydrazine implies a hydrogen bonding (2.84 and 2.85 Å, respectively between the nitrogen atoms), leading to an obstruction of the basic site of these alkaloids. This could be an explanation for the low polarity of the upper isomers in solution. In contrast to this, the structure of the lower diastereomer **9b** shows hydrogen bonding between the oxygen atom of the 9-hydroxy group and the hydrazine N–H, leaving the quinuclidine nitrogen atom uninvolved. All structures exhibit a second intramolecular hydrogen bonding between the 6′-hydroxy function and the carbonyl oxygen of the NH-carbonyl moiety. Furthermore, the value for the torsion angle between the two carbamate carbonyl functions bound to the hydrazine varies from 69.7 to 77.8°, a distortion from the classical rectangle between the two hydrazine carbonyl functions,[44] which also seems to arise from the intramolecular hydrogen bonding.

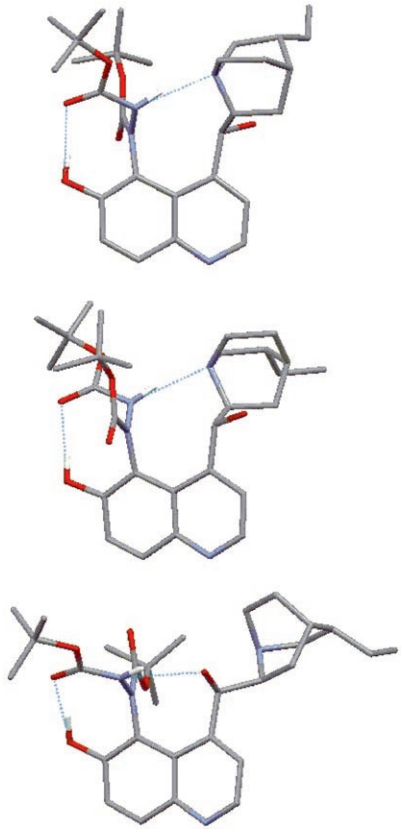


Figure 1. X-ray structures of the 5′-aminated cinchona alkaloids showing the intramolecular hydrogen bonding: **8a** (upper isomer, top), **9a** (upper isomer, middle) and **9b** (lower isomer, bottom).

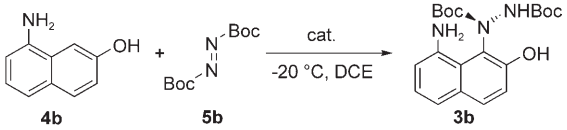
The relative stereochemistry of all other aminated cinchona alkaloid derivatives was assigned on the basis of these three X-ray structures and the respective TLC R_f values.

To verify if this intramolecular hydrogen bonding is also present in solution and if it affects the basicity of the upper diastereomer, NMR experiments were carried out in an attempt to determine the pK_a values of the new compounds.[45] Upon protonation of the quinuclidine nitrogen atom the signals of the protons in close proximity to it are shifted downfield in the NMR. When equimolar amounts of hydrocupreine **6** and either the upper **9a** or the lower diastereomer **9b**, were mixed in CD_3OD and then treated with aliquots of TFA, these chemical shifts could be recorded. Unfortunately, it was not possible to determine accurate pK_a values, as the line broadening due to the rotamers present in the new compounds prevented such measurements. Nevertheless, a qualitative conclusion can be drawn from the experiments. In the case of the mixture containing the upper isomer **9a**, the hydrocupreine (**6**) was first fully protonated, before the signals of the upper isomer started to change, suggesting a difference of approximately two pK_a units. In contrast to this, both compounds in the second mixture—the lower isomer **9b** and **6**—were protonated from the start, suggesting that the pK_a values had a greater similarity to each other (see Supporting Information). As expected, the results of analogous experiments for **7** and either **8a** or **b**, resembled the above described behaviour. This supports the hypothesis that the intramolecular hydrogen bonding, between the quinuclidine nitrogen atom and the NH of the hydrazine, revealed by the X-ray structure of the upper isomers **8a** and **9a**, is also present in solution, thereby decreasing the basicity of the upper isomers.

Furthermore, as soon as the upper isomer **9a** was protonated, it started to isomerise to the lower diastereomer. Consequently, at the end of the titration both mixtures, irrespective of which aminated isomer (**9a** or **b**) was present, contained the same two species (**6**+H^+ and **9**+H^+).

Amination of 2-naphthols: A reinvestigation of the amination of 8-amino-2-naphthol (**4b**) was then started, utilising the whole new family of aminated cinchona alkaloids (Table 2). All reactions were carried out on a 0.2 mmol scale by using a stoichiometric amount of D*t*BuAD (**5b**) and 20 mol% of the various catalysts at −20°C in 1,2-dichloroethane. Full conversion was achieved overnight in the pres-

Table 2. Catalyst screening for the organocatalysed asymmetric Friedel–Crafts reaction of 8-amino-2-naphthol (**4b**) with di-*tert*-butyl azodicarboxylate **5b**.[a]

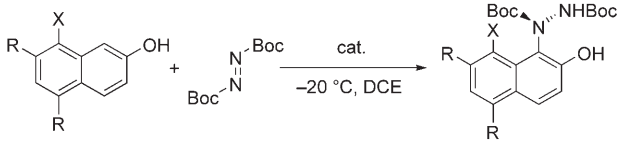


4b **5b** **3b**

Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**8a** (upper)	96	73	69
2	**8b** (lower)	16	87	87
3	**9a** (upper)	96	50	−63[d]
4	**9b** (lower)	16	91	−96[d]
5	**11a** (upper)	96	38	48
6	**11b** (lower)	16	92	70
7	**13a** (upper)	96	0	n.d.
8	**13b** (lower)	96	33	−33[d]
9	**15** (lower)	16	82	92
10	**9b**[e] (lower)	16	90	−96[d]

[a] Reaction carried out by using **4b** (0.20 mmol), **5b** (0.20 mmol) and catalyst (0.04 mmol) in DCE (4 mL). [b] Yield of isolated product after flash chromatography. [c] The *ee* was determined by HPLC. [d] The enantiomer *ent*-**3b** with the opposite sign of optical rotation was formed. [e] Only 5 mol% of the catalyst was used.

Table 3. Substrate screening for the organocatalysed asymmetric Friedel–Crafts reaction of 8-substituted-2-naphthols **4** with di-*tert*-butyl azodicarboxylate (**5b**).[a]



4 **5b** **3**

Entry	Substrate X, R	Product	Catalyst **8b**		Catalyst **9b**	
			ee [%][b]	Yield [%][c]	*ee* [%][b,d]	Yield [%][c]
1	NH_2, H **4b**	**3b**	87	87	−96	91
2	NHMe, H **4c**	**3c**	93	91	−96	94
3	NHBn, H **4d**	**3d**	98	92	−98	80
4	NHC_5H_{11}, H **4e**	**3e**	94	95	−94	98
5	$NHCH_2$(*o*-C_6H_4OH), H **4f**	**3f**	92	95	−94	93
6	NH_2, Br **4g**	**3g**	98	85	−96	95
7	NHBoc, H **4h**	**3h**	58	94	−96	71
8	Cl, H **4i**	**3i**	20	57	0	52

[a] Reaction carried out by using **4** (0.20 mmol), **5b** (0.20 mmol) and catalyst (0.04 mmol) in DCE (4 mL). [b] The *ee* was determined by HPLC. [c] Yield of isolated product after flash chromatography. [d] The enantiomer *ent*-**3** with the opposite sign of optical rotation was formed.

ence of most of the lower diastereomers, whereas the reactions catalysed by the upper diastereomers did not go to completion even after four days.

These improved results enabled us to prepare both enantiomers of the aminated 8-amino-2-naphthol **3b** in over 90% *ee*, and exceeded especially the optical purity of *ent*-**3b** when hydrocupreine was used as the catalyst at −20°C (from 22% *ee* using **6**, to 96% *ee* using **9b**, Table 2, entry 4). It should also be noted, that the catalyst loading could be decreased to 5 mol%, without influencing the yield or the enantiomeric excess (entry 10). Not only was the reactivity of the upper diastereomers considerably lower, but also the enantioselectivity induced by these catalysts was inferior in comparison with the lower diastereomers (entries 1–6). The catalyst **13b** with a protected 9-hydroxy function showed a diminished reactivity, while its upper diastereomer **13a** showed no reactivity at all. The results in Table 2 show that the catalysts **8b**, **9b** and **15** performed best in the Friedel–Crafts amination of **3b** and the substrate scope of this reaction was investigated next (Table 3).

It appears from Table 3 that a large variety of optically active, aminated 8-amino-2-naphthols **3b–h** were accessible by this reaction in high yield and enantiopurity (entries 1–7). Even additional substituents in the naphthol ring did not influence yield or enantioselectivity (entry 6). It has been found that substrates containing electron-withdrawing substituents, such as the N-Boc-protected amino-naphthol **4h**, gave a lower enantioselectivity when catalyst **8b** was used (entry 7), and the 8-chloro-2-naphthol (**4i**) reacted sluggishly to give a nearly racemic product with either catalyst **8b** or **9b** (entry 8).

Mechanistically, it seems plausible that both hydrocupreine (**6**) and the 8-amino-2-naphthol (**4b**) exist as zwitterionic species in solution, permitting the formation of a two-point-contact ion pair.[46] By this, one face of **4b** would be shielded, guiding the approaching D*t*BuAD (**5b**) to the other face of 8-amino-2-naphthol (**4b**) (Figure 2, left). In the case of the aminated hydrocupreidine **8b**, this face shielding would be enhanced by the 5′-substituent, explaining the increase in enantioselectivity (Figure 2, right).

