Tetrahedron 69 (2013) 4061–4065

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Expanding the scope of the **elpaN-type** library: glucose-derived bis(pyridine-2-carboxamide) ligands (**elpaN-Py**) for molybdenum-catalyzed asymmetric allylic alkylations

Matteo Lega [a,b,c], Rosario Figliolia [a,b], Christina Moberg [c,*], Francesco Ruffo [a,b,*]

[a] Dipartimento di Scienze Chimiche, Università di Napoli 'Federico II', Complesso Universitario di Monte S. Angelo, Via Cintia, 80126 Napoli, Italy
[b] Consorzio Interuniversitario di Reattività Chimica e Catalisi, Italy
[c] KTH School of Chemical Science and Engineering, Department of Chemistry, Organic Chemistry, SE 10044 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 21 January 2013
Received in revised form 26 February 2013
Accepted 18 March 2013
Available online 22 March 2013

Keywords:
Asymmetric catalysis
Molybdenum
Carbohydrates
Allylation
Microwave reactions

ABSTRACT

The **elpaN-Py** family of ligands, which represents a subset of the **elpaN-type** library based on D-glucose, is described. The ligands are structural analogs of the privileged bis(pyridine-2-carboxamides) derived from *trans*-1,2-diaminocyclohexane, and differ for the type of substitution in the coordinating functions present in positions 1 and 2. Their ability to induce high enantioselectivity in asymmetric allylic alkylations promoted by molybdenum under microwave irradiation has been successfully demonstrated, starting from both a linear (ee up to 99%) and a branched substrate (ee up to 96%). The multifunctional nature of the sugar scaffold was exploited for the preparation of a polar ligand, through deprotection of the hydroxyl groups in positions 3, 4 and 6. In this version, it was possible to verify the performance in catalysis in alternative solvents, such as ionic liquids and water.

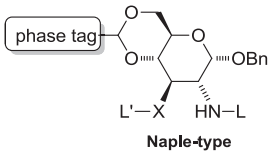
1. Introduction

Asymmetric allylic alkylations (AAA) have been widely studied in recent years due to their high synthetic versatility. The reactions are catalyzed by complexes of several different metals[1] (Pd, Mo, Ir, Cu, etc.), and a variety of substrates and nucleophiles may be used, leading to C–C and C–X (X=H, O, S, P) bond formation.[2] The stereo- and regiochemistry of the product are a function of the metal, the ligand, the nucleophile, and the substrate, thereby making it possible to access alternative reactivity by switching between different catalytic systems.

Among available catalytic systems, those based on Pd have been most widely explored,[3] but since Mo[4] and Ir[5] catalysts exhibit complementary regiochemistry when unsymmetrically substituted allyl derivatives are used, catalysts containing these metals are valuable. Typically, Pd complexes afford the achiral linear products from monosubstituted allylic substrates,[1] while Ir or Mo catalysts preferentially lead to the branched chiral products. Ir complexes have a wider scope,[5a,6] but the cheap catalyst precursor $Mo(CO)_6$ in combination with easily accessible bis(pyridine-2-carboxamides) ligands is attractive due to its low cost and high stability.[4a]

Moreover, when AAA catalyzed by Mo are performed under microwave irradiation (MW), $Mo(CO)_6$ can be used directly without any pretreatment and the product is usually obtained in less than 10 min with high regio- and stereoselectivity.[7] On this basis, Mo-catalyzed AAA have been successfully employed in a variety of synthetic applications.[8] A number of bis(pyridine-2-carboxamide) derivatives, obtained from 1,2-diaminocyclohexanes and pyridine carboxylic acids, have been successfully used as ligands in the Mo-catalyzed reaction.[9] Particularly high stereo- and regioselectivity have been observed with ligands substituted with π-donor groups on the pyridine nucleus.[10]

Attracted by the structural analogy between *trans*-1,2-diaminocyclohexane and 2,3-disubstituted glucose, we previously designed sugar versions[11] of the original ligands and described[12] their successful application in different catalytic reactions (**Naple-type** library in Fig. 1).



Naple-type

Fig. 1. The **Naple-type** library.

* Corresponding authors. Fax: +39 081 674090 (F.R.); fax: +46 8 7912333 (C.M.); e-mail addresses: kimo@kth.se (C. Moberg), ruffo@unina.it (F. Ruffo).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.075

In particular, we prepared and employed the bis(pyridine-2-carboxamide) ligand **Naple-py**[12f] (X=NH, L=L′=CO-*o*-py in Fig. 1) with excellent results in the AAA promoted by Mo.

A general problem encountered with ligands derived from naturally occurring compounds, like the **Naple-type** ligands, is that they usually can afford only one of the possible enantiomers of the product. In order to access also to the opposite enantioselectivity, we recently designed the library of **elpaN-type** ligands.[13] These ligands are pseudo-enantiomers of the **Naple-type** ligands as a result of the shift of the coordinating functions at C1 and C2 of the sugar backbone (Fig. 2).

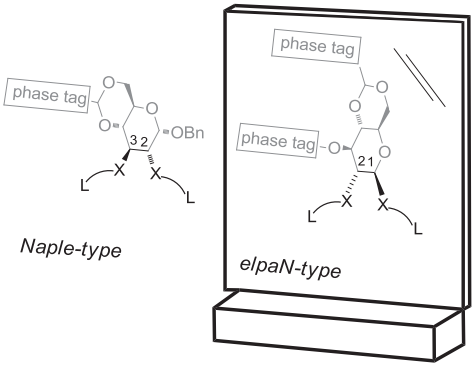
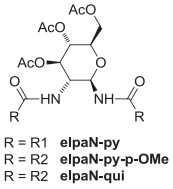
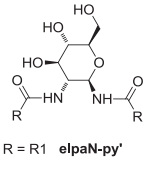


Fig. 2. **Naple-type** versus **elpaN-type** ligands.

