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2,2′-Bipyridine-3,3′-dicarboxylic carbohydrate esters and amides. Synthesis and preliminary evaluation as ligands in Cu(II)-catalysed enantioselective electrophilic fluorination

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ABSTRACT

A series of 10 new carbohydrate-substituted bipyridines were prepared from 2,2′-bipyridine-3,3′-dicarboxylic acid, itself easily available from *ortho*-phenanthroline. As a preliminary exploration of their use as chiral ligands, Cu(II)-catalysed asymmetric electrophilic fluorination of model β-ketoesters using these simple and easily accessible chiral bipyridines was studied. Only modest enantioselectivity was observed in this reaction, although the ee was in a similar range as those provided by known and more elaborate ligands.

1. Introduction

Carbohydrates are an inexpensive and natural source of chirality, which have demonstrated their efficiency in chirality control for a long time, either as chiral appendages inducing diastereofacial selectivity, as organocatalysts, or as chiral ligands in metallic complexes.[1] Among ligands, bipyridines are important systems due to their ability to efficiently complex metals by multifold bonding, notably for Cu cations.[2] However, only very few examples of carbohydrate bipyridinic systems have been reported in the literature (Scheme 1). These compounds were designed for bringing sugars close to metallic centres in Fe, Cu, Re, Tc, or Zn complexes, for applications towards molecular recognition (sugar–protein interactions),[3] asymmetric catalysis,[4] or fluorescence by radiolabelled systems.[5] Cyclodextrin bipyridine hybrids were also reported.[6]

Surprisingly, the readily available synthon 2,2′-bipyridine-3,3′-dicarboxylic acid **6**, which is commercially available or can be obtained in one step by simple permanganate oxidation of *ortho*-phenanthroline,[7] has never been used for preparing carbohydrate-substituted bipyridinic systems.

The purpose of the present paper is to describe the synthesis of a series of new monosaccharidic esters and amides of 2,2′-bipyridine-3,3′-dicarboxylic acid and to report a preliminary evaluation of their uses as chiral ligands in the copper(II)-catalysed asymmetric electrophilic fluorination.

2. Synthesis of bipyridine sugar diesters

The easily available 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (also referred to as diacetone glucose or DAG) was used as the first substrate. The ability of the bipyridine diacid **6** to provide the corresponding diester **7** proved to be rather low, either by reaction with the acid chloride derived from **6** or by direct coupling using EDCI/DMAP (Scheme 2).[8] Both the alcohol function in DAG and the carboxylic acids in **6** suffer from steric hindrance, explaining the moderate reactivity. Ester formation in **7** was confirmed by the characteristic CO band in the IR spectrum of diester **7** (ν(C=O) = 1732 cm^{-1}) and the typical shift downfield (+0.9 ppm) of H-3 (δ = 5.27 ppm) in the ^{1}H NMR spectrum compared to DAG. The EDCI/DMAP system, slightly more efficient and simpler to be set up, was then used for preparing the four other carbohydrate diesters **8**–**11** (Scheme 2). With the goal of having a change only at the chiral centre where the sugar and the bipyridine are connected, 1,2,5,6-di-*O*-isopropylidene-α-D-allofuranose, the epimer at C-3 of DAG, was used. The corresponding diester **8** was obtained in a significantly better yield (50%) than **7**, revealing an easier access to OH-3 in the *allo* substrate more likely to adopt a pseudo-equatorial position. Indeed, in the ^{1}H NMR spectrum of the allose derivative, the coupling constant between H-3 and H-4 ($J_{3,4}$ = 8.8 Hz) reflects a relationship close to a trans diaxial one,

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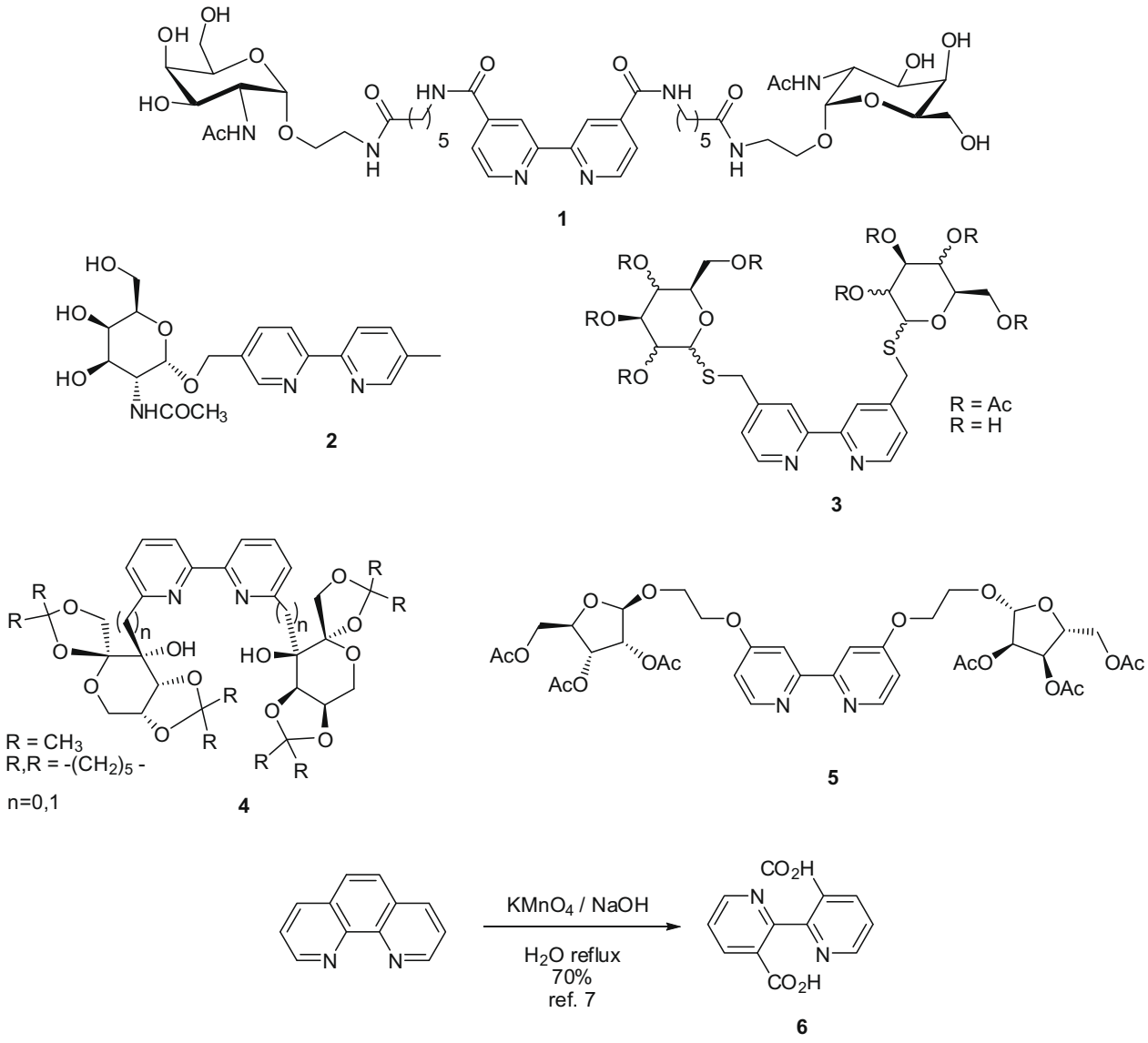