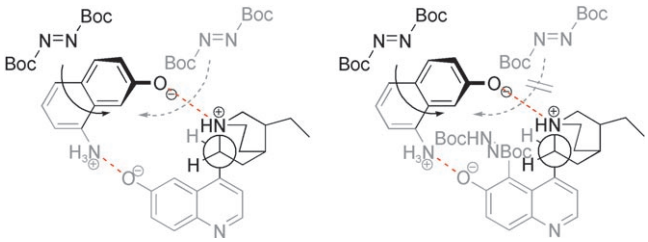
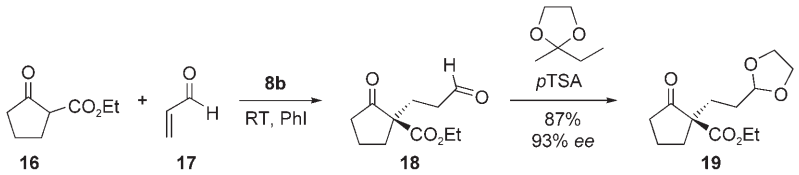


Figure 2. Possible intermediate in the hydrocupreidine **7** (left) and aminated hydrocupreidine **8b** (right) catalysed reaction of 8-amino-2-naphthol **4b** with di-*tert*-butyl azodicarboxylate **5b**. The parts shown in grey lie behind the plane of the paper and the 9-hydroxy function was omitted for clarity.

Ion pairing in this fashion would also explain why other substituents than amines at position 8 do not give high enantioselectivity (Table 3, entry 8).

This new class of cinchona alkaloids featuring a unique structure has already shown interesting properties and improved performance in the amination of 8-amino-2-naphthols. Further applications of these compounds or derivatives thereof might shed light on the mechanistical aspects of cinchona alkaloid catalysis and help tailoring catalysts to the special needs of a reaction.

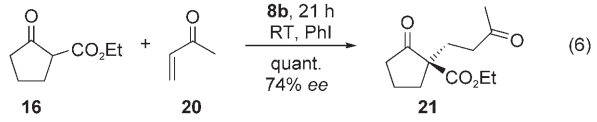
Michael additions: To further examine the scope and limitations of this new class of catalysts, their performance in the Michael addition of β-keto esters to acrolein was investigated. The enantioselective variant of this reaction was first published by Bergson and Långström by using 2-(hydroxymethyl)quinuclidine as the catalyst.[47] Although they never determined the enantiomeric excess, they noted the optical activity of their products. The first account of an application of cinchona alkaloids as catalysts for Michael additions was given by Wynberg and Helder. In their seminal work they added β-keto esters to acrolein and methyl vinyl ketone, in the presence of quinine and reported an enantiomeric excess of up to 76% *ee*.[34] Most recently, this enantiomeric excess was improved by using either phase-transfer catalysis or new derivatives of cinchona alkaloids.[48]



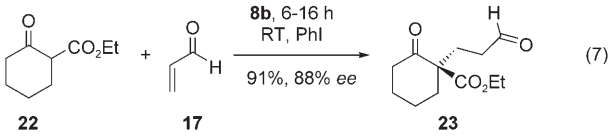
Scheme 1. Isolation of the Michael-addition product **18** as its acetal **19**.

By using the newly prepared cinchona derivatives, the addition of ethyl-2-oxocyclopentanone carboxylate (**16**) to acrolein (**17**) was investigated (Table 4). A solvent screening revealed that iodobenzene was an appropiate solvent for the catalyst screening process.

It appears from the results in Table 4 that the lower isomers of the diastereomeric pairs of catalysts provided high enantioselection. By using either **8b** or **9b**, both enantiomers of the product **18** can be prepared with excellent enantiomeric excess. Lowering the temperature did not have a positive effect on the optical purity (entries 10 and 11). The aldehyde **18** was isolated as its acetal **19** (Scheme 1), as it is known to be susceptible to an intramolecular aldol reaction.[49] Methyl vinyl ketone (**20**) as an additional Michael acceptor was examined and reacted with good enantioselectivity [Eq. (6)].

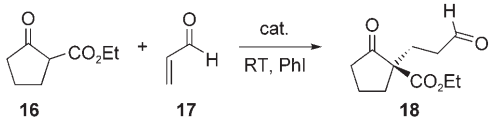


The alteration of the nucleophile, by using ethyl-2-oxocyclohexanone carboxylate (**22**) also resulted in a lower enantioselectivity in comparison to ethyl-2-oxocyclopentanone carboxylate (**16**) [Eq. (7)].



Comparison of the optical rotation of **23** to literature values enabled us to determine the absolute configuration of the product to be *R*.[50] The other Michael-addition products were assigned accordingly.

Table 4. Michael addition of ethyl-2-oxocyclopentanone carboxylate (**16**) to acrolein (**17**).[a]



Entry	Catalyst	*T* [°C]	*t* [h]	*ee* [%][b]
1	**8a** (upper)	RT	16	−16[c]
2	**8b** (lower)	RT	1	93
3	**9a** (upper)	RT	16[d]	2
4	**9b** (lower)	RT	1	−90[c]
5	**11a** (upper)	RT	16[d]	0
6	**11b** (lower)	RT	3	−20[c]
7	**13a** (upper)	RT	16[d]	0
8	**13b** (lower)	RT	16[d]	−14[c]
9	**15** (lower)	RT	5	54
10	**9b** (lower)	0	1	89
11	**9b** (lower)	−25	2	89

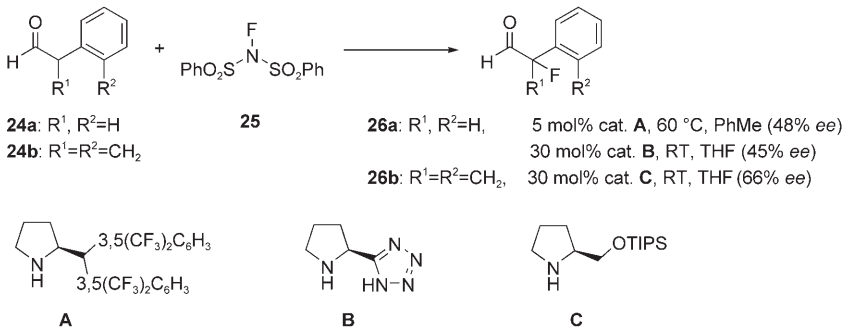
[a] Reaction carried out by using **16** (64 μmol), **17** (130 μmol) and catalyst (0.1 equiv) in iodobenzene (0.4 mL). Completion of the reaction was detected by TLC, then the reaction mixtures were filtered over a silica plug and analysed. [b] The *ee* was determined by GC analysis. [c] The enantiomer *ent*-**18** with the opposite sign of optical rotation was formed. [d] Conversion was not complete.

Fluorination of α-branched aldehydes: As outlined in the introduction, not only this new class of cinchona alkaloids can be used as organocatalysts; the product of the amination reaction, the aminated 8-amino-2-naphthol **3b** ([Eq. (1)] and Table 2) can also act as a new type of asymmetric organocatalyst.

We chose the fluorination of α-branched aldehydes to examine the applicability of these atropisomers as organocatalysts. So far, only two substrates, namely 2-phenylpropanal (**24a**) and indan-1-carbaldehyde (**24b**), have been fluorinated enantioselectively, by using *N*-fluorobenzenesulfonimide (**25**; NFSI) as the fluorine source and proline derivatives as the catalysts (Scheme 2).[38a,b]

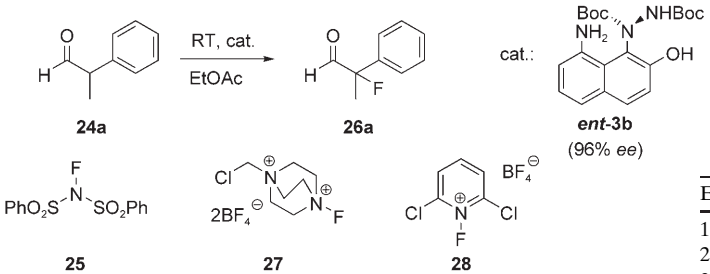
Intrigued by this challenge, we started to investigate different fluorine sources, namely NFSI (**25**), Selectfluor **27** and the pyridinium salt **28**, applying the racemic catalyst. Fortunately, in all cases product formation could be detected. Therefore the enantioenriched catalyst *ent*-**3b**, possessing 96% *ee*, was used in the reaction (Table 5).

This initial screening gave good results, as NFSI (**25**) not only led to full conversion, but the product already exhibited an enantiomeric excess not obtained so far. With NFSI



Scheme 2. α-Fluorination of α-branched aldehydes **24** according to Barbas and our group.[38a,b]

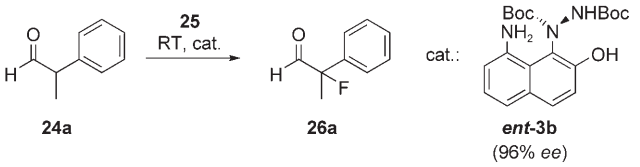
Table 5. Screening of fluorine sources for the organocatalytic asymmetric fluorination of 2-phenylpropanal (**24a**).[a]



Entry	Fluorine source	Conversion [%][b]	*ee* [%][c]
1	**25**	96	72
2	**27**	6	56
3	**28**	33	16

[a] Reaction carried out by using **24a** (0.25 mmol), fluorinating agent (0.25 mmol) and *ent*-**3b** (0.05 mmol) in EtOAc (0.5 mL) for 16 h. [b] Conversions are stated as the ratio of product to starting material as determined by GC analysis. [c] The *ee* was determined by chiral GC analysis.