This approach already led to successful results. In a preliminary study,[13] asymmetric allylic substitutions catalyzed by palladium yielded chiral products with high ee, and with opposite configuration with respect to those achieved with the original **Naple-type** library.

In this report, we describe the synthesis of a new subset of the **elpaN-type** bouquet (**elpaN-Py** series of Fig. 3), and its application in the Mo-catalyzed AAA promoted by MW.





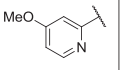
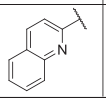
R	STRUCTURE	SUFFIX
R1		-py
R2		-py-*p*-OMe
R3		-qui

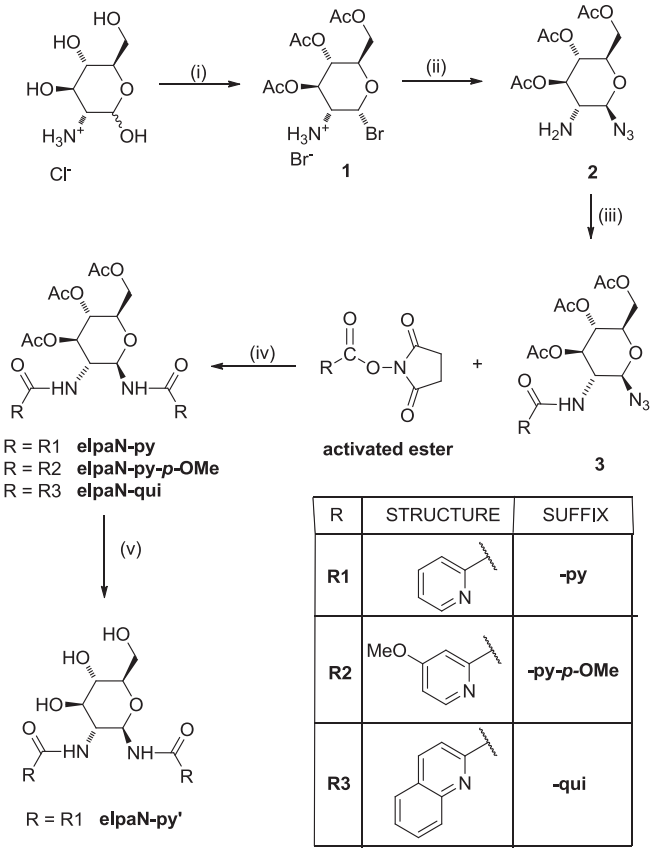
Fig. 3. The **elpaN-Py** series.

2. Results and discussion

2.1. Preparation of the ligands

The key intermediate in the synthesis of the ligands is the known 1-azido-2-aminoglucose derivative **2**,[14] whose synthesis from bromide **1** (step ii in Scheme 1) was significantly improved within this study. In fact, the dangerous silver azide, originally used for providing N_3^- and capturing Br^-, was safely substituted by the couple trimethylsilyl azide/*t*-BuOK, the latter acting as base, activator of the organic azide, and source of K^+ (*CAUTION: azides are highly energetic and potentially explosive compounds*).

The amino group of compound **2** was condensed with the desired acid (step iii), employing *N*,*N*′-dicyclohexylcarbodiimide



R	STRUCTURE	SUFFIX
R1		-py
R2		-py-*p*-OMe
R3		-qui

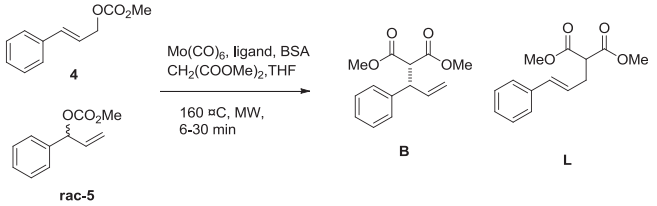
Scheme 1. Synthesis of the **elpaN-Py** ligands. (i) AcBr, 3 d; (ii) Me_3SiN_3, *t*-BuOK, THF, 18 h; (iii) DMAP, RCO_2H, DCC, DCM; (iv) PMe_3, DCM; (v) NH_3, MeOH.

(DCC) and 4-dimethylaminopyridine (DMAP). Compound **3** was converted into the ligand by a Staudinger reaction, using PMe_3 and the appropriate activated ester (step iv). This procedure is necessary because anomerization at C1 was usually observed when the azide was reduced to the amine by H_2 over Pd/C.

Finally, the acetate groups of the **elpaN-py** ligand were conveniently deprotected by stirring a methanolic solution of the ligand in the presence of ammonia to yield a ligand with free hydroxyl groups (step v). The deprotected ligand **elpaN-py**′ is soluble in water and ionic liquids (RTILs), but almost insoluble in DCM and toluene and was synthesized in order to explore the feasibility of a Mo-promoted AAA under unconventional conditions.[15]

2.2. Mo-catalyzed asymmetric allylic alkylations

The catalytic reactions (Scheme 2) were performed by using both a linear **4** and a branched allylic carbonate *rac*-**5**, which are crucial substrates because the knowledge of their reactivity provides the necessary information for assessing the qualities of the ligands.[16–18]



Scheme 2. Molybdenum-catalyzed AAA.