Scheme 1. Bipyridine carbohydrate systems.

allowing both substituents to stay in pseudo-equatorial positions, exactly as in the starting alcohol.[9] In contrast, for the glucose system ($J_{3,4}$ = 2.8 Hz) both substituents have to accommodate a *cis* relationship, making the reaction slower. The other diesters **9–11**, connected at primary positions of sugars, were prepared directly from fructose, ribose or partially protected galactose derivatives. Though not optimised, the moderate yields are largely balanced by the cheapness and the availability of the starting materials. Moreover, unreacted sugar substrates were easily recovered at the purification stage.

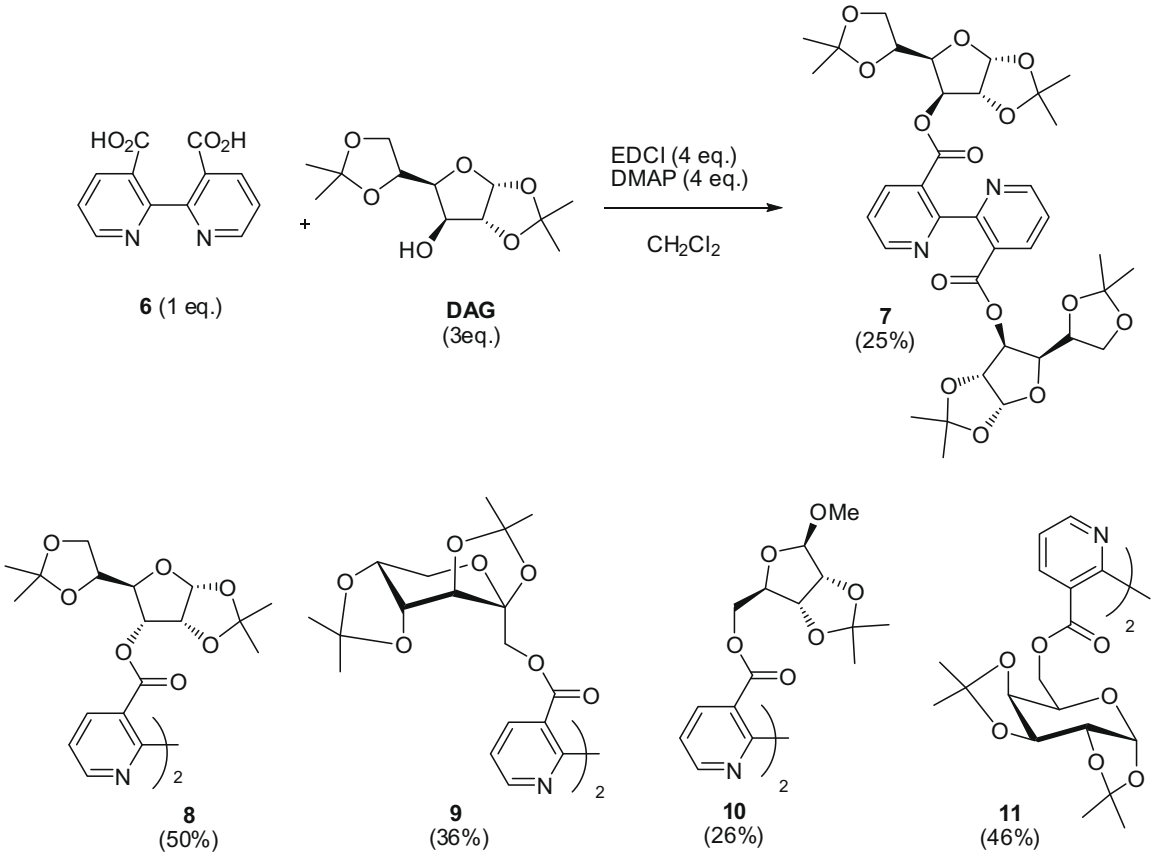
3. Synthesis of bipyridine sugar diamides

We then turned to the synthesis of amides in order to prepare bipyridine-carbohydrate hybrids with increased chemical stability than esters (Scheme 3). In the case of secondary amines (deoxyaminosugars obtained from the corresponding azidodeoxy sugars by hydrogenation), the diamides were prepared by coupling with diacid **6** using the HOBt/EDCI system. Chiral diamides **12** and **13**, derived from glucofuranose and allofuranose, and having a carbohydrate backbone that is exactly the same as that in diesters **7** and **8**, were obtained in 47% and 30% yields, respectively. The same procedure was applied to a glucosamine derivative, namely 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-amino-β-D-glucopyranose, leading to diamide **14** in 24% yield. The formation of the amide linkage was confirmed by the observation of H-3–NH couplings in the proton NMR spectra for gluco- and allofuranose derivatives **12** and **13** (J = 7.7 Hz and 9.2 Hz, respectively), and of H-2–NH coupling (J = 8.8 Hz) for the glucosamine-based amide **14**.

Two more diamides, substituted on primary position C-1 of fructose **15** and C-6 of galactose **16**, analogous to esters **9** and **11**, were then prepared. In this case, the shorter route, which directly converts the primary azidodeoxy substrate to the corresponding amide under Staudinger-Vilarrasa conditions,[10] led to the desired diamides in 21% and 26% yields, respectively. Trials for applying the latter method towards secondary systems **12–14** proved to be significantly less efficient than the amine-acid coupling using the HOBt/EDCI system.

4. Evaluation of the new bipyridine-carbohydrate hybrids as chiral ligands

The new bipyridine-carbohydrate diesters and diamides were then used in a preliminary investigation of their ability to complex



Scheme 2. Bipyridine sugar diesters **7**–**11**.

