Tetrahedron: *Asymmetry* 20 (2009) 340–350

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

N-Substituent effects on the diethylzinc addition to benzaldehyde catalysed by bicyclic 1,4-aminoalcohols

Dina Scarpi *, Ernesto G. Occhiato, Antonio Guarna

Dipartimento di Chimica Organica 'U. Schiff', Laboratory of Design, Synthesis and Study of Biologically Active Heterocycles (HeteroBioLab), Università degli Studi di Firenze, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Italy

ARTICLE INFO

Article history:
Received 4 December 2008
Accepted 23 January 2009
Available online 23 February 2009

ABSTRACT

Chiral enantiopure bicyclic 1,4-aminoalcohols were synthesised by a new methodology that provided a common precursor, which was easily N-functionalised with a wide variety of substituents. The final compounds were used as chiral ligands in a model study of the enantioselective addition of diethyl zinc to benzaldehyde, aimed at understanding the influence of the N-substituent on both the rate and stereoselectivity of the reaction. This set of experiments also provided interesting insight into the non-catalysed addition that occurred by employing commercially available Et_2Zn solutions.

1. Introduction

The asymmetric alkylation of aldehydes by diethylzinc has been used as a benchmark for potential chiral ligands,[1] since the first reports by Oguni[2] and Noyori.[3] In particular, the transition state model proposed by Noyori and Yamakawa in 1995[3b] has been largely used to rationalise the experimental data in almost every subsequent work.

Over the past few years, this application has been more deeply studied with some interesting papers being published, reporting observations concerning the structure–activity relationship.[4] Generally,[5] 1,2-amino alcohols have proven to be the best ligands for the diethylzinc addition to carbonyls, but a few examples of 1,3- and 1,4-amino alcohols have also been investigated, among which the chiral 1,4-amino alcohols reported by us, whose structure is based on a 6,8-dioxa-3-aza-bicyclo[3.2.1]octane scaffold.[6]

The application of *N*-methyl amino alcohol **1** (Scheme 1) as a chiral ligand[6b] in the addition of Et_2Zn to aromatic aldehydes resulted in the corresponding (*S*)-alcohols with an ee ranging from 92% to 98%. Analogously, the phenylacetylene Et_2Zn-catalysed addition to aromatic aldehydes afforded the corresponding (*R*)-propargylic alcohols with an ee ranging from 68% to 70%. In both cases, **1** was employed at 15% mol.

In the context of gaining further mechanistic insights into the Et_2Zn addition to aromatic aldehydes, the results obtained so far with this class of 1,4-amino alcohols prompted us to further investigate the relationship between the nature of the N-substituent and the chiral induction ability of the corresponding chiral ligand.

In particular, as we had already obtained data concerning the influence of the steric hindrance of *N*-alkyls (i.e., the less hindered, the more stereoselective), which were congruent with the transition state model[6a] elaborated on the basis of the literature,[3b] we decided to also explore the steric and electronic effects of groups, such as aryl, fluoroalkyl and sulfonyl that were capable of affecting the ability of the N atom to coordinate to the Zn atom. Benzaldehyde was chosen as a model substrate for the organozinc addition. To realise this, we had to elaborate a new and more general synthesis of the bicyclic scaffold, that could be easily and readily N-fuctionalised.

Moreover, in addition to the results obtained by employing these new chiral ligands in the model reaction, we herein report a set of experiments showing the presence of a non-catalysed addition occurring when using commercially available Et_2Zn solutions and these having a strong influence on the enantiomeric purity of the final product at times.

2. Results and discussion

The synthesis that we reported most recently[6b] of this class of compounds was planned in order to obtain *N*-methyl amino alcohol **1** (Scheme 1) starting from commercially available reagents from the chiral pool, that is, **3** and **4**.

With this in mind, we considered a similar synthetic route, where the starting *N*-methyl amine **4** was replaced by the corresponding primary amine **5** (Scheme 2).

We started the synthesis by adding lactone **3** to a solution of a pre-formed aluminum amide, obtained by mixing aminoacetaldehyde dimethyl acetal **5** and $AlMe_3$. The reaction gave amidoalcohol **6**, formed in 95% yield, which required no purification for the next step. Selective O-benzylation[7] was achieved by treatment of **6** with

* Corresponding author. Tel.: +39 055 4573502; fax: +39 055 4573531.
E-mail address: dina.scarpi@unifi.it (D. Scarpi).