Table 6. Screening of solvents for the organocatalytic asymmetric fluorination of 2-phenylpropanal (**24a**) by using NFSI (**25**).[a]



Entry	Solvent	Conversion [%][b]	*ee* [%][c]
1	acetone	78	72
2	toluene	83	64
3	THF	79	70
4	MeCN	92	78
5	dioxane	76	68
6	DMF	94	76
7	CH_2Cl_2	91	62
8	EtOAc	96	72
9	*i*PrOH	85	85
10	MeOH	32	84
11	hexane	95	86

[a] Reaction carried out by using **24a** (0.25 mmol), **25** (0.25 mmol) and *ent*-**3b** (0.05 mmol) in solvent (0.5 mL) for 16 h. [b] Conversions are stated as the ratio of product to starting material as determined by GC analysis. [c] The *ee* was determined by chiral GC analysis.

of hexane/*i*PrOH 9:1 was used. Furthermore, it was not possible to analyse all reaction products by GC analysis, making a derivatisation of the raw products necessary. Two procedures are described for derivatisation, either reduction to the alcohol **29** by using $NaBH_4$[38a–d] or oxidation to the acid by using NaOCl.[38b] Both were tried, but because of its ease the reduction was established as the method of choice. Table 7 shows the enantioselective α-fluorination of aldehydes **24** by using NFSI **25**.

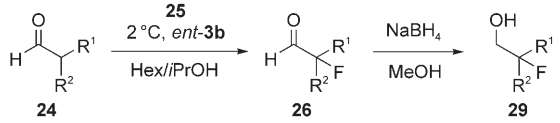
(**25**) as the fluorine source the influence of the solvent on the reaction course was then thoroughly examined. Table 6 shows the results for the screening of different solvents for the organocatalytic fluorination of **24a**.

To our surprise the reaction worked in all tested solvents, with good conversions and moderate to good enantioselectivity, irrespective of the polarity of the solvent. Only in MeOH, the conversion was low, possibly due to concomitant formation of the hemiacetal or acetal (Table 6, entry 10). The highest enantiomeric excess was obtained when the reaction was carried out in either MeOH, *i*PrOH or hexane. By using hexane as the solvent, 90% conversion was reached within 3 h at room temperature. The speed of the reaction and the impossibility for acetal formation, resulted in hexane becoming the solvent of choice. A decrease in catalyst loading to 10 mol% led to a slower reaction, but without diminishing the enantiomeric excess. Cooling the reaction to 4°C finally enhanced the enantiomeric excess to 90% *ee* with 95% conversion after 16 h.

Under these optimised reaction conditions additional substrates were examined. Unfortunately, not all substrates were sufficiently soluble in hexane, hence a solvent mixture

Good enantioselectivity was achieved when R^1 was an aromatic substituent without substitution (Table 7, entry 1) or with electron-withdrawing substituents (entries 2 and 3). The fluorinated 1,2,3,4-tetrahydronaphthalene-1-carbaldehyde **26e** could only be isolated as the aldehyde and decomposed in our hands upon reduction to **29e**. Generally, the α-fluorinated aldehydes themselves are known to be unstable.[51] Nonetheless, a good enantiomeric excess of 78% was achieved for this substrate (entry 4). In the case of two aliphatic substituents the enantioselectivity of the reaction dropped significantly (entries 5–7). Surprisingly, linear aldehydes like 3-phenyl propanal did not react at all under the given conditions and the same holds true for ketones, for example, acetone or cyclohexanone. *No side products could be detected and raw yields and spectra suggested good conversions and purities. However, only moderate yields could be isolated after column chromatography.* This could possibly originate

Table 7. Enantioselective α-fluorination of α-branched aldehydes **24** by using NFSI (**25**).[a]



Entry	Aldehyde	R^1	R^2	Product	Yield [%][b]	*ee* [%][c]
1	**24a**	Ph	Me	**29a**	36	90 (88)[d]
2	**24c**	4-NO_2-C_6H_4	Me	**29c**	56	78 (68)[d]
3	**24d**	4-Br-C_6H_4	Me	**29d**	60	90 (86)[d]
4	**24e**	$-(C_6H_4)(CH_2)_3-$		**26e**	55[f]	78(77)[e]
5	**24f**	Bu	Et	**29f**[g]	27	7 (3)[e]
6	**24g**	CH_2(4-*i*PrC_6H_4)	Me	**29g**	29	30 (28)[d]
7	**24h**	*c*Hex	Me	**29h**	10	31[e]

[a] Reaction carried out by using aldehyde **24** (0.50 mmol), NFSI (**25**; 0.60 mmol) and catalyst *ent*-**3b** (0.05 mmol, 96% *ee*) in hexane/*i*PrOH 9:1 (1.0 mL) for 16 h. [b] Yield after flash chromatography, variations due to instability of the products. [c] The *ee* of the alcohol **29** (*ee* with **3b** [87% *ee*]). [d] The *ee* was determined by chiral HPLC analysis. [e] The *ee* was determined by chiral GC analysis. [f] The aldehyde **26e** was isolated and analysed. [g] The catalyst *ent*-**3b** (0.3 equiv) was added over 72 h.

from the instability of the products towards column chromatography.

Mechanistically, the chiral induction in this reaction could originate from shielding of one of the faces of the intermediate enamine, limiting the NFSI to attack only from the opposite face. The X-ray structure of a functionalised product **30**[21] (Figure 3, left and middle) from the amination of 8-amino-2-naphthol shows that the substituents of the naphthol are oriented nearly parallel to each other and close to rectangular to the naphthol core. Furthermore, the X-ray structure suggests hydrogen bonding between the amide NH moiety to the carbonyl oxygen atom of the carbonylbenzyloxy (Cbz) group. The geometry of the intermediate could possibly be stabilised by a similar intramolecular hydrogen bonding from the enamine NH to the carbonyl oxygen atom bound to N-1 (Figure 3, right).

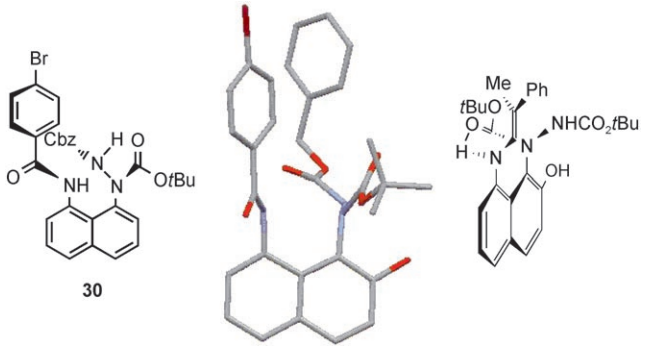


Figure 3. Functionalised product **30**[21] (left and middle) and possible enamine intermediate formed from the organocatalyst *ent*-**3b** and 2-phenylpropanal **24a**.

An intermediate of this kind should have an *E*-geometry at the enamine, which would only permit the NFSI to attack from the *Si*-face of the enamine, yielding (*S*)-2-fluoro-2-phenylpropanal ((*S*)-**26a**). This predicted configuration could be confirmed by a single-crystal X-ray analysis of the 4-bromobenzoyl hydrazone derivative **31** (Figure 4).[52]

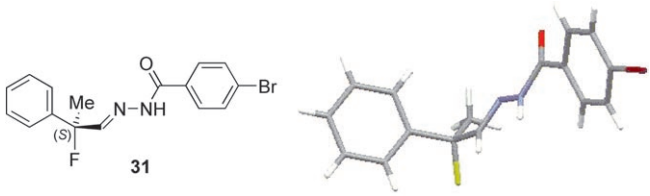


Figure 4. X-ray crystallographic structure of the benzoyl hydrazone derivative **31**.

The diminished enantioselection in the reactions, for which aliphatic α-branched aldehydes are used could be a result of an *E*/*Z*-isomerism of the intermediate enamine. This would cause undistinguishable faces of the enamine, thereby preventing a stereoselective attack by the NFSI.

In summary, we have prepared a new class of compounds consisting of nine 5′-aminated 6′-hydroxy cinchona alkaloids which combine non-biaryl atropisomerism with the catalytic properties of the cinchona alkaloids. A set of atropo-diastereomeric cinchona alkaloids exhibits strongly differing physical and catalytical properties, due to intramolecular hydrogen bonding from the hydrazine NH to the quinuclidine nitrogen atom, present in the less polar diastereoisomer. By this, the basic site of the molecule is blocked which was also confirmed by NMR experiments. These new catalysts demonstrated a good performance in the asymmetric Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds (up to 93% *ee*), as well as advanced performance in the asymmetric Friedel–Crafts amination of various 2-naphthols. The aminated 8-amino-2-naphthol itself was used as an organocatalyst in the asymmetric α-fluorination of α-branched aldehydes, yielding the fluorinated compounds in up to 90% *ee*. This is the first example of an organocatalyst in which the chirality originates from non-biaryl atropisomerism. Further applications of these new catalysts and derivatives thereof are now being investigated in our laboratories.