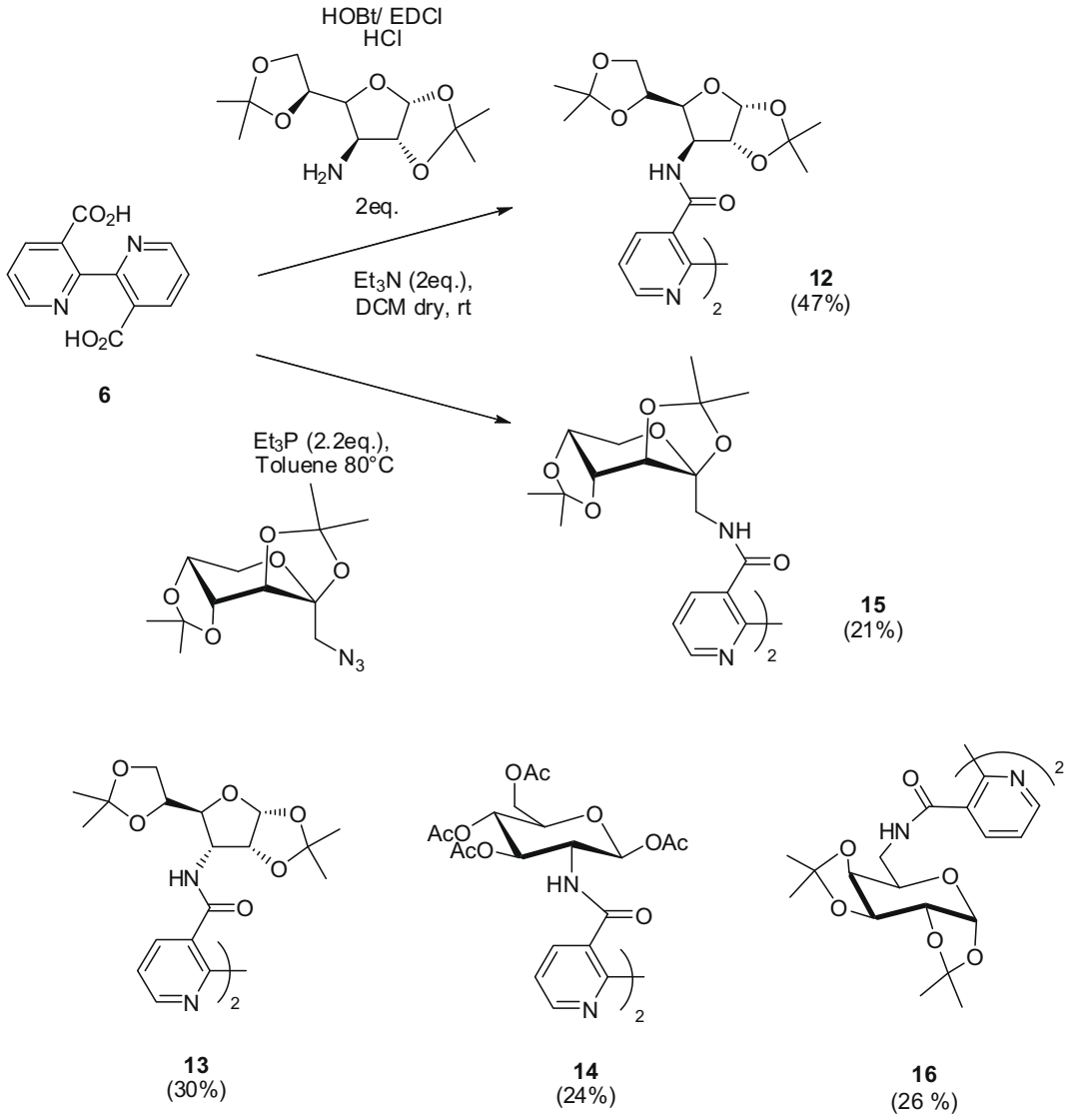
metallic species within the context of electrophilic fluorination. This reaction has become a classical tool in the optimisation process of bioactive compounds,[11] since it often increases the metabolic resistance[12] and the lipophilicity[13] of the molecules, thus contributing to the improvement of pharmacokinetic properties of potential lead drugs.[14] Indeed, due to the high electronegativity and the specific properties of the fluorine atom and the specific physico-chemical properties of fluorinated organic compounds in a wide range of applications (fluoropolymers, pharmaceutical and agrochemical products, material science, etc.), organofluorine chemistry has attracted considerable interest.[13–17] One of the methods for introducing a fluorine atom is the use of reagents that behave as 'F$^+$' species,[18] and since the pioneering work of Differding et al. 20 years ago,[19] various stereoselective versions of this reaction have been reported.[11c,20] Indeed, chirality in drugs can originate from stereogenic centres bearing fluorine atoms, as, for example, in Fluticasone, or Flindokalner (post-stroke neuroprotection)[21,22] and in GSK-23A (hypoglycemia agents),[23] two compounds under development. Two approaches can be distinguished, one based on the use of chiral fluorinating agents,[19,24] and the second involving chiral catalysts (metal catalysis or organocatalysis), associated with achiral and commercially available electrophilic fluorinating reagents.[16,25–27] Only one report of bipyridine/Cu-mediated enantioselective C–F bond formation has yet been published by Shibata et al. who used DNA as a chiral ligand.[28] In keeping with catalysis with bipyridine complexes of copper(II), we studied the Cu(II)-mediated asymmetric fluorination of some β-keto esters in the presence of our new bipyridinic systems.

The ability of the 2,2′-bipyridine-3,3′-dicarboxylic scaffold to catalyse the fluorination of β-ketoesters with *N*-fluoro-bis-(benzenzesulfonyl)imide (NFSI) as a fluorinating agent was first checked in the case of the simpler methyl diester **17**[7] (prepared using the method that is same as that used for the sugar ones), and two β-ketoesters, a linear one **18** and a cyclic one **19** (Scheme 4). Two other fluorinating agents were also used, namely 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), also called 'Selectfluor®', and *N,N*′-difluoro-2,2′-bipyridinium bis-(tetrafluoroborate). However, NFSI proved to provide faster and higher yielding reactions (Scheme 4), giving fluorinated β-ketoesters **20** and **21** in 61% and 64% yields, respectively.

The new carbohydrate bipyridine hybrids were then used in the same reaction, using ketoester **18** and **19** as well as the benzyltetralone substrate **22** (Scheme 5, Table 1). Chiral diesters were evaluated first, giving good yields of fluorinated compounds **20**, **21** and **23**. In terms of enantioselectivity, the results were compared to those arising from other chiral systems: a bipyridine dicarboxylic ester derived from (−) menthol **24** (prepared by the same method) and two bis-oxazolines, Box 1 and Box 2, known as efficient chelates for Cu(II) already used in asymmetric electrophilic fluorination.[26]

Glucofuranose derivative **7** gave modest enantiomeric excesses (up to 27% ee) that were comparable to those obtained with Box 1 (32% ee) under exactly the same conditions. It should be noted that the latter Box ligands can give excesses up to 85% in other conditions, notably using more constrained substrates.[26] Also, better results were reported using ether results in Et_2O as solvent, though in the case of the new bipyridine ligands described here, no improvement of the ee was observed compared to CH_2Cl_2. With the allofuranose derivative **8**, a reversal of the enantioselectivity was observed, in a modest though significant pseudo-enantiomeric effect.