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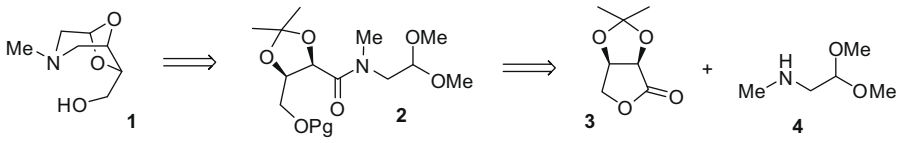
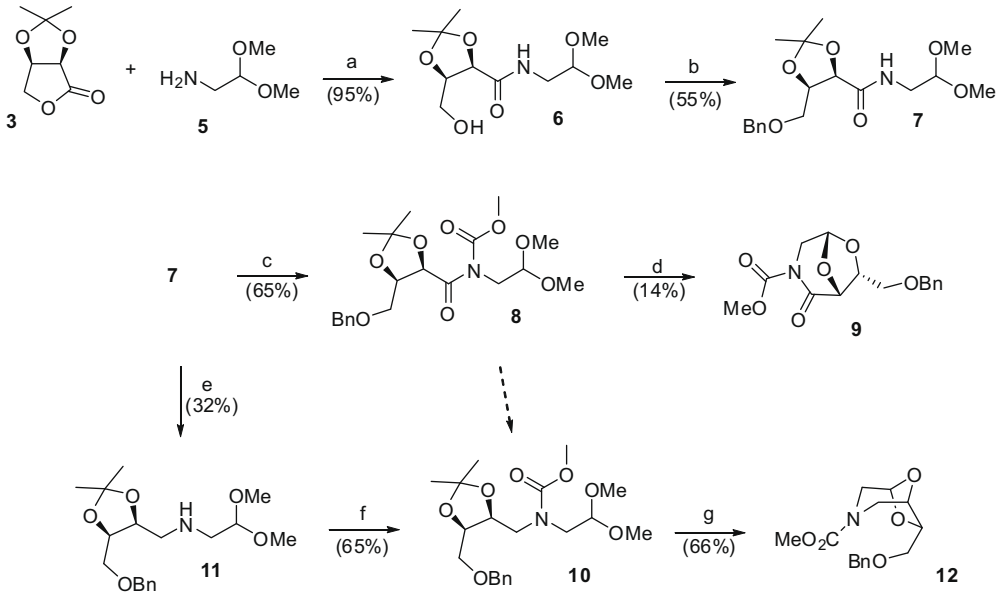
doi:10.1016/j.tetasy.2009.01.021



Scheme 1. Retrosynthetic analysis of the *N*-methyl amino alcohol **1**.



Scheme 2. (a) $AlMe_3$ 2.0 M in hexane, DCM, 0 °C→rt, 18 h; (b) KOH, cat. 18-C-6, BnBr, THF, rt, 70′; (c) *n*BuLi 1.8 M in hexane, $ClCO_2Me$, THF, −70 °C, 4 h; (d) $SiO_2{\cdot}H_2SO_4$, toluene, reflux, 10′; (e) $BH_3{\cdot}SMe_2$, THF, reflux, 1 h; (f) $ClCO_2Me$ (1.3 equiv), Et_3N (1.3 equiv), DCM, 0 °C→rt, 1 h; (g) TFA–DCM, 1:2, 0 °C→rt, 18 h.

KOH in anhydrous THF, in the presence of a catalytic amount of 18-crown-6 ether, followed by the addition of benzyl bromide. Product **7**, obtained in 55% yield, was then protected as an *N*-carbomethoxy amide; the reaction required the deprotonation of the amide by *n*BuLi at low temperature, followed by the slow addition of methyl chloroformate. Compound **8** was obtained in a 65% yield after purification. The cyclisation step was performed by treatment of the *N*-carbomethoxy amide **8** under catalysis of sulfuric acid adsorbed on silica gel in refluxing toluene. Cyclic compound **9** was obtained in a disappointing 14% yield after purification from many by-products. This reaction usually affords the cyclic scaffold with fairly good yields and in the case of the analogous *N*-methyl system, the lactam was obtained in a 48% yield. Therefore, the low yield was probably due to the presence of the *N*-carbomethoxy moiety; once the hydrolysis of the acetals takes place, the molecule is still too rigid and hindered to cyclise to compound **9**. To increase the flexibility of the molecule, we decided to reduce the amide bond in **8** and cyclise the *N*-methyl amine **10** under literature conditions.[8] Unfortunately, the reduction by $BH_3{\cdot}SMe_2$ of *N*-carbomethoxyl amide **8** to *N*-carbomethoxyl amine **10** failed and in more drastic conditions resulted only in the deprotection and decomposition of the starting material. Therefore, to synthesise compound **10**, we had to first perform the amide reduction and then the amide protection. The reduction of amide **7** by $BH_3{\cdot}SMe_2$ afforded compound **11** after 1h at reflux in 32% yield; *N*-carbomethoxyl protection proceeded smoothly under standard conditions and compound **10** was finally obtained in a 65% yield. The cyclisation step was then performed with an excess of trifluoroacetic acid and afforded compound **12** in 66% yield. The overall yield starting from **3** and **5** was 7% after five steps.