Experimental Section

General: The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 400, 100 and 377 MHz, respectively. The chemical shifts are reported in ppm downfield to $CHCl_3$ ($\delta = 7.26$), $CHDCl_2$ ($\delta = 5.32$) or CHD_2CN ($\delta = 1.94$) for ^{1}H NMR spectra, ($\delta = 77.0$), ($\delta = 53.5$) or ($\delta = 1.2$) for ^{13}C NMR spectra relative to the central $CDCl_3$, CD_2Cl_2 or CD_3CN resonance, and relative to 2,2,2-trifluoroacetophenone ($\delta = -71.8$) for ^{19}F NMR spectra, respectively. Around half of the NMR spectra show rotamers and therefore doubling of the signal set or line broadening. Therefore all ^{1}H and ^{13}C spectra with rotamer influence are available in the Supporting Informa-

tion. Flash chromatography (FC) was carried out by using Merck silica gel 60 (230–400 mesh). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The enantiomeric excesses of the products were determined by HPLC using a Daicel Chiralpak AD, Chiralcel OD or Chiralcel OJ column with *i*PrOH/hexane as the eluent or by GC using an Astec G-TA column.

Materials: Naphthols **4a** and **b**, diazocarboxylates **5a–c**, hydroquinine, hydroquinidine, diazabicyclo[3.2.0]undecene (DBU), the β-ketoesters **16** and **22**, acrolein, metyl vinyl ketone, NFSI, Selectfluor®, the pyridinium salt **28**, sodiumborohydride, pentane, Et_2O, EtOAc, toluene, 1,2-dichloroethane (DCE), CH_2Cl_2, MeOH, iodobenzene, acetone, THF, MeCN, dioxane, DMF, hexane and *i*PrOH were obtained from Aldrich and used as received. Catalysts **6**, **7**, **10** and **12** were prepared according to literature procedures.[23,39,40] The naphthols **4c–f** were prepared by reductive amination of **4b** with the corresponding aldehydes; **4g** was obtained by bromination of **4b**; **4h** was obtained by N-Boc-protection of **4b** and **4i** was obtained from **4b** by diazotation and reaction with copper(I)chloride. α-Branched aldehydes **24c–e** and **h** were prepared from the corresponding ketones by Wittig reaction with methoxymethyl triphenylphosphonium chloride in THF by using LDA, followed by reaction with *p*-toluolsulfonic acid in dioxane/water 1:1, following known procedures.[53]

General procedure for the amination of the cinchona alkaloids: The cinchona alkaloid (1.0 equiv) was placed in a 25 mL round-bottomed flask. The solid was suspended in dichloromethane (10 mL per 1 g cinchona alkaloid) and then azodicarboxylate (**5**; 1.2 equiv) was added. When the starting material could no longer be detected by TLC or when the suspension turned into a dark orange solution, the solvent was evaporated and the raw product purified by FC.

Characterisation data for the cinchona alkaloid derivatives

(S)-(+)-Hydrocupreidine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**8a**)*: The title compound was prepared according to the general procedure by using hydrocupreidine (**7**; 1.0 g, 3.20 mmol) and D*t*BuAD (**5b**; 890 mg, 3.84 mmol). Elution with pentane/EtOA*c* 50:50 to EtOAc/MeOH/24% aq NH_3 95:5:1 gave the product (1.24 g, 72%). R_f=0.67 (EtOAc/MeOH/aq NH_3 90:10:1); R_f=0.18 (pentane/EtOAc 50:50); $[\alpha]_D^{20}$=+81.9 (*c*=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2, 20°C): δ= 10.75/10.60 (s, 1H), 8.37 (d, *J*=4.6 Hz, 1H), 7.89/7.88 (d, *J*=9.2 Hz, 1H), 7.58/7.53 (d, *J*=4.5 Hz, 1H), 7.28/7.26 (d, *J*=9.2 Hz, 1H), 5.63/5.61 (br s, 1H), 3.69/3.53 (br s, 1H), 3.03–2.93 (m, 1H), 2.92–2.84 (m, 1H), 2.72–2.64 (m, 1H), 2.60–2.51 (m, 1H), 2.51–2.43 (m, 1H), 2.39–2.31/2.26–2.18 (m, 1H), 1.66–1.57 (m, 1H), 1.55–1.43 (m, 2H), 1.42–1.35 (m, 11H), 1.34–1.26 (m, 7H), 0.98 (s, 3H), 0.99–0.95/0.95–0.89 (m, 1H), 0.82/0.75 ppm (t, 3H, *J*=7.3 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2, 20°C): δ=161.2, 161.1, 155.8, 155.4, 154.4, 153.9, 149.3, 148.5, 146.9, 146.6, 144.8, 144.6, 133.3, 133.1, 124.2, 124.0, 122.4, 120.0, 119.4, 118.9, 118.6, 82.4, 82.2, 82.0, 81.9, 71.0, 70.3, 60.2, 60.0, 50.1, 49.6, 48.3, 47.9, 37.4, 37.3, 28.1, 28.0, 27.9, 27.8, 27.6, 26.4, 25.2, 25.2, 16.5, 16.5, 12.0, 11.9 ppm; HRMS: *m*/*z*: calcd: 543.3184; found: 543.3181 $[C_{29}H_{42}N_4O_6+H]^+$.

(R)-(+)-Hydrocupreidine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**8b**)*: The title compound was prepared according to the general procedure by using hydrocupreidine (**7**; 1.0 g, 3.20 mmol) and D*t*BuAD (**5b**; 890 mg, 3.84 mmol). Elution with EtOAc/MeOH/24% aq NH_3 95:5:1 to EtOAc/MeOH/24% aq NH_3 90:10:1 gave the product (0.37 g, 21%). R_f=0.29 (EtOAc/MeOH/aq NH_3 90:10:1); R_f=0.61 (EtOAc/MeOH/aq NH_3 50:50:1); $[\alpha]_D^{20}$=+134.2 (*c*=1.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=8.40 (m, 1H), 7.86 (d, *J*=9.1 Hz, 1H), 7.44 (d, *J*=3.8 Hz, 1H), 7.33 (d, *J*=9.1 Hz, 1H), 5.71/5.54 (s, 1H), 3.27 (br s, 1H), 3.15–2.98 (m, 1H), 2.95–2.58 (m, 3H), 2.13–1.99/1.97–1.86 (m, 1H), 1.83/1.76 (br s, 1H), 1.72–1.58 (m, 2H), 1.58–1.49 (m, 6H), 1.48–1.33 (m, 13H), 1.24 (s, 6H), 0.92–0.78 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=159.3, 155.2, 146.5, 144.7, 132.8, 126.5, 123.5, 122.9, 120.6, 120.1, 83.0, 82.6, 70.3, 58.8, 58.2, 50.4, 50.0, 48.6, 37.3, 37.5, 28.2, 28.1, 27.9, 27.0, 26.6, 25.9, 25.5, 25.0, 24.9, 23.3, 12.1, 11.9 ppm; HRMS: *m*/*z*: calcd: 543.3184; found: 543.3115 $[C_{29}H_{42}N_4O_6+H]^+$.

(S)-(−)-Hydrocupreine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**9a**)*: The title compound was prepared according to the general procedure by using hydrocupreine **6** (1.0 g, 3.20 mmol) and D*t*BuAD (**5b**; 890 mg, 3.84 mmol). Elution with pentane/EtOAc 50:50 to EtOAc/MeOH/24% aq NH_3 95:5:1 gave the product (0.42 g, 24%). R_f=0.16 (pentane/EtOAc 50:50); $[\alpha]_D^{20}$=−14.6 (*c*=0.06 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=12.12/11.89 (br s, 1H), 10.99/10.76 (s, 1H), 8.62/8.60 (d, *J*=4.6 Hz, 1H), 8.04/8.03 (d, *J*=9.2 Hz, 1H), 7.67/7.63 (d, *J*=4.6 Hz, 1H), 7.46/7.44 (d, *J*=9.2 Hz, 1H), 6.61/6.35 (s, 1H), 3.42 (m, 1H), 3.00 (m, 1H), 2.71 (m, 2H), 2.29–2.10 (m, 2H), 2.07–1.96 (m, 1H), 1.94–1.73 (m, 2H), 1.55–1.45 (m, 15H), 1.36–1.28 (m, 1H), 1.28–1.19 (m, 2H), 1.18–1.15 (m, 5H), 0.84–0.73 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=161.1, 156.0, 155.5, 154.5, 154.1, 148.3, 147.8, 146.7, 146.6, 145.0, 144.7, 133.6, 133.3, 123.9, 122.9, 122.8, 119.8, 119.0, 118.4, 118.2, 82.3, 82.2, 82.1, 81.9, 70.6, 70.0, 59.8, 56.5, 56.1, 53.0, 42.5, 42.1, 37.1, 28.3, 28.1, 27.8, 27.4, 27.0, 25.8, 16.2, 16.0, 11.8 ppm; HRMS: *m*/*z*: calcd: 543.3184; found: 543.3185 $[C_{29}H_{42}N_4O_6+H]^+$.