The influence of temperature and of the metal was investigated in the case of the reactions of ketoester **19** using ligand **7** (Tables 2



Scheme 3. Synthesis of diamides **12**–**16**.

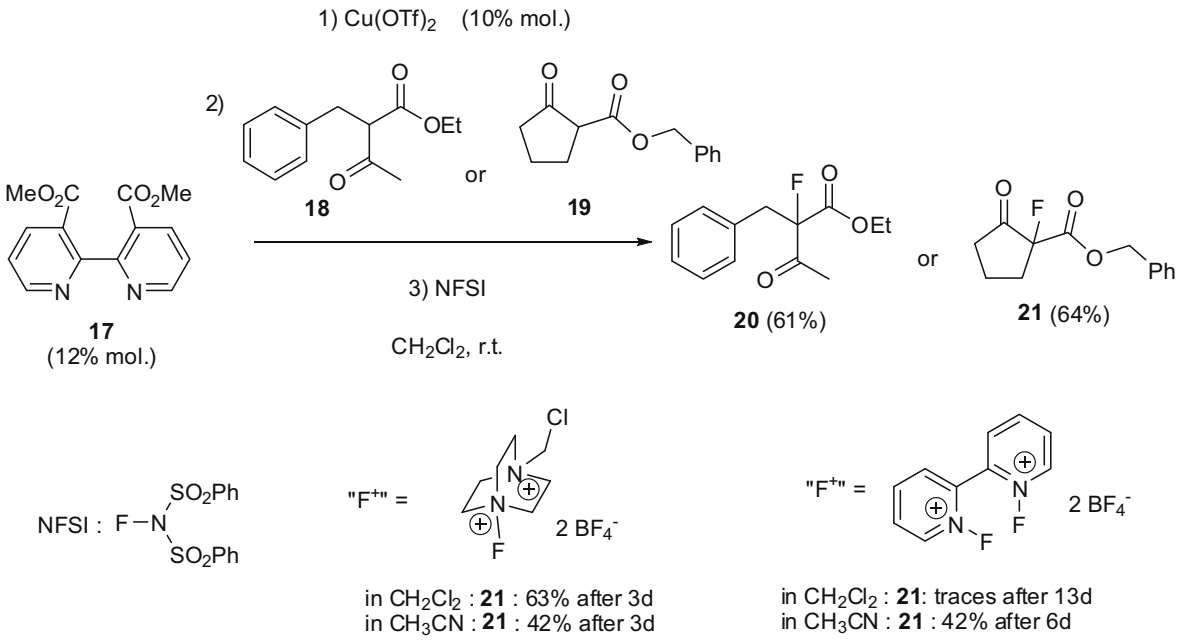
and 3). Lowering the temperature was found to have a limited, though consistent, effect on the ee, but the reaction became too slow to be performed conveniently. Regarding the metal, copper(II) triflate clearly gave the fastest reactions and best enantioselectivity than Zn, Ni and Pd. Unlike in the case of Shibata's system,[26b] addition of $Ni(ClO_4)_2$ did not improve the ee (entry 4). Moreover La, Sc and Yb, did not deliver any ee, likely because of their lower ability to form tetradentate complexes, unlike the other group of metals.[29] The geometry of the new complexes was not determined, however, planar or pseudo planar tetradentate structures are those mostly reported in the literature for copper 2,2′-bipyridine-3,3′-disubstituted systems,[30] though octaedric structures have also been found in a polymeric chloranilate complex.[31] In most examples, the bipyridine adopts a *cis* conformation, though a *trans* conformation was also suggested.[28,30b,32]

Finally, the five bipyridine sugar hybrids connected via an amide link **12–16** were evaluated as ligands, using β-ketoester **21** which gave the best results with ester ligands (Table 4), only using copper as the metal which proved to give the best results.

Fluorination using the amide catalysts proceeded in similar yields as for esters. Regarding the enantioselectivity, some differences were observed compared to esters. The selectivity for the glucose amide **12** was reversed compared to that for the glucose ester **7** (ee in the same range) and in this case, the glucose and allose systems led to the same major enantiomer, without any pseudo-enantiomeric effect. A significant 20% ee, again towards the same enantiomer, was observed in the case of the galactose-based amide ligand **16**, whereas the corresponding ester **11** led to no measurable selectivity. The fructose amide gave no selectivity, neither the secondary amide derived from glucosamine **14**, though more constraint. These results show that the presence of the two extra nitrogen atoms contributes to the geometry of the intermediate complex, even though the amide nitrogen atoms, being protonated, are not believed to be involved in the coordination of the metal. Indeed, deprotonation has been shown to be critical for such a participation of amides in metal complexation.[33]

5. Conclusion

The first examples of chiral 2,2′-bipyridine-3,3′-dicarboxylic acid carbohydrate esters and amides have been prepared and used as chiral ligands in the Cu(II)-mediated electrophilic fluorination reaction. A first observation is that this type of bipyridine is able



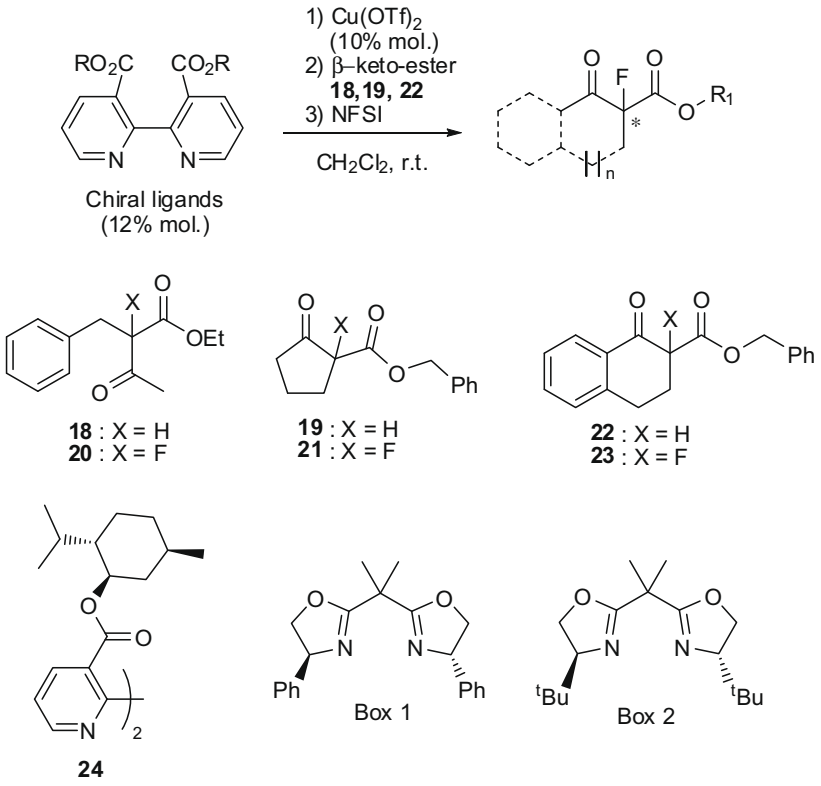
Scheme 4. Electrophilic fluorination mediated by **17**.

to catalyse the reaction. In terms of asymmetric induction, modest enantiomeric excesses were obtained compared to those obtained through the best literature reports. However, the selectivity was found to be in a similar range as those obtained, under identical conditions, using other systems previously described. The simplicity of the overall synthetic sequence from *ortho*-phenanthroline and the availability of carbohydrate derivatives are the main advantages of these new ligands.