According to experimental conditions previously developed,[12f] $Mo(CO)_6$, ligand, allylic carbonate **4**, dimethyl malonate, and *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) were mixed in THF and heated at 160 °C in the microwave cavity under air. After the desired reaction time, conversions and branched/linear ratios were determined by ^{1}H NMR spectroscopy, and enantioselectivities by chiral HPLC.

The different performances of the ligands were assessed by using 4 mol% of Mo catalyst, a ligand/metal ratio of 1.3:1 and a nucleophile/substrate ratio of 1.1:1. The results of the reactions of the linear substrate **4** are shown in Table 1. As expected, **Naple-type**[12f] and **elpaN-type** ligands afforded products with opposite absolute configurations, the latter leading preferentially to the (*S*)-**B** product. Except for the ligand containing a quinoline group (entry 4), which was expected to be the less active and selective,[16] good conversions, yields, regioselectivity, and stereoselectivity were observed.

Table 1
Molybdenum-catalyzed asymmetric substitutions of **4** using **elpaN-Py** ligands[a]

Entry	**elpaN-py** ligand	Conversion[b] (%)	Isolated yield[c] (%)	**B**/**L**[a]	ee[d] (%)
1	**-py**	94	72	17:1	96 (*S*)
2	**-py-*p*-OMe**	78	66	21:1	95 (*S*)
3	**-py′**	73	55	6:1	86 (*S*)
4	**-qui**	67	41	24:1	90 (*S*)

[a] Reaction conditions: dimethyl malonate (0.77 mmol), allylic carbonate **4** (0.71 mmol), BSA (208 μL), THF (2 mL), 160 °C.
[b] Determined by NMR spectroscopy of the crude reaction mixture.
[c] Yield of product isolated by column chromatography (EtOAc/petroleum ether=1:5).
[d] Determined by chiral HPLC Daicel OD-H (0.46 cm i.d. 25 cm) column.

In analogy with the results obtained for the ligands derived from 1,2-diaminocyclohexane,[17] the presence of π-donating substituents in the 4-position of the pyridyl rings increased the enantio- and site selectivity.[10] Thus, ligand **elpaN-py-*p*-OMe** was more selective than **elpaN-py** (entries 1 vs 2).

A catalyst containing the deprotected ligand **elpaN-py′** resulted in a similar activity, but lower regio- and stereoselectivity compared to the acetylated ligand (entries 1 vs 3). As expected, lower amounts of catalyst resulted in lower conversion and lower regioselectivity (entries 1 vs 5), although the enantioselectivity was still good (97% ee).

Branched substrates, such as *rac*-**5**, often react with lower enantioselectivity than their linear isomers as a result of a memory effect,[17] explained on the basis of the known mechanism of the Mo-promoted AAA.[18] The allylic carbonate reacts with the Mo precursor by oxidative addition leading to a (η^3-allyl)molybdenum complex. This reaction proceeds through a stereospecific *syn* displacement of the carbonate, and for this reason the two enantiomers of **5** produce two diastereoisomeric complexes. The system will equilibrate via $\eta^3-\eta^1-\eta^3$ isomerization, and if this process is slow compared to the nucleophilic attack, which also occurs by a *syn* mechanism, a memory effect may be observed, leading to lower enantioselectivity. The results for reactions of substrate *rac*-**5** are reported in Table 2.

As expected, the branched substrate **5** resulted in lower enantio- and regioselectivity than the linear substrate, but still acceptable levels of enantioselectivity (88–96% ee (*S*)). Conversions observed for this substrate were lower but still good in all cases. The trend was analogous to that experienced for substrate **4**, except that ligand **elpaN-qui** gave the highest branched/linear ratio (entry 4).

The performance of ligand **elpaN-py′** was also tested in water and in hydrophilic RTIL, taking advantage of its solubility in these solvents. Disappointingly, when water was used as solvent, the main product obtained from the allylic carbonate **4**, as well as from the corresponding acetate, consisted of a mixture of the branched and linear alcohols. The hydrolysis was, at least in part, catalyzed by the metal complex as shown by the formation of only the linear product from the Mo-free background reaction, thus suggesting a π-allylic intermediate in the hydrolysis. In the ionic liquid $bmimBF_4$, the allylic carbonate afforded the allylic ether in racemic form, mainly as product of a background decarboxylation, while the allylic acetate did not react.

Table 2
Molybdenum-catalyzed asymmetric substitutions of *rac*-**5** using **elpaN-Py** ligands[a]

Entry	**elpaN-Py** ligand	Time (min)	Cat. (mol %)	Conv.[b] (%)	Isolated yield[b] (%)	**B**/**L**[c]	ee[d] (%)
1	**-py**	6	4	94	65	14:1	98 (*S*)
2	**-py-*p*-OMe**	6	4	92	70	25:1	99 (*S*)
3	**-py′**	6	4	100	72	6:1	97 (*S*)
4	**-qui**	6	4	51	45	15:1	90 (*S*)
5	**-py-*p*-OMe**	30	1	23	16	14:1	97 (*S*)

[a] Reaction conditions: dimethyl malonate (0.77 mmol), allylic carbonate *rac*-**5** (0.71 mmol), $Mo(CO)_6$ (0.026 mmol, 4 mol%), ligand (0.034 mmol), BSA (208 μL), THF (2 mL), 160 °C, 6 min.
[b] Determined by NMR spectroscopy of the crude reaction mixture.
[c] Yield of product isolated by column chromatography (EtOAc/petroleum ether=1:5).
[d] Determined by chiral HPLC Daicel OD-H (0.46 cm i.d. 25 cm) column.