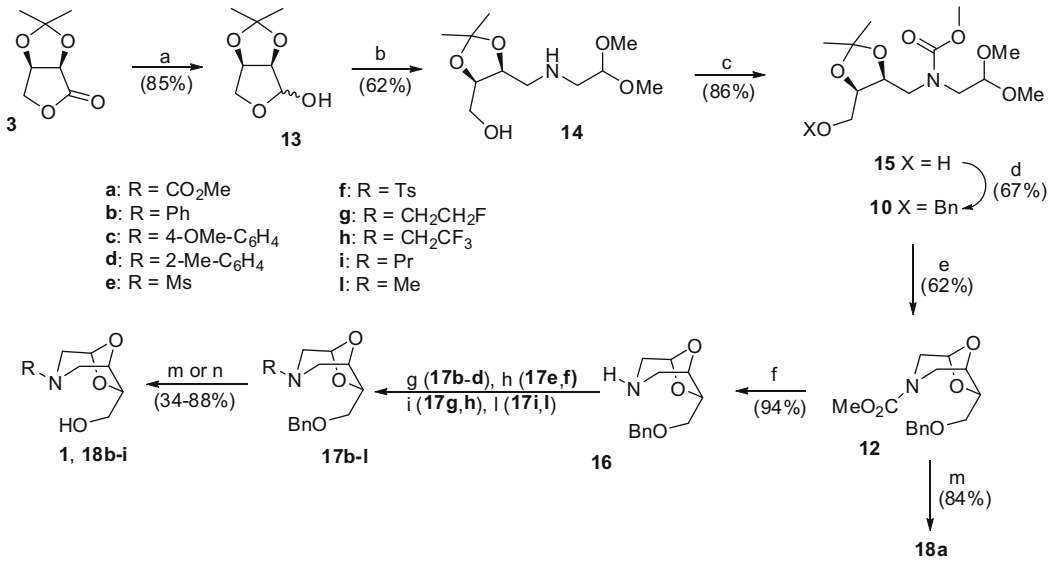
A critical analysis of the experimental data suggested to us that the amide bond could be better reduced in an earlier stage and that this route did not represent a general method for obtaining the free 1,4-amino alcohol as we planned.

Therefore, we started the synthesis under conditions similar to the literature conditions,[8] and modified the scheme after the reductive amination (Scheme 3).

Compound **13** was obtained in 85% yield by $NaBH_4$ reduction of commercially available lactone **3** at pH 4–7 in water.[9] Amino alcohol **14** was then obtained by the reductive amination of **13** with amine **5**, $NaBH_3CN$ at pH 6,[10] in 62% yield. N-Carbomethoxylation was obtained by treatment of **14** with 2.6 equiv of methyl chloroformate followed by selective O-deprotection with catalytic K_2CO_3 in methanol of the *N*-,*O*-carbomethoxy compound (86% yield).[11] The O-benzylation, performed on **15**, afforded compound **10** which was finally cyclised to product **12** in 62% yield. This alternative route that eliminates any inconvenience due to the presence of the amide functional group, allowed us to increase the yield in intermediate **12** from 7% to 19% over five steps.

The first N-functionalised amino alcohol was directly obtained from **12** by debenzylation with H_2 over Pd/C (84% yield). All other functionalisations required the N-deprotection that was obtained by treatment of compound **12** with an excess of KOH in a refluxing mixture of methanol and water in a 4:1 ratio for 48 h. Compound **16** was thus obtained in 94% yield and we did not observe any decomposition or changes in the stereochemistry in the bicyclic structure. Compound **16** was then used as the starting material for all subsequent N-functionalisation.

We first tried on our substrate, the conditions reported by Chan and Lam for N-arylations with arylboronic acids and cupric