6. Experimental

6.1. General

CH_2Cl_2 was dried over molecular sieves before use. Other reagents were used as received. NMR spectra were recorded with a Bruker Avance 300 instrument. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300, 75 and 282 MHz, respectively. Chemical



Scheme 5. Asymmetric fluorination of β-ketoesters with new chiral ligands.

Table 1
Asymmetric fluorination of β-ketoesters **18**, **19** and **22** with ligands **7**–**11** and **24**

Entry	Ligands	**20**[a]	**21**[a]	**23**[a]
1	**7**	75% (9%)	77% (27%)	54% (18%)
2	**8**	n.d.	57% *(14%)*[b]	62% *(9%)*[b]
3	**9**	84% (<5%)	68% (<5%)	47% (<5%)
4	**10**	63% (<5%)	82% (<5%)	70% (<5%)
5	**11**		59% (<5%)	
6	**24**	67% (<5%)	64% (<5%)	67% (<5%)
7	Box 1	78% (17%)	60% (32%)	55% (27%)
8	Box 2	50% (5%)	68% (7%)	60% (<5%)

[a] Isolated yields. In parentheses: ee.
[b] Other enantiomer as major product.

shifts are given in ppm relative to TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as an internal reference. Coupling constants are given in Hertz. Flash chromatography was performed on silica gel 60 M (0.04–0.063 mm).

Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus. IR spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer; spectral width of 4000–400 cm^{-1} was set with 4 cm^{-1} resolution. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at room temperature. The enantiomeric excesses (ee) were determined by chiral HPLC (Chiralcel OJ-H column; hexane/iPrOH and/or Chiralpak® AD-H™). Starting carbohydrates derivatives (partially protected alcohols, amines and azides) are all known compounds either available commercially or prepared by standard procedures.

6.2. Typical procedure for the preparation of chiral ligands 7–11, 17, 24

The alcohol (1.5 mmol) was added to a solution of 2,2′-bipyridine-3,3-dicarboxylic acid (**6**, 0.5 mmol) in dry dichloromethane (3 mL). DMAP (2 mmol) and EDCI HCl (2 mmol) were then added, and the mixture was stirred overnight. The reaction mixture was washed with NH_4Cl (saturated aqueous solution) and water, dried over $MgSO_4$ and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography when necessary.

6.3. Bis(3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)-2,2′-bipyridine-3,3′-dicarboxylate 7

White solid. IR ν(C=O) = 1732 cm^{-1}; $[\alpha]_D = -67$ (c 0.5, $CHCl_3$); mp 163–167 °C; LRMS(ESI) m/z for $C_{36}H_{45}N_2O_{14}$ $(M+H)^+$ = 729.1; HRMS (ESI) m/z calculated $(M+H)^+$ 729.28653, found 729.28686; ^{1}H NMR: δ = 8.78 (dd, J = 4.9, J = 1.7, 2H), 8.35 (dd, J = 8.0, J = 1.7, 2H), 7.48 (dd, J = 8.0, J = 4.9, 2H), 5.62 (d, J = 3.8, 2H), 5.27 (d, J = 2.8, 2H), 4.34 (d, J = 3.8, 2H), 4.11 (dd, J = 7.9, J = 2.8, 2H), 4.03–3.89 (m, 6H), 1.47 (s, 6H), 1.36 (s, 6H), 1.27 (s, 6H), 1.25 (s, 6H). ^{13}C NMR: δ = 164.4, 151.9, 151.9, 138.6, 125.4, 123.1, 112.4, 109.6, 105.0, 83.0, 79.8, 77.4, 72.2, 67.4, 26.9, 26.7, 26.3, 25.4. Anal. Calcd for $C_{36}H_{44}N_2O_{14}$: C, 59.33; H, 6.09. Found: C, 59.52; H, 5.98.

Table 2
Temperature effect on asymmetric **7**-mediated fluorination of **19**

Entry	Temperature (°C)	Yield[a] (%)	ee (%)
1	rt	77	27
2	0	76	29
3	−28	75[b]	32

[a] Isolated yields.
[b] Incomplete conversion after 8 days.

Table 3
Metal effect on asymmetric **7**-mediated fluorination of **19**

Entry	Metallic catalyst	Yield[a] (%)	ee (%)	Reaction time
1	$Cu(OTf)_2$	77	27	Overnight
2	$Zn(OTf)_2$	68	15	5 days
3	$PdCl_2$	42	9	8 days[b]
4	$Ni(ClO_4)_2{\cdot}2H_2O$	77	10	Overnight
5	$Sc(OTf)_3$	68	0.5	2.5 days
6	$Yb(OTf)_3{\cdot}2H_2O$	71	0.5	1.75 days
7	$La(OTf)_3$	80	1	2 weeks [b]

[a] Isolated yields.
[b] Incomplete conversion.

6.4. Bis(3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-yl)-2,2′-bipyridine-3,3′-dicarboxylate 8

White solid. $[\alpha]_D$ = + 138 (c 0.5, $CHCl_3$); mp 126–127 °C; LRMS(ESI) m/z for $C_{36}H_{45}N_2O_{14}$ $(M+H)^+$ = 729.1; HRMS (ESI) m/z calculated $(M+H)^+$ 729.28653, found 729.28758; ^{1}H NMR: δ = 8.71 (dd, J = 4.8, J = 1.6, 2H), 8.33 (dd, J = 7.9, J = 1.6, 2H), 7.42 (dd, J = 7.9, J = 4.8, 2H), 5.72 (d, J = 3.7, 2H), 4.91 (dd, J = 4.8, J = 8.8, 2H), 4.70 (dd, J = 3.7, J = 4.8, 2H), 4.17 (ddd, J = 6.3, J = 7.0, J = 3.7, 2H), 3.95 (dd, J = 8.6, J = 7.0, 2H), 3.94 (dd, J = 8.8, J = 3.6, 2H), 3.77 (dd, J = 8.6, J = 6.3, 2H), 1.47 (s, 6H), 1.34 (s, 6H), 1.28 (s, 6H), 1.24 (s, 6H). ^{13}C NMR: δ = 164.7, 158.8, 151.6, 138.4, 125.3, 122.8, 113.2, 109.6, 103.9, 77.6, 77.1, 74.7, 72.8, 65.0, 26.8, 26.6, 26.2, 25.1. Anal. Calcd for $C_{36}H_{44}N_2O_{14}$: C, 59.33; H, 6.09. Found: C, 59.17; H, 6.17.