(R)-(−)-Hydrocupreine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**9b**)*: The title compound was prepared according to the general procedure by using hydrocupreine (**6**; 1 g, 3.2 mmol) and D*t*BuAD (**5b**; 890 mg, 3.84 mmol). Elution with EtOAc/MeOH/24% aq NH_3 95:5:1 to EtOAc/MeOH/24% aq NH_3 90:10:1 gave the product (0.98 g, 56%). R_f=0.35 (EtOAc/MeOH/aq NH_3 90:10:1); $[\alpha]_D^{20}$=−85.6 (*c*=0.96 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=8.59 (d, *J*=4.6 Hz, 1H), 7.95 (d, *J*=9.1 Hz, 1H), 7.48 (d, *J*=4.6 Hz, 1H), 7.38 (d, *J*=9.2 Hz, 1H), 5.61–5.43 (m, 1H), 3.38–3.20 (m, 1H), 3.13–3.00 (m, 1H), 2.99–2.85 (m, 1H), 2.60–2.41 (m, 3H), 1.98–1.88 (m, 1H), 1.87–1.76 (m, 2H), 1.75–1.63 (m, 2H), 1.56 (s, 3H), 1.53–1.32 (m, 13H), 1.28–1.21 (m, 6H), 0.93–0.85 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=159.2, 155.0, 146.5, 144.7, 144.1, 132.6, 126.3, 123.0, 122.7, 120.5, 82.9, 82.7, 71.2, 58.3, 57.1, 41.7, 37.1, 28.1, 27.8, 27.5, 25.2, 24.1, 21.0, 14.1, 12.1 ppm; HRMS: *m*/*z*: calcd: 543.3184; found: 543.3187 $[C_{29}H_{42}N_4O_6+H]^+$.

(S)-(−)-β-Isocupreidine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**11a**)*: The title compound was prepared according to the general procedure by using β-isocupreidine (**10**; 100 mg, 0.32 mmol) and D*t*BuAD (**5b**; 89 mg, 0.38 mmol). Elution with pentane/EtOAc 50:50 to EtOAc/MeOH/24% aq NH_3 95:5:1 gave the product (79 mg, 45%). R_f= 0.32 (pentane/EtOAc 50:50); $[\alpha]_D^{20}$=−32.5 (*c*=1.03 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=11.08/10.87 (s, 1H), 10.85/10.72 (s, 1H), 8.66/8.64 (d, *J*=4.5 Hz, 1H), 8.03/7.99 (d, *J*=9.2 Hz, 1H), 7.76/7.74 (d, *J*=4.5 Hz, 1H), 7.40/7.39 (d, *J*=9.2 Hz, 1H), 5.97/5.83 (s, 1H), 3.52/3.50 (d, *J*=13.8 Hz, 1H), 3.04–2.83 (m, 3H), 2.67/2.59 (d, *J*=13.8 Hz, 1H), 2.08–1.96 (m, 1H), 1.71–1.59 (m, 3H), 1.56–1.46 (m, 16H), 1.15–1.10 (m, 5H), 0.97/0.92 ppm (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=161.6, 161.1, 156.5, 155.9, 154.7, 146.4, 146.4, 146.3, 144.4, 144.1, 141.7, 133.9, 133.5, 125.0, 122.4, 119.3, 119.1, 118.5, 117.8, 82.7, 82.5, 77.9, 77.7 72.1, 72.0, 56.8, 56.7, 53.6, 53.6, 45.8, 33.5, 33.1, 28.2, 28.1, 28.1, 27.7, 27.6, 27.5, 27.4, 23.2, 22.2, 22.1, 7.3 ppm; HRMS: *m*/*z*: calcd: 541.3026; found: 541.3033 $[C_{29}H_{40}N_4O_6+H]^+$.

(R)-(−)-β-Isocupreidine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**11b**)*: The title compound was prepared according to the general procedure by using β-isocupreidine (**10**; 100 mg, 0.32 mmol) and D*t*BuAD (**5b**; 89 mg, 0.38 mmol). Elution with EtOAc/MeOH/24% aq NH_3 95:5:1 to EtOAc/MeOH/24% aq NH_3 90:10:1 gave the product (78 mg, 45%). R_f=0.35 (EtOAc/MeOH/aq NH_3 90:10:1); $[\alpha]_D^{20}$=−2.8 (*c*=0.59 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=10.67 (br s, 1H), 9.30 (br s, 1H), 8.69/8.66 (d, *J*=4.6 Hz, 1H), 8.04/8.03 (d, *J*=9.1 Hz, 1H), 7.53/7.49 (d, *J*=4.6 Hz, 1H), 7.44 (t, *J*=8.7 Hz, 1H), 5.85/5.78 (s, 1H), 3.53–3.42 (m, 2H), 3.16–2.92 (m, 2H), 2.62 (dd, *J*=4.8 Hz, *J*= 13.9 Hz, 1H), 2.18–2.06 (m, 2H), 1.70–1.58 (m, 3H), 1.51/1.50/1.48 (s, 14H), 1.27 ppm (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=159.7, 159.5, 156.1, 155.4, 154.2, 153.6, 146.7, 146.6, 145.2, 145.1, 140.9, 140.7, 134.2, 133.7, 127.3, 126.8, 122.9, 122.9, 121.5, 121.4, 119.9, 118.8, 83.3, 83.1, 82.8, 82.5, 78.7, 78.5, 74.2, 74.1, 56.3, 56.3, 54.1, 46.6, 46.6, 31.2, 31.2, 28.1, 28.1, 27.8, 26.9, 26.9, 24.9, 24.8, 23.7, 23.7, 7.4, 7.3 ppm; HRMS: *m*/*z*: calcd: 541.3026; found: 541.3023 $[C_{29}H_{40}N_4O_6+H]^+$.

(R)-(+)-9-Benzyl-6′-hydroxyquinine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert-*butyl ester) (**13a**)*: The title compound was prepared according to the general procedure by using 9-benzyl-6′-hydroxyquinine (**12**; 305 mg, 0.76 mmol) and D*t*BuAD (**5b**; 210 mg, 0.91 mmol). Elution with pentane/EtOAc/aq NH_3 80:20:1 to 40:60:1 gave the product (48 mg, 10%). R_f=0.65 (pentane/EtOAc 50:50); $[\alpha]_D^{20}$=+49.8 (*c*=0.15 in $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 11.96/11.73 (s, 1H), 11.02/10.82 (s, 1H), 8.68/8.64 (d, J = 4.5 Hz, 1H), 8.08 (dd, J = 1.3 Hz, J = 9.2 Hz, 1H), 7.65/7.58 (d, J = 4.5 Hz, 1H), 7.50/7.48 (dd, J = 9.2 Hz, 1H), 7.42–7.30 (m, 5H), 5.76–5.62 (m, 1H), 5.50/5.45 (s, 1H), 5.00–4.88 (m, 2H), 4.49–4.39 (m, 2H), 3.40–3.28 (m, 1H), 3.10–3.00 (m, 1H), 2.87–2.70 (m, 2H), 2.62–2.50 (m, 1H), 2.37–2.10 (m, 2H), 1.96–1.75 (m, 2H), 1.59–1.49 (m, 15H), 1.28 ppm (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 161.0, 156.0, 155.4, 154.5, 153.9, 146.8, 145.0, 141.3, 141.1, 138.0, 137.7, 133.9, 133.6, 128.5, 128.4, 127.8, 127.6, 127.3, 127.1, 123.0, 118.2, 114.7, 114.5, 82.4, 82.4, 82.1, 79.5, 78.9, 71.7, 71.1, 60.2, 59.9, 54.8, 54.3, 42.5, 42.1, 39.6, 30.3, 28.3, 28.3, 28.3, 28.2, 28.0, 26.9, 26.8, 17.5, 17.3 ppm; HRMS: m/z: calcd: 631.3496; found: 631.3470 $[C_{36}H_{46}N_4O_6+H]^+$.

(S)-(−)-9-Benzyl-6′-hydroxyquinine-5′-(hydrazine-N,N′*-dicarboxylic acid* tert*-butyl ester) (**13b**)*: The title compound was prepared according to the general procedure by using 9-benzyl-6′-hydroxyquinine (**12**; 305 mg, 0.76 mmol) and D*t*BuAD (**5b**; 210 mg, 0.91 mmol). Elution with pentane/EtOAc/aq NH_3 40:60:1 to 0:100:1 gave the product (328 mg, 68 %). R_f = 0.22 (pentane/EtOAc 50:50); $[\alpha]_D^{20}$ = −62.3 (c = 1.02 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 11.40/11.14 (s, 1H), 8.71–8.67 (m, 1H), 8.07/8.03 (d, J = 9.4 Hz, 1H), 7.57/7.55 (d, J = 4.9 Hz, 1H), 7.47/7.41 (d, J = 9.2 Hz, 1H), 7.31–7.21 (m, 3H), 7.19–7.12 (m, 2H), 5.85–5.72 (m, 1H), 5.37–5.46 (m, 1H), 5.04–4.90 (m, 2H), 4.14–3.98 (m, 2H), 3.42–3.02 (m, 3H), 2.84–2.56 (m, 2H), 2.35–2.08 (m, 2H), 1.87–1.68 (m, 3H), 1.52–1.44 (m, 13H), 1.13 ppm (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 161.2, 160.3, 156.8, 156.6, 154.3, 154.0, 146.7, 145.2, 145.0, 143.6, 142.7, 141.6, 141.5, 137.5, 137.4, 134.1, 133.7, 128.9, 128.7, 128.3, 128.3, 127.8, 127.7, 127.6, 125.5, 123.3, 123.0, 120.2, 119.7, 119.4, 119.0, 114.6, 114.3, 83.2, 82.8, 82.7, 82.0, 78.6, 78.3, 69.5, 69.0, 59.0, 58.6, 56.1, 55.1, 42.3, 42.1, 40.0, 39.5, 30.3, 28.2, 28.1, 27.7, 27.6, 27.1, 27.1, 20.5, 19.8 ppm; HRMS: m/z: calcd: 631.3496; found: 631.3503 $[C_{36}H_{46}N_4O_6+H]^+$.