3. Conclusions

This work demonstrates the validity of a strategy, namely that it is possible to prepare libraries of pseudo-enantiomeric ligands from easily accessible natural compounds, with both synthetic and economic benefits.[11b,12b,19]

In particular, the library **elpaN-type**, based on 1,2-disubstituted D-glucose, was expanded through the preparation of the bis(pyridine-2-carboxamide) derivatives **elpaN-Py**. The ligands were obtained in both protected and deprotected versions, and this has allowed us to verify their ability in the AAA promoted by Mo under traditional and non-conventional conditions. High enantioselectivities were accomplished in the former case, starting from both a linear and a branched allylic substrates. In water, although the enantioselective process was almost ineffective, a peculiar reactivity was disclosed, that could be the subject of further future research.

4. Experimental section

4.1. General

THF and toluene were dried by using a Glass-contour solvent dispensing system. Dichloromethane was distilled from CaH_2. The microwave heating was performed with a Smith CreatorTM single mode cavity from Personal Chemistry AB, Uppsala, Sweden equipped with magnetic stirrer and automatic temperature control. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 400 or 200 MHz, and 100.6 and 50.3 MHz. The ^{1}H and ^{13}C chemical shifts are reported using $CHCl_3$ (for spectra recorded in $CDCl_3$), HDO (for proton spectra recorded in water) or dioxane (for carbon spectra recorded in water) as internal standards.

4.2. Synthesis of 3,4,6-tri-*O*-acetyl-1-β-azido-D-glucosamine (2)

Compound **1**[14] (6.17 g, 13.7 mmol) was dissolved in THF (100 mL). $TMSN_3$ (1.30 mL, 10.0 mmol) and *t*-BuOK (2.36 g, 21.0 mmol) were added, and the system was stirred for 18 h at rt (*CAUTION: azides are highly energetic and potentially explosive compounds*). The suspension was filtered and the solvent was

removed under reduced pressure, leading to a slightly yellow solid. This solid was dissolved in DCM (5 mL), the solution was filtered, and petroleum ether was added, affording pure compound **2** as a slightly yellow solid (yield: 4.24 g, 95%). [α] −8.0 (*c* 1.0, 586 nm, 25 °C, $CHCl_3$); lit. (−11.5).[14]

4.3. Synthesis of the activated esters, R=-py and -qui

2-Pyridine carboxylic acid or 2-quinoline carboxylic acid (5.0 mmol), DCC (1.03 equiv), and *N*-hydroxysuccinimide (1.0 equiv) were suspended in THF (50 mL) and the solution was stirred overnight. The suspension was filtered, and the solvent was evaporated under reduced pressure. The crude product was dissolved in DCM and precipitated as a yellow solid by the addition of petroleum ether. The resulting product was used without any further purification (yield: 41 and 65%, respectively, 0.46 g and 0.90 g). *Activated* ***Ester-py***: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.83 (d, ^3J=4.6 Hz, 1H, aromatic), 8.21 (d, ^3J=7.8 Hz, 1H, aromatic), 7.91 (td, ^3J=1.4, 7.8 Hz, 1H, aromatic), 7.59 (dd, ^3J=4.6, 7.8 Hz, 1H, aromatic), 2.92 (s, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=169.2, 160.8, 150.9, 144.5, 137.7, 128.9, 127.1, 26.1. *Activated* ***Ester-qui***: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.36 (d, ^3J=8.5 Hz, 1H, aromatic), 8.31 (d, ^3J=8.5 Hz, 1H, aromatic), 8.21 (d, ^3J=8.5 Hz, 1H, aromatic), 7.92 (d, ^3J=8.5 Hz, 1H, aromatic), 7.83 (t, ^3J=7.6 Hz, 1H, aromatic), 7.71 (t, ^3J=7.6 Hz, 1H, aromatic), 2.95 (s, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ=169.0, 160.9, 147.9, 143.9, 137.7, 131.1, 131.0, 129.9, 130.0, 127.8, 121.7, 25.9. *R=-**py-p-OMe***: The acid (5.0 mmol), DCC (2.5 equiv), and *N*-hydroxysuccinimide (1.1 equiv) were suspended in THF (130 mL) and the solution was stirred overnight. The suspension was filtered, and the solvent was evaporated under reduced pressure. The crude product was extracted twice with boiling *n*-hexane in order to remove excess DCC. The solid was dissolved in EtOAc (50 mL), the solution was filtered, and then washed with EtOAc (2×25 mL). The solvent was removed under reduced pressure, leading to the crude product that was used with no further purification (yield: 580 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.65 (d, ^3J=5.7 Hz, 1H, aromatic), 7.72 (d, 1H, ^3J=2.5 Hz, aromatic), 7.09 (dd, ^3J=2.5, 5.7 Hz, 1H, aromatic), 3.94 (s, 3H, OMe), 2.91 (s, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ=171.9, 187.0, 166.9, 160.6, 151.7, 141.4, 113.3, 56.0, 25.9.