6.5. Bis(1-deoxy-2,3:4,5-di-O-isopropylidene-β-D-fructopyranos-1-yl)-2,2′-bipyridine-3,3′-dicarboxylate 9

White foam. $[\alpha]_D = -12$ (c 0.5, $CHCl_3$); mp 85–89 °C; LRMS(ESI) m/z for $C_{36}H_{45}N_2O_{14}$ $(M+H)^+$ = 729.1; HRMS (ESI) m/z calculated $(M+H)^+$ 729.28653, found 729.28759; ^{1}H NMR: δ = 8.74 (dd, J = 4.8, J = 1.6, 2H), 8.34 (dd, J = 7.9, J = 1.6, 2H), 7.40 (dd, J = 7.9, J = 4.8, 2H), 4.54 (dd, J = 7.9, J = 2.6, 2H), 4.46 (d, J = 11.7, 2H), 4.19 (bdd, J = 7.9, J = 0.8, 2H), 4.14 (d, J = 2.6, 2H), 4.04 (d, J = 11.7, 2H), 3.85 (dd, J = 13.0, J = 1.7, 2H), 3.70 (dd, J = 13.0, J = 0.8, 2H), 1.45 (s, 6H), 1.38 (s, 6H), 1.29 (s, 6H), 1.22 (s, 6H). ^{13}C NMR: δ = 165.1, 158.7, 151.6, 138.0, 125.8, 122.7, 109.1, 108.8, 101.3, 70.8, 70.3, 70.0, 65.8, 61.3, 26.5, 25.9, 25.4, 24.1. Anal. Calcd for $C_{36}H_{44}N_2O_{14}$: C, 59.33; H, 6.09. Found: C, 59.61; H, 6.41.

6.6. Bis(5-deoxy-1-O-methyl,2,3-O-isopropylidene-β-D-ribofuranos-5-yl)-2,2'-bipyridine-3,3′-dicarboxylate 10

Colorless oil. $[\alpha]_D = -45$ (c 0.5, $CHCl_3$); LRMS(ESI) m/z for $C_{30}H_{37}N_2O_{12}$ $(M+H)^+$ = 617.1; HRMS (ESI) m/z calculated $(M+H)^+$ 617.23410, found 617.23479; ^{1}H NMR: δ = 8.75 (br d, J = 4.5, 2H),

Table 4
Asymmetric fluorination of **19** with ligands **12**–**16**[a]

Entry Ligands	1 **12**	2 **13**	3 **14**	4 **15**	5 **16**	6 **Box 1**	7 **Box 2**
21[a]	70% *(23%)*[b]	68% *(19%)*[b]	78% *(6%)*[b]	75% (<5%)	75% *(20%)*[b]	60% (32%)	68% (7%)

[a] Isolated yields. In parentheses: ee.
[b] Other enantiomer as major product (compared to ligand **7**).

8.42 (dd, J = 7.9, J = 1.3, 2H), 7.44 (dd, J = 7.9, J = 4.5, 2H), 4.89 (br s, 2H), 4.51 (d, J = 5.8, 2H), 4.41 (d, J = 5.8, 2H), 4.13–4.05 (m, 6H), 3.24 (s, 6H), 1.44 (s, 6H), 1.28 (s, 6H). ^{13}C NMR: δ = 165.0, 159.6, 151.9, 138.7, 132.6, 122.9, 112.6, 109.4, 85.1, 83.8, 81.8, 65.3, 55.0, 26.5, 25.0. Anal. Calcd for $C_{30}H_{36}N_2O_{12}$: C, 58.44; H, 5.88. Found: C, 58.18; H, 6.05.

6.7. Bis(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)-2,2′-bipyridine-3,3′-dicarboxylate 11

White solid. $[\alpha]_D$ = −46 (c 0.5, $CHCl_3$); mp 153–154 °C; LRMS(E-SI) m/z for $C_{36}H_{45}N_2O_{14}$ $(M+H)^+$ = 729.0; HRMS (ESI) m/z calculated $(M+H)^+$ 729.28653, found 729.28756; ^{1}H NMR: δ = 8.68 (br d, J = 4.8, 2H), 8.33 (dd, J = 7.8, J = 1.4, 2H), 7.39 (dd, J = 7.8, J = 4.8, 2H), 5.41 (d, J = 4.9, 2H), 4.51 (dd, J = 7.9, J = 2.3, 2H), 4.24–4.12 (m, 6H), 3.99 (dd, J = 7.9, J = 1.7, 2H), 3.84 (br td, J = 1.7, J = 6.4, 2H), 1.41 (s, 6H), 1.37 (s, 6H), 1.27 (s, 6H), 1.25 (s, 6H). ^{13}C NMR: δ = 165.3, 159.1, 151.5, 138.4, 125.5, 122.6, 109.4, 108.6, 96.0, 70.7, 70.5, 70.4, 65.4, 63.8, 26.0, 25.9, 24.9, 24.4. Anal. Calcd for $C_{36}H_{44}N_2O_{14}$: C, 59.33; H, 6.09. Found: C, 59.61; H, 6.01.

6.8. Dimethyl 2,2′-bipyridine-3,3′-dicarboxylate 17

White solid. Mp 155–156 °C; LRMS(ESI) m/z for $C_{14}H_{13}N_2O_4$ $(M+H)^+$ = 273.1; HRMS (ESI) m/z calculated $(M+H)^+$ 273.08698, found 273.08699; ^{1}H NMR: δ = 8.69 (dd, J = 4.8, J = 1.65, 2H), 8.31 (dd; J = 8.0, J = 1.65, 2H), 7.39 (dd, J = 8.0, J = 4.8, 2H), 3.64 (s, 6H). ^{13}C NMR: δ = 166.4, 159.7, 151.9, 138.5, 125.8, 123.1, 52.6.