(R)-(+)-Hydrocupreidine-5′-(hydrazine-N,N′*-dicarboxylic acid benzyl ester) (**15**)*: The title compound was prepared according to the general procedure by using hydrocupreidine (**7**; 147 mg, 0.47 mmol) and DBnAD (**5c**; 168 mg, 0.56 mmol). Elution with EtOAc/MeOH/24 % aq NH_3 100:0:0 to 80:20:1 gave the product (143 mg, 50 %). R_f = 0.60 (EtOAc/MeOH/aq NH_3 50:50:1); $[\alpha]_D^{20}$ = +54.3 (c = 0.55 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 8.59 (d, J = 4.6 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 4.5 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.42–6.98 (m, 9H), 6.80–6.30 (m, 1H), 5.40–5.03 (m, 3H), 4.67 (s, 4H), 3.93 (dd, J = 8.9 Hz, J = 11.8 Hz, 1H), 3.77–3.56 (m, 0.5H), 3.43 (t, J = 11.4 Hz, 1H), 3.25–2.82 (m, 1H), 2.54–2.24 (m, 0.5H), 1.96–1.50 (m, 6H), 1.20–1.06 (m, 1H), 0.93 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 161.0, 160.4, 159.6, 159.2, 158.7, 158.7, 158.1, 147.5, 146.9, 146.0, 145.8, 144.1, 142.7, 137.3, 137.0, 136.8, 136.3, 133.5, 133.4, 129.7, 129.6, 129.6, 129.5, 129.3, 129.3, 128.9, 128.8, 128.2, 128.0, 127.7, 125.8, 125.7, 125.5, 124.3, 124.2, 123.5, 123.1, 122.1, 121.9, 121.8, 121.7, 70.7, 70.4, 69.3, 68.9, 68.3, 67.9, 65.2, 62.0, 61.6, 61.2, 51.9, 51.6, 26.4, 26.3, 26.1, 25.3, 24.6, 24.5, 22.2, 18.8, 18.4, 18.4, 17.9, 11.8 ppm; HRMS $[C_{35}H_{38}N_4O_6+H]^+$: calcd: 611.2870; found: 611.2866.

General procedure for the amination of 2-naphthols: The catalyst (DBU for racemates; 0.04 mmol, 0.2 equiv) was added to naphthol **4** (0.20 mmol) in a 4 mL vial, and then everything was dissolved in 1,2-dichloroethane (4.0 mL, 0.05 M). The vial was closed with a screw lid and put into a freezer at −20 °C, where the solution was stirred for at least 30 min. After this period the D*t*BuAD (**5b**; 46 mg, 0.20 mmol) was added and the solution stirred overnight. The product was purified by FC.

N-*(8-Amino-2-hydroxy-1-naphthyl)hydrazine*-N,N′*-dicarboxylic acid* tert*-butyl ester (**3b**)*: The title compound was prepared according to the general procedure by using 8-amino-2-naphthol (**4b**; 32 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/$Et_2$0 = 75:25 gave the product (68 mg, 87 %). R_f = 0.38 (pentane/$Et_2$0 50:50); $[\alpha]_D^{20}$ = −64.3 (c = 2.0 in $CDCl_3$, sample with 84 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 9.39 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 3.88 (s, 2H), 1.48/1.39 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 157.6, 154.4, 152.1, 139.0, 131.0, 130.8, 123.3, 121.9, 119.4, 116.4, 82.7, 82.6, 28.1, 27.9 ppm; HRMS: m/z: calcd: 412.1848; found: 412.1840 $[C_{20}H_{27}N_3O_5+Na]^+$; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 80:20); flow rate: 1.0 mL min^{-1}; τ_{major} = 5.8 min, τ_{minor} = 7.5 min.

N-*(8-Methylamino-2-hydroxy-1-naphthyl)hydrazine*-N,N′*-dicarboxylic acid* tert*-butyl ester (**3c**)*: The title compound was prepared according to the general procedure by using 8-methylamino-2-naphthol (**4c**; 35 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/$Et_2$0 80:20 gave the product (74 mg, 91 %). R_f = 0.35 (pentane/$Et_2$0 50:50); $[\alpha]_D^{20}$ = −71.2 (c = 1.0 in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 9.16 (br s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.32 (s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.25–7.00 (m, 2H), 6.81 (d, J = 7.4 Hz, 1H), 4.35 (br s, 1H), 2.95 (s, 3H), 1.50/1.45 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 157.6, 154.4, 152.5, 143.5, 131.3, 131.2, 130.9, 123.7, 120.6, 119.3, 109.9, 83.0, 82.8, 32.7, 28.2, 28.0 ppm; HRMS $[C_{21}H_{29}N_3O_5+Na]^+$: calcd: 426.2005; found: 426.2014; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 90:10); flow rate: 1.0 mL min^{-1}; τ_{minor} = 6.5 min, τ_{major} = 7.9 min.

N-*(8-Benzylamino-2-hydroxy-1-naphthyl)hydrazine*-N,N′*-dicarboxylic acid* tert*-butyl ester (**3d**)*: The title compound was prepared according to the general procedure by using 8-benzylamino-2-naphthol (**4d**; 50 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/$Et_2$0 75:25 gave the product (88 mg, 92 %). R_f = 0.27 (pentane/$Et_2$0 50:50); $[\alpha]_D^{20}$ = −58.6 (c = 0.50 in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 9.19 (s, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.50–7.40 (m, 4H), 7.40–7.30 (m, 2H), 7.30–7.19 (m, 3H), 6.86 (d, J = 7.5 Hz, 1H), 4.59 (br s, 1H), 4.37 (d, J = 12.8 Hz, 2H), 1.50 (s, 9H), 1.34 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 157.7, 153.7, 152.8, 142.3, 139.2, 131.3, 131.2, 131.0, 128.9, 128.0, 127.6, 124.4, 123.5, 123.4, 120.9, 120.4, 119.4, 110.7, 82.8, 82.6, 50.1, 28.2, 27.8 ppm; HRMS: m/z: calcd: 502.2318; found: 502.2314 $[C_{27}H_{33}N_3O_5+Na]^+$; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 85:15); flow rate: 1.0 mL min^{-1}; τ_{minor} = 7.0 min, τ_{major} = 7.8 min.

N-*(8-(2,2-Dimethylpropylamino)-2-hydroxy-1-naphthyl)hydrazine*-N,N′*-dicarboxylic acid* tert*-butyl ester (**3e**)*: The title compound was prepared according to the general procedure by using 8-(2,2-dimethylpropylamino)-2-naphthol (**4e**; 46 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/$Et_2$0 90:10 gave the product (87 mg, 95 %). R_f = 0.40 (pentane/$Et_2$0 50:50); $[\alpha]_D^{20}$ = −100.0 (c = 0.92 in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 9.28 (s, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.63/7.46 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.26–7.18 (m, 2H), 6.81 (d, J = 7.4 Hz, 1H), 4.43 (s, 1H), 3.10–2.96 (m, 1H), 2.88 (d, J = 10.7 Hz, 1H), 1.58 (s, 1H), 1.47 (s, 9H), 1.41 (s, 5H), 1.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 157.4, 153.9, 151.8, 143.2, 131.4, 131.1, 130.7, 123.7, 120.4, 120.0, 119.5, 109.6, 109.1, 83.0 57.9, 57.7, 31.0, 28.1, 27.9 ppm; HRMS: m/z: calcd: 482.2631; found: 482.2599 $[C_{25}H_{37}N_3O_5+Na]^+$; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 98:2); flow rate: 1.0 mL min^{-1}; τ_{major} = 6.3 min, τ_{minor} = 7.6 min.

N-*(8-(2′-Hydroxybenzylamino)-2-hydroxy-1-naphthyl)hydrazine*-N,N′*-dicarboxylic acid* tert*-butyl ester (**3f**)*: The title compound was prepared according to the general procedure by using 8-(2-hydroxybenzylamino)-naphthalen-2-ol (**4f**; 53 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/$Et_2$0 85:15 gave the product (94 mg, 95 %) of product. R_f = 0.20 (pentane/$Et_2$0 50:50); $[\alpha]_D^{20}$ = +22.0 (c = 1.48 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.69 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 7.7 Hz, 1H), 7.26–7.18 (m, 3H), 6.95–6.89 (m, 3H), 4.51 (d, J = 12.4 Hz, 1H), 4.30 (d, J = 12.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 1H), 1.50 (s, 9H), 1.27 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 157.9, 155.2, 154.6, 152.6, 131.4, 131.3, 130.9, 129.9, 129.0, 124.7, 123.6, 121.1, 120.7, 119.1, 116.3, 111.1, 82.9, 82.7, 47.1, 28.2, 27.8 ppm; HRMS: m/z: calcd: 518.2267; found: 518.2278 $[C_{27}H_{33}N_3O_6+Na]^+$; the *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; τ_{major} = 17.6 min, τ_{minor} = 20.5 min.