4.4. Synthesis of 3

Compound **2** (1.32 g, 4.00 mmol) was dissolved in DCM (25 mL) for the synthesis of **3-py** and **3-qui**, or THF (50 mL) for the synthesis of **3-py-*p*-OMe**. DMAP (49 mg, 0.40 mmol), the desired acid (4.20 mmol) and DCC (1.24 g, 6.00 mmol) were added in this order, and the solution was stirred for the desired time. DCU was removed by filtration, and the solution was concentrated under reduced pressure. The crude product was precipitated by slow addition of petroleum ether, and washed twice with the same solvent. The compound was extracted twice with boiling *n*-hexane and isolated as a white solid after further purification by flash chromatography (silica/crude=50:1 w/w).

Product	Reaction time (h)	Eluent ratio (EtOAc/PE+3% TEA)	Yield (%)
3-py	2	1:1	68
3-py-*p*-OMe	18	3:1	57
3-qui	18	3:2	60

Compound ***3-py***: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.49 (d, ^3J=4.2 Hz, 1H, aromatic), 8.12 (d, $^3J_{NH,2\text{-}H}$=7.9 Hz, 1H, NH), 7.79 (td, ^3J=1.4, 7.7 Hz, 1H, aromatic), 7.40–7.32 (m, 1H, aromatic), 5.41 (t, $^3J_{3\text{-}H,2\text{-}H}$=$^3J_{3\text{-}H,4\text{-}H}$=9.9 Hz, 1H, 3-H), 5.10 (t, $^3J_{4\text{-}H,3\text{-}H}$=$^3J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 4.93 (d, $^3J_{1\text{-}H,2\text{-}H}$=9.2 Hz, 1H, 1-H), 4.26 (dd, $^3J_{6\text{-}H,5\text{-}H}$=4.8 Hz, $^3J_{6\text{-}H,6'\text{-}H}$=12.4 Hz, 1H, 6-H), 4.15 (dd, $^3J_{6'\text{-}H,5\text{-}H}$=1.9 Hz, 1H, 6′-H), 4.03 (q, 1H, 2-H), 3.83–3.79 (m, 1H, 5-H), 2.06 (s, 3H, AcO), 1.98 (s, 3H, AcO), 1.87 (s, 3H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=170.8, 170.6, 169.5, 164.8, 148.9, 148.3, 137.6, 126.8, 122.7, 88.7, 74.2, 72.0, 68.4, 62.0, 54.3, 20.9, 20.8, 20.7. ***3-py-p-OMe***: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.31 (d, ^3J=5.6 Hz, 1H, aromatic), 8.21 (d, $^3J_{NH,2\text{-}H}$=8.2 Hz, 1H, NH), 7.69 (dd, ^3J=2.4, 12.7 Hz, 1H, aromatic), 6.94–6.90 (m, 1H, aromatic), 5.46 (t, $^3J_{3\text{-}H,2\text{-}H}$=$^3J_{3\text{-}H,4\text{-}H}$=9.5 Hz, 1H, 3-H), 5.14 (t, $^3J_{4\text{-}H,3\text{-}H}$=$^3J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 4.97 (d, $^3J_{1\text{-}H,2\text{-}H}$=9.2 Hz, 1H, 1-H), 4.31 (dd, $^3J_{6\text{-}H,5\text{-}H}$=4.8 Hz, $^3J_{6\text{-}H,6'\text{-}H}$=12.4 Hz, 1H, 6-H), 4.20 (dd, $^3J_{6'\text{-}H,5\text{-}H}$=2.1 Hz, 1H, 6′-H), 4.07 (q, 1H, 2-H), 3.90 (s, 3H, OMe), 3.88–3.83 (m, 1H, 5-H), 2.11 (s, 3H, AcO), 2.03 (s, 3H, AcO), 1.93 (s, 3H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ=171.1, 170.8, 169.8, 167.4, 165.1, 151.2, 149.7, 113.9, 108.1, 89.0, 74.5, 72.3, 68.8, 62.3, 56.0, 54.6, 21.1, 21.0, 20.9. ***3-qui***: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.35 (d, $^3J_{NH,2\text{-}H}$=9.0 Hz, 1H, NH), 8.25 (q, ^3J=8.5 Hz, 2H, aromatic), 8.07 (d, ^3J=8.5 Hz, 1H, aromatic), 7.83 (d, ^3J=8.1 Hz, 1H, aromatic), 7.73 (t, ^3J=7.7 Hz, 1H, aromatic), 7.58 (t, ^3J=7.5 Hz, 1H, aromatic), 5.51 (t, $^3J_{3\text{-}H,2\text{-}H}$=$^3J_{3\text{-}H,4\text{-}H}$=9.9 Hz, 1H, 3-H), 5.14 (t, $^3J_{4\text{-}H,3\text{-}H}$=$^3J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 5.02 (d, $^3J_{1\text{-}H,2\text{-}H}$=9.2 Hz, 1H, 1-H), 4.30 (dd, $^3J_{6\text{-}H,5\text{-}H}$=4.7 Hz, $^3J_{6\text{-}H,6'\text{-}H}$=12.4 Hz, 1H, H-6), 4.17 (dd, $^3J_{6',5\text{-}H}$=1.8 Hz, 1H, 6′-H), 4.09 (q, 1H, 2-H), 3.86 (m, 1H, 5-H), 2.09 (s, 3H, AcO), 2.00 (s, 3H, AcO), 1.88 (s, 3H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ=171.1, 170.9, 169.8, 165.4, 149.0, 146.8, 138.1, 130.7, 130.2, 130.0, 128.6, 128.1, 119.2, 89.0, 74.5, 72.3, 68.8, 62.3, 54.7, 21.1, 21.0, 20.9.