6.9. Bis[(2*R*,5*S*)-5-methyl-2-(1-methylethyl)cyclohexyl]2,2′-bipyridine-3,3′-dicarboxylate 24

Yellow solid. $[\alpha]_D$ = −50 (c 0.5, $CHCl_3$); mp 90–93 °C; LRMS(ESI) m/z for $C_{32}H_{45}N_2O_4$ $(M+H)^+$ = 521.2; HRMS (ESI) m/z calculated $(M+H)^+$ 521.33738, found 521.33714; ^{1}H NMR: δ = 8.77 (dd, J = 4.9, J = 1.7, 2H), 8.46 (dd, J = 7.9, J = 1.7, 2H), 7.48 (dd, J = 7.9, J = 4.9, 2H), 4.71 (td, J = 10.6, J = 10.6, J = 4.3, 2H), 1.86 (m, 2H), 1.60–1.50 (m, 6H), 1.35 (m, 2H), 0.99–0.56 (m, 26H). ^{13}C NMR: δ = 164.8, 159.8, 151.4, 138.6, 125.6, 122.6, 75.3, 46.8, 40.5, 34.1, 31.3, 25.6, 22.8, 22.0, 21.0, 15.8. Anal. Calcd for $C_{32}H_{44}N_2O_4$: C, 73.81; H, 8.52. Found: C, 73.59; H, 8.77.

6.10. General procedure for amine coupling: preparation of chiral ligands 12–14

2,2′-Dipyridine-3,3′-dicarboxylic acid (0.25 mmol, 1 equiv) was dissolved in dry dichloromethane (3 mL) under a nitrogen atmosphere. Hydroxybenzotriazole (HOBt, 101 mg, 0.75 mmol, 3 equiv) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride salt (144 mg, 0.75 mmol, 3 equiv) were then added. The reaction mixture was cooled in an ice bath and triethylamine (70 μL, 0.5 mmol, 2 equiv) was added. Finally, the amine (0.5 mmol, 2 equiv) was added. The organic layer was then washed with water. The crude product was dried over $MgSO_4$ and was purified by flash chromatography to give the corresponding 2,2′-bipyridine-3,3′-carboxamide.

6.11. *N,N′*-Bis-(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-1-yl)-2,2′-bipyridine-3,3′-carboxamide 12

White solid. $[\alpha]_D$ = −39 (c 0.5, $CHCl_3$); mp 105–109 °C; LRMS(E-SI) m/z for $C_{36}H_{46}N_4O_{12}Na$ $(M+Na)^+$ = 749.2; HRMS (ESI) m/z calculated $(M+Na)^+$ 749.30099, found 749.30112; ^{1}H NMR: δ = 8.57 (dd, J = 4.8, J = 1.6, 2H), 8.00–7.93 (m, J = 7.7, J = 7.8, J = 1.6, 4H) 7.32 (dd, J = 7.8, J = 4.8, 2H), 5.38 (d, J = 3.5, 2H), 4.31 (dd, J = 7.7, J = 3.6, 2H), 4.16 (d, J = 3.5, 2H), 4.01–3.98 (m, 4H), 3.84–3.76 (m, 4H), 1.44 (s, 6H), 1.34 (s, 6H), 1.29 (s, 6H), 1.21 (s, 6H). ^{13}C NMR: δ = 167.8, 156.2, 150.0, 136.5, 131.8, 123.3, 112.0, 109.8, 104.6, 84.2, 78.9, 72.6, 67.4, 53.5, 27.1, 26.9, 26.4, 25.7.

6.12. *N,N′*-Bis-(3-deoxy-1,2 :5,6-di-*O*-isopropylidene-α-D-allofuranos-1-yl)-2,2′-bipyridine-3,3′-carboxamide 13

White solid. $[\alpha]_D$ = + 48 (c 0.5, $CHCl_3$); mp 120–122 °C; LRMS(E-SI) m/z for $C_{36}H_{47}N_4O_{12}$ $(M+H)^+$ = 727.1; HRMS (ESI) m/z calculated $(M+H)^+$ 727.318499, found 727.316524; ^{1}H NMR: δ = 8.65 (dd, J = 4.8, J = 1.6, 2H), 7.99 (dd, J = 7.8, J = 1.6, 2H), 7.41 (dd, J = 7.8, J = 4.8, 2H), 7.09 (br d, J = 9.2, 2H), 5.76 (d, J = 3.6, 2H), 4.40 (dd, J = 4.8, J = 3.6, 2H), 4.17 (td, J = 9.3, J = 4.8, 2H), 4.05 (td, J = 6.5, J = 3.6, 2H), 3.98 (dd, J = 8.0, J = 6.5, 2H), 3.85 (dd, J = 8.0, J = 6.5, 2H), 3.75 (dd, J = 9.3, J = 3.6, 2H), 1.44 (s, 6H), 1.38 (s, 6H), 1.32 (s, 6H), 1.26 (s, 6H). ^{13}C NMR: δ = 167.6, 156.5, 150.3, 136.3, 132.0, 123.3, 112.6, 109.7, 104.4, 79.0, 78.5, 75.4, 64.7, 53.3, 26.7, 26.5, 26.4, 25.5.

6.13. *N,N′*-Bis-(1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-glucopyranos-1-yl)-2,2′-bipyridine-3,3′-carboxamide 14

White gum. $[\alpha]_D$ = + 30 (c 0.5, $CHCl_3$); LRMS(ESI) m/z for $C_{40}H_{48}N_4O_{20}$ $(M+H)^+$ = 903.1; HRMS (ESI) m/z calculated $(M+H)^+$ 903.2784, found 903.2805; ^{1}H NMR: δ = 8.52 (dd, J = 4.8, J = 1.5, 2H), 7.97 (d, J = 8.8, 2H), 7.87 (dd, J = 7.8, J = 1.5, 2H), 7.34 (dd, J = 7.8, J = 4.8, 2H), 5.59 (d, J = 8.8, 2H), 5.18 (t, J = 9.8, J = 9.8, 2H), 5.00 (t, J = 9.8, J = 9.8, 2H), 4.21 (dd, J = 12.4, J = 4.3, 2H), 4.17–4.08 (m, 2H), 4.03 (dd, J = 12.4, J = 2.1, 2H), 3.80 (ddd, J = 9.8, J = 4.3, J = 2.1, 2H), 2.02 (s, 12H), 1.96 (s, 6H), 1.95 (s, 6H), 1.26 (s, 6H). ^{13}C NMR: δ = 170.5, 170.4, 169.2, 169.0, 168.1, 156.1, 149.8, 136.2, 130.8, 123.2, 91.9, 72.3, 72.0, 68.2, 61.6, 53.2, 20.9, 20.6, 20.5.

6.14. General procedure for azide coupling: preparation of chiral ligands 15 and 16

6.14.1. Azide coupling

2,2′-Dipyridine-3,3′-dicarboxylic acid (61 mg, 0.25 mmol, 1 equiv) was dissolved in toluene (1.5 mL) under a nitrogen atmosphere. The azide (0.5 mmol, 2 equiv) and triethylphosphine (550 μL, 1 M in THF, 0.55 mmol, 2.2 equiv) were premixed in toluene (1 mL) for two minutes and were then added to the reaction mixture. The resulting solution was heated at 80 °C. The organic layer was then washed several times with water. The crude product was dried over $MgSO_4$ and was purified by flash chromatography to give the corresponding 2,2′-bipyridine-3,3′-carboxamide.