N-*(8-Amino-5,7-dibromo-2-hydroxy-1-naphthyl)hydrazine*-N,N′*-dicarboxylic acid* tert*-butyl ester (**3g**)*: The title compound was prepared according to the general procedure by using 8-amino-5,7-dibromo-2-naphthol (**4g**; 63 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/$Et_2$0 75:25 gave the product (91 mg, 85 %). R_f = 0.30 (pentane/$Et_2$0 50:50); $[\alpha]_D^{20}$ = −56.0 (c = 4.10 in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ =

9.66 (s, 1H), 8.14 (d, $J=9.3$ Hz, 1H), 7.71 (s, 1H), 7.38 (s, 1H), 7.34 (d, $J=9.3$ Hz, 1H), 4.43 (s, 2H), 1.48 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta=157.8$, 153.9, 149.6, 143.1, 139.9, 136.7, 130.6, 130.3, 127.4, 125.5, 122.8, 122.3, 121.1, 113.9, 85.1, 83.5, 28.1, 28.0, 27.9 ppm; HRMS: *m/z*: calcd: 570.0038; found: 570.0074 $[C_{20}H_{25}{}^{79}Br^{80}BrN_3O_5+Na]^+$; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 90:10); flow rate: 1.0 mL min^{-1}; $\tau_{minor}=3.6$ min, $\tau_{major}=4.1$ min.

N-*(8-(Carbamic acid* tert*-butyl ester)-2-hydroxy-1-naphthyl)hydrazine-*N,N′*-dicarboxylic acid* tert*-butyl ester, (**3h**)*: The title compound was prepared according to the general procedure by using (7-hydroxy-naphthalen-1-yl)carbamic acid *tert*-butyl ester (**4h**; 52 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). Elution with pentane/Et_20 67:33 gave the product (92 mg, 94 %). $R_f=0.31$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=+1.7$ ($c=0.62$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): $\delta=9.64$ (br s, 1H), 7.74 (d, $J=8.9$ Hz, 1H), 7.67 (d, $J=8.2$ Hz, 1H), 7.54–7.48 (m, 1H), 7.39 (br s, 1H), 7.28 (t, $J=7.8$ Hz, 1H), 7.23 (d, $J=9.0$ Hz, 1H), 6.56 (br s, 1H), 1.61 (s, 9H), 1.57–1.40 ppm (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta=137.8$, 131.6, 131.4, 130.7, 129.1, 129.0, 128.2, 125.2, 122.9, 119.6, 86.8, 82.8, 82.6, 81.1, 28.3, 28.1, 27.7 ppm; HRMS: *m/z*: calcd: 512.2373; found: 512.2368 $[C_{25}H_{35}N_3O_7+Na]^+$; the *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; $\tau_{minor}=11.3$ min, $\tau_{major}=14.1$ min.

N-*(8-Chloro-2-hydroxy-1-naphthyl)hydrazine-*N,N′*-dicarboxylic acid* tert*-butyl ester (**3i**)*: The title compound was prepared according to the general procedure by using 8-chloro-2-naphthol (**4h**; 36 mg, 0.20 mmol) and **8b** (22 mg, 0.04 mmol). The reaction was stirred for 8 d at −20 °C without reaching full conversion by TLC. Elution with pentane/Et_20 91:9 gave the product (47 mg, 57 %). $R_f=0.70$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=+15.6$ ($c=0.58$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta=10.17/10.05$ (s, 1H), 7.77/7.76 (d, $J=9.0$ Hz, 1H), 7.69/7.68 (dd, $J=1.2$ Hz, $J=8.0$ Hz, 1H), 7.54/7.51 (dd, $J=1.2$ Hz, $J=8.5$ Hz, 1H), 7.29/7.28 (d, $J=9.0$ Hz, 1H), 7.20/7.18 (t, $J=8.1$ Hz, 1H), 6.98/6.96 (s, 1H), 1.54/1.53/1.52/1.28 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta=159.2$, 158.7, 155.6, 155.0, 154.4, 131.9, 131.5, 131.0, 130.7, 130.3, 130.1, 128.7, 128.5, 128.0, 127.7, 125.6, 125.4, 123.0, 122.9, 120.1, 119.0, 83.5, 83.3, 82.6, 82.4, 28.1, 28.1, 27.8 ppm; HRMS: *m/z*: calcd: 431.1350; found: 431.1348 $[C_{20}H_{25}ClN_2O_5+Na]^+$; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 99:1); flow rate: 1.0 mL min^{-1}; $\tau_{minor}=8.3$ min, $\tau_{major}=10.0$ min.

Michael additions

*1-(2-[1,3]Dioxolan-2-yl-ethyl)-2-oxocyclopentanecarboxylic acid ethyl ester (**19**)*: Catalyst **8b** (27 mg, 0.05 mmol, 0.1 equiv) and iodobenzene (2.5 mL) were added to ethyl-2-oxocyclopentanone carboxylate (**16**; 74 μL, 0.50 mmol) in a 4 mL vial, and the solution was stirred for 30 min. Acrolein (**17**; 67 μL, 1.0 mmol, 2.0 equiv) was then added and the solution was stirred for a further 1 h at room temperature. After this time, TLC control showed full conversion and the reaction mixture was purified over a short silica plug, eluting with Et_2O. The Et_2O was evaporated and then 2-ethyl-2-methyl-1,3-dioxolane (75 μL, 0.6 mmol, 1.2 equiv) and *p*-toluolsulfonic acid (19 mg, 0.1 equiv) were added. The solution was stirred for 4 h, until GC control showed full conversion and the raw product was then purified by FC. Elution with pentane/Et_20 50:50 gave the product (92 mg, 87 %). $R_f=0.14$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=-14.3$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta=4.77$ (t, $J=4.4$ Hz, 1H), 4.08 (q, $J=7.1$ Hz, 2H), 3.90–3.82 (m, 2H), 3.81–3.73 (m, 2H), 2.48–2.40 (m, 1H), 2.39–2.29 (m, 1H), 2.24–2.13 (m, 1H), 2.01–1.77 (m, 4H), 1.73–1.56 (m, 2H), 1.45–1.55 (m, 1H), 1.17 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta=214.5$, 170.7, 103.8, 64.7, 61.2, 59.6, 37.7, 32.8, 29.0, 27.5, 19.4, 13.9 ppm; HRMS: *m/z*: calcd: 279.1208; found: 279.1207 $[C_{13}H_{20}O_5+Na]^+$; the *ee* was determined by GC analysis using an Astec G-TA column (70 °C to 180 °C, 10 °C min^{-1}, then 20 min 180 °C): $\tau_{minor}=21.6$ min, $\tau_{major}=21.8$ min.

*2-Oxo-1-(3-oxobutyl)cyclopentanecarboxylic acid ethyl ester, (**21**)*: Catalyst **8b** (7 mg, 0.013 mmol, 0.1 equiv) and iodobenzene (0.8 mL) were added to ethyl-2-oxocyclopentanone carboxylate (**16**; 20 μL, 0.128 mmol) in a 4 mL vial, and the solution was stirred for 30 min. Methyl vinyl ketone (**20**; 21 μL, 0.256 mmol, 2 equiv) was then added and the solution stirred for 21 h at room temperature. After this time, TLC control showed full conversion and the reaction mixture was purified by FC. Elution with pentane/Et_20 80:20 to 50:50 gave the product (29 mg, quant. yield). $R_f=0.25$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=-4.4$ ($c=1.41$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta=4.14$ (dq, $J=0.8$ Hz, $J=7.1$ Hz, 2H), 2.68 (ddd, $J=5.7$ Hz, $J=9.6$ Hz, $J=17.8$ Hz, 1H), 2.36 (m, 1H), 2.11 (s, 1H), 2.07 (m, 1H), 1.92 (m, 4H), 1.22 ppm (t, $J=7.1$ Hz, 3H). The *ee* was determined by GC using an Astec G-TA column (70 °C to 170 °C, 10 °C min^{-1}, then 10 min 170 °C): $\tau_{minor}=16.5$ min, $\tau_{major}=16.7$ min. The spectroscopic data were in agreement with the literature.[54]

*2-Oxo-1-(3-oxopropyl)cyclohexanecarboxylic acid ethyl ester (**23**)*: The catalyst **8b** (7 mg, 0.013 mmol, 0.1 equiv) and iodobenzene (0.8 mL) were added to ethyl-2-oxocyclohexanone carboxylate (**22**; 20 μL, 0.128 mmol) in a 4 mL vial, and the solution was stirred for 30 min. Then acrolein **17** (17 μL, 0.256 mmol, 2 equiv) was added and the solution stirred for 16 h at room temperature. After this time, TLC control showed full conversion and the reaction mixture was purified by FC. Elution with pentane/Et_20 80:20 to 50:50 gave the desired product (26 mg, 91 %). $R_f=0.22$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=+81.7$ ($c=0.86$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta=9.72$ (s, 1H), 4.22–4.16 (m, 2H), 2.62–2.56 (m, 5H), 2.17–2.16 (m, 1H), 2.04–1.97 (m, 1H), 1.91–1.84 (m, 1H), 1.76–1.75 (m, 1H), 1.65–1.59 (m, 1H), 1.48–1.44 (m, 1H), 1.26 ppm (t, $J=7.2$ Hz, 3H); the *ee* was determined by GC using an Astec G-TA column (70 °C to 170 °C, 10 °C min^{-1}, then 25 min 170 °C): $\tau_{minor}=18.1$ min, $\tau_{major}=18.5$ min. The spectroscopic data were in agreement with the literature.[55]

General procedure for the α-fluorination of α-branched aldehydes 24: The catalyst (0.1 equiv), hexane (0.9 mL) and *i*PrOH (0.1 mL) were added to the α-branched aldehyde **24** (0.50 mmol) in a 4 mL vial. After 30 min stirring at 2 °C, NFSI **25** (189 mg, 0.60 mmol, 1.2 equiv) was added and the reaction mixture stirred overnight.

Workup A: The mixture was filtered and the residue rinsed with hexane. The solvents were evaporated.