4.5. Synthesis of the elpaN ligands

The desired intermediate **3** (1.35 mmol) and the desired activated ester (1.25 equiv) were dissolved in dry DCM (15 mL) under inert atmosphere. The solution was cooled to −78 °C and a solution of 0.89 M PMe_3 in dry toluene (1.50 mL, 1.69 mmol) was slowly added. The system was warmed to rt, and when evolution of N_2(g) ceased, the reaction was quenched by the addition of a saturated solution of Na_2CO_3 (15 mL). The organic phase was separated, and the water was extracted with DCM (2×20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was precipitated by slow addition of petroleum ether and washed twice with the same solvent. The compounds were isolated as white solids by flash chromatography (silica/crude=50:1 w/w).

Product	Eluent ratio (EtOAc/PE+3% TEA)	Yield (%)
elpaN-py	1:0	58
elpaN-py-*p*-OMe	1:0	41
elpaN-qui	2:1	67

Compound ***elpaN-py***: [α] −38.4 (*c* 1.0, 586 nm, 25 °C, CH_2Cl_2); mp 107 °C; ν_{max} (Nujol): 1751 (C=O ester), 1669 (C=O amide) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.06 (d, $^3J_{NH,1\text{-}H}$=9.6 Hz, 1H, NH), 8.57 (d, ^3J=4.7 Hz, 1H, aromatic), 8.33 (d, ^3J=4.7 Hz, 1H, aromatic), 8.31 (d, $^3J_{NH,2\text{-}H}$=9.6 Hz, 1H, NH), 8.10 (d, ^3J=7.8 Hz, 1H, aromatic), 8.00 (d, ^3J=7.8 Hz, 1H, aromatic), 7.70 (m, 2H, aromatic), 7.33 (m, 2H, aromatic), 5.57 (t, $^3J_{1\text{-}H,NH}$=$^3J_{1\text{-}H\text{-}2\text{-}H}$, 1H, 1-H), 5.47 (t, $^3J_{3\text{-}H,2\text{-}H}$=$^3J_{3\text{-}H,4\text{-}H}$=10.0 Hz, 1H, 3-H), 5.24 (t, $^3J_{4\text{-}H,3\text{-}H}$=$^3J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 4.58 (q, 1H, 2-H), 4.36 (dd, $^3J_{6\text{-}H,5\text{-}H}$=4.2 Hz, $^3J_{6\text{-}H,6'\text{-}H}$=12.4 Hz, 1H, 6-H), 4.14 (dd, $^3J_{H6',5\text{-}H}$=2.0 Hz, 1H, 6′-H), 4.10–3.90 (m, 1H, 5-H), 2.09 (s, 3H, AcO), 2.05 (s, 3H, AcO), 1.94 (s, 3H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ=170.8 (2C), 169.5, 165.3, 165.2, 148.8, 148.6, 148.4, 148.2, 137.0 (2C), 126.6, 126.4, 122.6, 122.2, 79.9, 73.7, 73.1, 68.3, 62.0, 52.9, 20.8, 20.7, 20.6. HRMS (ESI) calcd for $C_{24}H_{26}N_4NaO_9$ [*M*+Na]$^+$: 537.1597, found 537.1581. ***elpaN-py-p-OMe***: [α] −7.4 (*c* 1.0, 586 nm, 25 °C, CH_2Cl_2); mp 102 °C; ν_{max} (Nujol): 1739 (C=O