6.15. *N,N′*-Bis-(1-deoxy-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranos-1-yl)-2,2′-bipyridine-3,3′-carboxamide 15

White gum. $[\alpha]_D$ = −31 (c 1.0, $CHCl_3$); LRMS(ESI) m/z for $C_{36}H_{48}N_4O_{12}$ $(M+H)^+$ = 727.1; HRMS (ESI) m/z calculated $(M+H)^+$ 727.3190, found 727.3185; ^{1}H NMR: δ = 8.65 (dd, J = 4.8, J = 1.6, 2H), 8.04 (dd, J = 7.9, J = 1.6, 2H), 7.37–7.30 (m, J = 7.9, J = 4.8, 4H), 4.51 (dd, J = 7.8, J = 2.5, 2H), 4.18–4.16 (m, J = 2.5, 4H), 3.79 (dd, J = 13.1, J = 2.0, 2H), 3.68–3.63 (m, 4H), 3.40 (dd, J = 13.8, J = 5.0, 2H), 1.48 (s, 6H), 1.33 (s, 6H), 1.30 (s, 12H).^{13}C NMR: δ = 167.7, 155.7, 149.8, 136.5, 132.3, 122.8, 109.1, 108.4, 102.3, 71.8, 70.6, 70.2, 61.4, 41.2, 26.2, 25.8, 25.0, 24.1.

6.16. *N,N′*-Bis-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)-2,2′-bipyridine-3,3′-carboxamide 16

White solid. $[\alpha]_D$ = −19 (c 0.5, $CHCl_3$); mp 123–125 °C; LRMS(E-SI) m/z for $C_{36}H_{48}N_4O_{12}$ $(M+H)^+$ = 727.1; HRMS (ESI) m/z calculated $(M+H)^+$ 727.3190, found 727.3201; ^{1}H NMR: δ = 8.63 (dd, J = 4.9,

J = 1.6, 2H), 7.98 (dd, J = 7.8, J = 1.6, 2H), 7.44 (t, J = 5.2, 2H), 7.36 (dd, J = 7.8, J = 4.9, 2H), 5.41 (d, J = 5.0, 2H), 4.53 (dd, J = 7.9, J = 2.3, 2H), 4.26 (dd, J = 5.0, J = 2.3, 2H), 3.98 (dd, J = 1.8, J = 7.9, 2H), 3.86 (m, 2H), 3.51 (ddd, J = 13.7, J = 6.4, J = 5.2, 2H), 3.30 (ddd, J = 13.7, J = 6.4, J = 5.2, 2H), 1.46 (s, 6H), 1.41 (s, 6H), 1.30 (s, 12H).^{13}C NMR: δ = 168.5, 156.3, 150.2, 136.6, 132.5, 123.3, 109.7, 109.1, 96.6, 71.7, 71.1, 70.9, 66.0, 40.8, 26.4, 26.3, 25.4, 24.7.

6.17. Typical procedure for electrophilic fluorination

Ligands **7–11** and **24** or **12–16** (0.03 mmol) and copper(II) triflate (0.025 mmol) were premixed in dry dichloromethane, for 2 h, under a nitrogen atmosphere. The β-ketoester **18**, **19**, **or 22** (0.25 mmol) was then added followed by NFSI (0.375 mmol) and the reaction was monitored by TLC and ^{19}F NMR. At the end of the reaction, the solvent was removed under vacuum and the product was purified by flash chromatography. Chiral HPLC led to two distinctive peaks, the second one being the major enantiomer for esters in most cases except for ligand **8**, and the first one being the major for all sugar amide ligands. The absolute configuration of the major enantiomer was not determined, however, in Ref.[26a], *R,R*-Box1-catalysed fluorination of ketoester **22** was found to give the (+) isomer as major product. By analogy to these results the (−) sign is believed to be major enantiomer based on our reference experiment using (*S,S*)-Box 1.

6.18. Ethyl 2-fluoro-2-benzylacetoacetate 20

Colorless oil. ^{1}H NMR: δ = 7.31–7.22 (m, 5H), 4.24 (q, J = 7.1, 2H), 3.45 (dd, J = 25.4, J = 14.8, 1H), 3.39 (dd, J = 25.4, J = 14.8, 1H), 2.15 (d, J = 5.2, 3H), 1.26 (t, J = 7.1). ^{13}C NMR: δ = 202.8 (d, J_{C-F} = 29.6), 166.1(d, J_{C-F} = 25.8), 133.5, 130.8 (d, J_{C-F} = 1.1), 128.8, 127.8, 100.4 (d, J_{C-F} = 200.3), 63.1, 40.2 (d, J_{C-F} = 20.3), 26.7, 14.3. ^{19}F NMR: δ = −165.07 (tq, J = 25.4, J = 5.2). Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.36; H, 6.59.

6.19. Benzyl 1-fluoro-2-oxo-cyclopentanecarboxylate 21

Yellow oil. ^{1}H NMR: δ = 7.35–7.34 (m, 5H), 5.28 (d, J = 12.1, 1H), 5.22 (d, J = 12.1, 1H), 2.62–2.48 (m, 3H), 2.35 (m, 1H), 2.11 (m, 2H). ^{13}C NMR: δ = 207.4 (d, J_{C-F} = 16.5), 167.4 (d, J_{C-F} = 27.4), 135.1, 129.11, 129.07, 128.6, 94.8 (d, J_{C-F} = 200.3), 68.2, 36.1, 34.0 (d, J_{C-F} = 20.8), 18.5 (d, J_{C-F} = 3.3). ^{19}F NMR: δ = −164.4 (t, J = 20.8). Anal. Calcd for $C_{13}H_{13}FO_3$: C, 66.09; H, 5.55. Found: C, 66.18; H, 5.47.

6.20. Benzyl 2-fluoro-1-tetralone-2-carboxylate 23

Yellow oil. ^{1}H NMR: δ = 8.10 (m, 1H), 7.57 (m, 1H), 7.42–7.26 (m, 7H), 5.33 (d, J = 12.4, 1H), 5.24 (d, J = 12.4, 1H), 3.15 (m, 1H), 3.02 (m, 1H), 2.74 (m, 1H), 2.56 (m, 1H). ^{13}C NMR: δ = 188.6 (d, J_{C-F} = 18.7), 167.3 (d, J_{C-F} = 26.3), 143.2, 135.1, 135.0, 131.0, 129.2, 129.0, 128.92, 128.86, 128.4, 127.7, 93.4 (d, J_{C-F} = 193.7), 67.8, 32.0 (d, J_{C-F} = 22.5), 24.9 (d, J_{C-F} = 7.1). ^{19}F NMR: δ = −164.9 (dd, J = 22.9, J = 11.5). Anal. Calcd for $C_{18}H_{15}FO_3$: C, 72.47; H, 5.07. Found: C, 72.86; H, 5.38.

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