Workup B: The mixture was diluted with Et_2O and washed with saturated NH_4Cl/KI solution. The aqueous phase was extracted with Et_2O and the combined organic phases washed with sat. $Na_2S_2O_3$ solution, sat. Na_2CO_3 solution and sat. NaCl solution. The solvents were evaporated after drying over Na_2SO_4.

Reduction: The raw aldehyde **26** was dissolved in MeOH and $NaBH_4$ (2.0 equiv) was added. After full conversion was detected by TLC, $KHSO_4$ solution (1 M) and CH_2Cl_2 were added and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by FC.

*2-Fluoro-2-phenylpropan-1-ol (**29a**)*: The title compound was prepared according to the general procedure by using 2-phenylpropanal (**24a**; 67 mg, 0.50 mmol) and workup procedure A. Elution with pentane/Et_20 75:25 gave the product (28 mg, 36 %). $R_f=0.39$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=+10.4$ ($c=0.51$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta=$ 7.39–7.32 (m, 5H); 3.89–3.70 (m, 2H); 1.85 (b, 1H); 1.70 ppm (d, $J=$ 22.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta=141.4$ (d, $J=$ 21.7 Hz); 128.4 (d, $J=1.5$ Hz); 124.4 (d, $J=9.2$ Hz); 97.9 (d, $J=172$ Hz); 69.6 (d, $J=25.1$ Hz); 23.1 ppm (d, $J=24.4$ Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20 °C): $\delta=-157.6$ ppm; HRMS: *m/z*: calcd: 177.0692; found: 177.0671 $[C_9H_{11}FO+Na]^+$; the *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; $\tau_{major}=$ 12.6 min, $\tau_{minor}=14.3$ min.

*2-Fluoro-2-(4′-nitrophenyl)propan-1-ol (**29c**)*: The title compound was prepared according to the general procedure and workup procedure B by using 2-(4′-nitrophenyl)propanal (**24c**; 90 mg, 0.50 mmol), which could only be obtained in 75 % purity, the impurity being 4-nitroacetophenone. Elution with pentane/Et_20 75:25 to 50:50 gave the product (67 mg, 56 %). $R_f=0.14$ (pentane/Et_20 50:50); $[\alpha]_D^{20}=-8.7$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): $\delta=8.25$ (d, $J=8.9$ Hz, 2H), 7.55 (d, $J=8.9$ Hz, 2H), 3.86 (dd, $J=2.6$ Hz, ^3J(H,F)$=21.0$ Hz, 2H), 1.85 (br s, 1H), 1.72 ppm (d, ^3J(H,F)$=22.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): $\delta=148.8$ (d, $J=22.0$ Hz), 147.2, 125.6 (d, $J=9.9$ Hz), 123.5, 97.5 (d, $J=$ 175 Hz), 68.8 (d, $J=24.8$ Hz), 23.1 ppm (d, $J=24.4$ Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20 °C): $\delta=-158.2$ ppm; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 90:10); flow rate: 1.0 mL min^{-1}; $\tau_{minor}=13.5$ min, $\tau_{major}=15.2$ min.

*2-Fluoro-2-(4′-bromophenyl)propan-1-ol (**29d**)*: The title compound was prepared according to the general procedure by using 2-(4′-bromophenyl)propanal (**24d**; 107 mg, 0.50 mmol) and workup procedure A. Elution with pentane/Et_2O 80:20 gave the product (70 mg, 60%). R_f=0.20 (pentane/Et_2O 50:50); $[\alpha]_D^{20}$=−12.4 (c=0.70 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=7.50 (d, J=8.5 Hz, 2H), 7.23 (d, J=8.3 Hz, 2H), 3.84–3.66 (m, 2H), 2.16 (s, 1H), 1.66 ppm (d, ^3J(H,F)=22.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=140.5 (d, J=22.1 Hz), 131.5 (d, J=1.3 Hz), 126.3 (d, J=9.3 Hz), 121.9 (d, J=1.5 Hz), 97.5 (d, J=173 Hz), 69.2 (d, J=25.0 Hz), 23.0 ppm (d, J=24.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20°C): δ=−157.8 ppm; the *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate: 1.0 mL min^{-1}; τ_{major}=13.8 min, τ_{minor}=18.1 min.

*1-Fluoro-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**26e**)*: The title compound was prepared according to the general procedure by using 1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**24e**; 80 mg, 0.50 mmol). After the reaction was finished, saturated $NaHCO_3$ solution was added to the reaction mixture. The aqueous phase was extracted with Et_2O, the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by FC. Elution with pentane/Et_2O 30:1 gave the product (49 mg, 55%). The product contained 5% of the starting aldehyde. R_f=0.50 (pentane/Et_2O 6:1); $[\alpha]_D^{20}$=−9.1 (c=1.06 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C) δ=9.71 (d, ^3J(F,H)=6.0 Hz, 1H), 7.23–7.11 (m, 5H), 2.81–2.66 (m, 2H), 2.16–2.04 (m, 2H), 1.84–1.02 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C) δ=197.9 (d, J=38.8 Hz), 138.9 (d, J=3.9 Hz), 129.6 (d, J=3.0 Hz), 129.6, 128.5 (d, J=4.0 Hz), 126.7 (d, J=2.3 Hz), 95.5 (d, J=182 Hz), 29.5 (d, J=21.0 Hz), 28.8, 18.4 ppm (d, J=2.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20°C): δ=−142.3 ppm; the *ee* was determined by GC using a Astec G-TA column (70°C to 130°C, 5°C min^{-1}, then 20 min 130°C): τ_{minor}=19.2 min, τ_{major}=19.7 min.

*2-Ethyl-2-fluorohexan-1-ol (**29f**)*: The title compound was prepared according to the general procedure by using 2-ethylhexanal (**24f**; 78 μL, 0.50 mmol) and workup procedure B. After 24 and 48 h another 0.1 equivalents of catalyst were added. Elution with pentane/Et_2O 85:15 gave the product (20 mg, 27%). R_f=0.41 (pentane/Et_2O 50:50); $[\alpha]_D^{20}$=+1.3 (c=0.45 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=3.60 (d, ^3J(H,F)=20.7 Hz, 2H), 1.87 (brs, 1H), 1.74–1.59 (m, 4H), 1.38–1.24 (m, 4H), 0.93–0.87 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=99.8 (d, J=168 Hz), 66.1 (d, J=24.0 Hz), 32.7 (d, J=22.4 Hz), 26.1 (d, J=23.3 Hz), 25.3 (d, J=6.6 Hz), 23.1, 14.0, 7.60 ppm (d, J=8.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20°C): δ=−161.6 ppm; HRMS of the 4-bromobenzoylhydrazone: calcd: 365.0641; found: 365.0655 $[C_{15}H_{20}{}^{79}BrFN_2O+Na]^+$, calcd: 367.0621; found: 367.0618 $[C_{15}H_{20}{}^{81}BrFN_2O+Na]^+$; the *ee* was determined by GC using a Astec G-TA column (70°C to 100°C, 10°C min^{-1}, then 20 min 100°C): τ_{minor}=8.8 min, τ_{major}=9.0 min.

*2-Fluoro-3-(4′-isopropylphenyl)-2-methyl-propan-1-ol (**29g**)*: The title compound was prepared according to the general procedure by using 2-methyl-3-(4′-isopropylphenyl)propanal (**24g**; 100 μL, 0.50 mmol) and workup procedure B. Elution with pentane/Et_2O 75:25 gave the product (30 mg, 29%). R_f=0.40 (pentane/Et_2O 50:50); $[\alpha]_D^{20}$=+9.1 (c=1.45 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=7.17 (s, 4H), 3.59 (d, J=19.6 Hz, 2H), 2.99–2.84 (m, 3H), 1.90 (brs, 1H), 1.28 (d, J=21.5 Hz, 3H), 1.25 ppm (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=147.2, 133.2 (d, J=5.9 Hz), 130.3, 126.3, 97.4 (d, J=170 Hz), 67.5 (d, J=23.8 Hz), 41.9 (d, J=22.9 Hz), 33.7, 24.0, 20.9 ppm (d, J=23.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20°C): δ=−154.6 ppm; HRMS: m/z: calcd: 233.1318; found: 233.1323 $[C_{13}H_{19}FO+Na]^+$; the *ee* was determined by HPLC using a Chiralcel OJ column (hexane/*i*PrOH 99:1); flow rate: 1.0 mL min^{-1}; τ_{minor}=16.7 min, τ_{major}=19.5 min.

*2-Cyclohexyl-2-fluoropropan-1-ol (**29h**)*: The title compound was prepared according to the general procedure by using 2-cyclohexylpropanal (**24h**; 71 mg, 0.50 mmol) and workup procedure A. Elution with pentane/Et_2O 85:15 gave the desired product (8 mg, 10%). R_f=0.30 (pentane/Et_2O 50:50); $[\alpha]_D^{20}$=−15.0 (c=0.32 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ=3.73–3.52 (m, 2H), 1.84–1.64 (m, 5H), 1.23 (d, ^3J(H,F)=22.8 Hz, 3H), 1.28–1.11 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ=99.9 (d, J=168 Hz), 66.9 (d, J=23.4 Hz), 42.9 (d, J=21.2 Hz), 27.7 (d, J=7.7 Hz), 26.4, 26.3, 26.2, 17.6 ppm (d, J=24.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, 20°C): δ=−158.1 ppm; the *ee* was determined by GC using a Astec G-TA column (70°C to 100°C, 8°C min^{-1}, then 25 min 100°C): τ_{minor}=22.1 min, τ_{major}=23.9 min.

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