ester), 1652 (C=O amide) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=8.97 (d, $^3J_{NH,1\text{-}H}$=9.3 Hz, 1H, NH), 8.58 (d, ^3J=5.6 Hz, 1H, aromatic), 8.22 (d, $^3J_{NH,2\text{-}H}$=9.4 Hz, 1H, NH), 8.11 (d, ^3J=5.6 Hz, 1H, aromatic), 7.57 (s, 1H, aromatic), 7.51 (s, 1H, aromatic), 6.83–6.78 (m, 1H, aromatic), 6.75–6.69 (m, 1H, aromatic), 5.46 (t, $^3J_{1\text{-}H,NH}$=$^3J_{1\text{-}H,2\text{-}H}$, 1H, 1-H), 5.38 (t, $^3J_{3\text{-}H,2\text{-}H}$=$^3J_{3\text{-}H,4\text{-}H}$=9.9 Hz, 1H, 3-H), 5.17 (t, $^3J_{4\text{-}H,3\text{-}H}$=$^3J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 4.47 (q, 1H, 2-H), 4.29 (dd, $^3J_{6\text{-}H,5\text{-}H}$=4.1 Hz, $^3J_{6\text{-}H,6'\text{-}H}$=12.4 Hz, 1H, 6-H), 4.07 (dd, $^3J_{6'\text{-}H,5\text{-}H}$=1.8 Hz, 1H, 6′-H), 3.93–3.88 (m, 1H, 5-H), 3.76 (s, 6H, 2OMe) 2.06 (s, 3H, AcO), 1.98 (s, 3H, AcO), 1.88 (s, 3H, AcO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=171.2, 171.1, 169.9, 167.2, 167.1, 165.7, 165.6, 151.1, 151.0, 149.9, 149.7, 113.6, 113.4, 108.3, 108.0, 80.3, 74.1, 73.4, 68.7, 62.4, 55.9 (2C), 53.4, 21.2, 21.1, 21.0. HRMS (MALDI) calcd for $C_{26}H_{30}N_4O_{11}$ $[M]^+$: 574.1911, found 574.5331. ***elpaN-qui***: [α] −150 (*c* 1.0, 586 nm, 25 °C, CH_2Cl_2); mp 117 °C; ν_{max} (Nujol): 1742 (C=O ester), 1674 (C=O amide) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.36 (d, $^3J_{NH,1\text{-}H}$=9.2 Hz, 1H, NH), 8.48 (d, $^3J_{NH,2\text{-}H}$=9.5 Hz, 1H, NH), 8.22 (d, ^3J=8.8 Hz, 1H, aromatic), 8.15–8.10 (m, 2H, aromatic), 8.05–7.99 (m, 2H, aromatic), 7.83 (d, ^3J=8.5 Hz, 1H, aromatic), 7.76–7.70 (m, 2H, aromatic), 7.65 (d, ^3J=8.8 Hz, 1H, aromatic), 7.58–7.53 (m, 2H, aromatic), 7.45 (t, ^3J=7.5 Hz, 1H, aromatic), 5.66 (t, $^3J_{1\text{-}H,NH}$=$^3J_{1\text{-}H,2\text{-}H}$, 1H, 1-H), 5.54 (t, $^3J_{3\text{-}H,2\text{-}H}$=$^3J_{3\text{-}H,4\text{-}H}$=9.9 Hz, 1H, 3-H), 5.27 (t, $^3J_{4\text{-}H,3\text{-}H}$=$^3J_{4\text{-}H,5\text{-}H}$, 1H, 4-H), 4.69 (q, 1H, 2-H), 4.37 (dd, $^3J_{6\text{-}H,5\text{-}H}$=4.2 Hz, $^3J_{6\text{-}H,6'\text{-}H}$=12.4 Hz, 1H, 6-H), 4.07 (dd, $^3J_{6'\text{-}H,5\text{-}H}$=1.8 Hz, 1H, 6′-H), 3.92–3.88 (m, 1H, 5-H), 2.07 (s, 3H, AcO), 2.04 (s, 3H, AcO), 1.91 (s, 3H, AcO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ=171.2, 170.0, 169.0, 166.0 (2C), 148.8, 148.7, 146.9, 146.6, 137.7, 137.6, 130.7, 130.5, 130.4, 130.4, 129.8, 129.6, 128.6, 128.4, 127.9, 127.8, 119.3, 119.0, 80.6, 74.3, 73.6, 68.8, 62.4, 53.6, 21.1, 21.0, 20.9. HRMS (ESI) calcd for $C_{32}H_{31}N_4O_9$ $[M+H]^+$: 615.2091, found 615.2071.

4.6. Synthesis of elpaN-py′

The **elpaN-py** ligand (0.50 mmol) was dissolved in MeOH (10 mL) under a NH_3 atmosphere. After 20 h the solvent was removed under vacuum, affording the pure product as a solid in quantitative yield. Relevant NMR data: ***elpaN-py′***: [α] −26.0 (*c* 1.0, 586 nm, 25 °C, CH_2Cl_2); ν_{max} (Nujol): 1669 (C=O amide) cm^{-1}. ^1H NMR (400 MHz, D_2O): δ=8.42 (m, 2H, aromatic), 7.75 (m, 2H, aromatic), 7.41 (m, 2H, aromatic), 5.37 (d, $^3J_{1\text{-}H,NH}$=$^3J_{1\text{-}H\text{-}2\text{-}H}$=9.65 Hz, 1H, 1-H), 4.18 (t, $^3J_{2\text{-}H,NH}$=9.9 Hz, 1H, 2-H), 3.81 (m, 2H, 6-H and 3-H), 3.70 (dd, $^3J_{6'\text{-}H,5\text{-}H}$=4.9 Hz, 1H, 6′-H), 3.58 (m, 2H, 5-H and 4-H); ^{13}C NMR (100.6 MHz, D_2O) δ=171.0, 170.5, 151.8, 151.6, 151.3, 150.7, 141.2 (2C), 130.6, 130.2, 125.7, 125.5, 82.0, 80.8, 76.8, 72.5, 63.5, 57.8. HRMS (ESI) calcd for $C_{18}H_{20}N_4NaO_6$ $[M+Na]^+$: 411.1281, found 411.1279.

4.7. Microwave-assisted allylic alkylations

General procedure: two different stock solutions were prepared: solution N, containing the nucleophile, was prepared by adding dimethyl malonate (880 μL, 7.70 mmol) to a suspension of 60% NaH in mineral oil (27 mg, 0.68 mmol) in THF (10 mL), and solution S, containing the substrate, was prepared by dissolving the allylic carbonate (**4** or **5**) (7.1 mmol) in THF (10 mL). Then the appropriate ligand (0.034 mmol) and $Mo(CO)_6$ (6.9 mg, 0.026 mmol) were transferred to a flame-dried SmithProcess VialTM. Solution N (1 mL), solution S, and BSA (208 μL, 0.85 mmol) were added in this order, and the suspension was heated in the microwave cavity at 160 °C for the desired time. The brown solution obtained was diluted with Et_2O to a total volume of 10 mL, resulting in a dark precipitate. A sample of the solution was filtered through silica gel and analyzed by ^1H NMR spectroscopy to determine the conversion and the regioselectivity. The crude product was then purified by chromatography on silica gel (eluent: petroleum ether/EtOAc, 5:1). The ees were determined by HPLC using a Daicel OD-H (0.46 cm i.d. 25 cm) column, 0.05:99.5 isopropanol/hexane, UV 254 nm, retention times: (*S*)-**B**: 19 min; (*R*)-**B**: 35 min. The structures of the products were confirmed by comparison with published spectroscopic data:[18] ^1H NMR (400 MHz, $CDCl_3$): δ=7.25–7.14 (m, 5 Hz, aromatic), 5.92 (ddd, ^3J=17.0, 10.2, 8.2 Hz, 1H), 5.06 (d, ^3J=17.0 Hz, 1H), 5.02 (d, ^3J=10.2 Hz, 1H), 4.04 (dd, ^3J=11.0, 8.2 Hz, 1H), 3.80 (d, ^3J=11.0 Hz, 1H), 3.68 (s, 3H), 3.42 (3H).

Acknowledgements

We are grateful to the Ministero dell'Istruzione, dell'Università e della Ricerca (Progetti di Ricerca di Interesse Nazionale – Bando 2009) for financial support, which allowed M.L. to perform work in Stockholm. The authors thank Dr. Mikhail Gorlov, Department of Chemistry, KTH, for a generous gift of some RTILs.

References and notes

1. Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297.
2. Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440.
3. Trost, B. M.; Crawley, M. L. *Top. Organometal. Chem.* **2012**, *38*, 321–340.
4. (a) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159–167; (b) Moberg, C. *Top. Organometal. Chem.* **2012**, *38*, 209–234.
5. (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691; (b) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organometal. Chem.* **2012**, *38*, 155–208.
6. Bartels, B.; Garcia-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569–2586.
7. Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3595–3598.
8. See for example: (a) Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320–14321; (b) Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275–2278.
9. (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104–1105; (b) Belda, O.; Moberg, C. *Coord. Chem. Rev.* **2005**, *249*, 727–740.
10. (a) Belda, O.; Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. *J. Org. Chem.* **2000**, *65*, 5868–5870; (b) Belda, O.; Moberg, C. *Synthesis* **2002**, 1601–1606.
11. We decided to use carbohydrates as building blocks for chiral ligands for various reasons: they are easily available, they are 'naturally chiral', they are highly functionalized, and their chemistry is extremely developed. For recent reviews on this topic see: (a) Steinborn, D.; Junicke, H. *Chem. Rev.* **2000**, *100*, 4283–4317; (b) Dièguez, M.; Pàmies, O.; Ruiz, A.; Diaz, Y.; Castillòn, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165–2192; (c) Dièguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189–3215; (d) Diaz, Y.; Castillòn, S.; Claver, C. *Chem. Soc. Rev.* **2005**, *34*, 702–713; (e) Dièguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621–4634; (f) Boysen, M. M. K. *Chem.—Eur. J.* **2007**, *13*, 8648–8659; (g) Dièguez, M.; Pàmies, O. *Chem.—Eur. J.* **2008**, *14*, 944–960; (h) Benessere, V.; De Roma, A.; Del Litto, R.; Ruffo, F. *Coord. Chem. Rev.* **2010**, *254*, 390–401; (i) Diéguez, M.; Pàmies, O.; Woodward, S. *Coord. Chem. Rev.* **2010**, *254*, 2007–2030.
12. (a) Borriello, C.; Cucciolito, M. E.; Panunzi, A.; Ruffo, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2467–2471; (b) Borriello, C.; Del Litto, R.; Panunzi, A.; Ruffo, F. *Tetrahedron: Asymmetry* **2004**, *15*, 681–686; (c) De Roma, A.; D'Errico, A.; Del Litto, R.; Magnolia, S.; Ruffo, F. *Tetrahedron: Asymmetry* **2006**, *17*, 2265–2269; (d) De Roma, A.; Ruffo, F.; Woodward, S. *Chem. Commun.* **2008**, 5384–5386; (e) Benessere, V.; De Roma, A.; Ruffo, F. *ChemSusChem* **2008**, *1*, 425–430; (f) Benessere, V.; Del Litto, R.; Moberg, C.; Ruffo, F. *Eur. J. Org. Chem.* **2009**, 1352–1356; (g) Benessere, V.; Ruffo, F. *Tetrahedron: Asymmetry* **2010**, *21*, 171–176; (h) Benessere, V.; Lega, M.; Ruffo, F.; Silipo, A. *Tetrahedron* **2011**, *67*, 4826–4831.
13. Benessere, V.; De Roma, A.; Del Litto, R.; Lega, M.; Ruffo, F. *Eur. J. Org. Chem.* **2011**, 5779–5782.
14. Bertho, A.; Révész, A. *Liebigs Ann. Chem.* **1953**, *581*, 11–16.
15. *Multiphase Homogeneous Catalysis*; Cornils, B., Ed.; Wiley-VCH: Weinheim, Germany, 2005.
16. Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929–1932.
17. Hughes, D. L.; Palucki, M.; Yasuda, N.; Reamer, R. A.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 2762–2768.
18. (a) Hughes, D. L.; Lloyd-Jones, G. C.; Krska, S. W.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Mathre, D. J.; Reamer, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5379–5384; (b) Krska, S. W.; Hughes, D. L.; Reamer, R. A.; Mathre, D. J.; Palucki, M.; Yasuda, N.; Sun, Y.; Trost, B. M. *Pure Appl. Chem.* **2004**, *76*, 625–633; (c) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 702–703.
19. (a) Rajanbabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101–4102; (b) Khiar, N.; Suárez, B.; Valdivia, V.; Fernández, I. *Synlett* **2005**, 2963–2967; (c) Grugel, H.; Albrecht, F.; Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2012**, *14*, 3780–3783.