Scheme 3. (a) $NaBH_4$ (3 equiv), H_2O pH 4–7, 0 °C, 3 h; (b) **5**, $NaBH_3CN$, MeOH pH 6, 0 °C→rt, 22 h; (c) (i) $ClCO_2Me$ (2.6 equiv), Et_3N (2.6 equiv), DCM, 0 °C→rt, 18 h; (ii) K_2CO_3 (5% mol), MeOH, rt, 3.5 h; (d) NaH, TBAI, BnBr, THF, 0 °C→rt, 7 h; (e) TFA–DCM, 1:2, 0 °C→rt, 18 h; (f) KOH, MeOH–H_2O, 4:1, reflux, 48 h; (g) $ArB(OH)_2$, $Cu(OAc)_2$, Et_3N, DCM, O_2, rt, 5 h; (h) MsCl or TsCl, Et_3N, DCM, rt, 28 h; (i) (i) 2-fluoroethyltosylate, $NaHCO_3$, DMF, 80 °C, 19 h or (ii) 2,2,2-trilfuoroethyl trifluoromethanesulfonate, $NaHCO_3$, abs. EtOH, reflux, 17 h; (l) (i) HCHO 37%, $NaBH_3CN$, pH 7, CH_3CN, rt, 4 h or (ii) CH_3CH_2CHO, $NaBH_3CN$, pH 6, MeOH, rt, 18 h; (m) 10% Pd/C, H_2, EtOAc, rt, 18 h; (n) 20% $Pd(OH)_2$/C, cyclohexene, abs EtOH, reflux 4–7.5 h.

acetate,[12] taking into account also the modifications recently reported for similar scaffolds.[10] Compound **16** was treated with phenylboronic acid (2 equiv), cupric acetate (1 equiv) and anhydrous pyridine (2 equiv) in anhydrous dichloromethane as a solvent in a vessel open to the air. After 45 h, the starting material was consumed but this was due to a side reaction, that is, the cyclic acetal opening. The use of triethylamine as a base resulted in **17b**, in 42% yield after purification. In the recent literature on the copper-mediated C–N bond formation,[13] the use of catalytic cupric acetate was reported either at room temperature or at 40 °C, and with oxygen as the vessel atmosphere. The target compound **17b** was obtained in 10–14% yield (cupric acetate was used in 10–14% mol amount), but the starting material **16** could be recovered in small amounts. Therefore, the subsequent N-arylations were performed under an oxygen atmosphere at room temperature and with a stoichiometric amount of cupric acetate. Since long reaction times (i.e., 18–24 h) proved only to afford more by-products, without an increase in yield, the reactions were stopped after 5 h. In this way, target compound **17b** was obtained in 50% yield; these conditions represent a good compromise between a fair yield and an acceptable loss of starting material. They were then applied to N-arylation of **16** with 4-methoxyphenylboronic acid (43% yield of **17c**) and *o*-tolylboronic acid, that, as expected, afforded **17d** in only 10% yield for steric reasons.

The preparation of *N*-sulfonylamides involved standard reaction conditions consisting of the addition of the suitable sulfonyl chloride (1.3 equiv) to a solution of **16** in DCM, in the presence of Et_3N as a base. Compounds *N*-mesyl **17e** and *N*-tosyl **17f** were obtained with 71% and 81% yield, respectively.

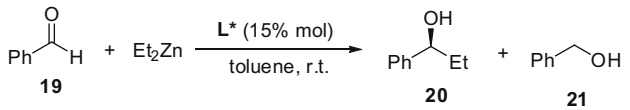
The *N*-fluoroalkyl derivatives were prepared by the nucleophilic substitution of 2-fluoroethyltosylate[14] and 2,2,2-trifluoroethyl trifluoromethanesulfonate[15] by **16**, under literature conditions,[16] while compounds **17g** and **17h**, were obtained in 70% and 65% yield, respectively.

Finally, to prove the new synthetic strategy as general as we planned, we decided to also synthesise the *N*-methyl derivative **1**. The *N*-methyl compound **17l** was obtained by reductive amination with 37% HCHO and $NaBH_3CN$ (44%);[17] analogously, *N*-propyl **17i** was obtained starting from **16** and propionaldehyde (53%).

To complete the synthesis of this series of N-functionalised 1,4-amino alcohols O-debenzylation was performed. However, the conditions reported above for **12** worked only for compounds **17e** and **17f**. In the case of **17b**, for example, O-debenzylation by hydrogenation over Pd/C in either CH_3OH or EtOAc failed unexpectedly; we supposed that the tertiary amine was able to poison the catalyst, even though removal of benzyl groups of *N*-aryl 3,4-dibenzyloxypyrrolidines was reported to work under these conditions, and in excellent yields.[18] If the presence of the tertiary amine was the problem, the use of a few drops of aqueous HCl could avoid the catalyst poisoning;[19] however, in our hands the only result was O-debenzylation and contemporary N-dearylation (88% yield) of **17b**. Therefore, we opted for the catalytic transfer hydrogenation performed over $Pd(OH)_2$/C in a refluxing mixture of cyclohexene and ethanol:[20] after 7 h, the desired product **18b** was obtained in a quantitative yield. These conditions were then applied to all compounds **17**, with the exception of sulfonamides **17e** and **17f**, where the problem of the tertiary amine did not exist.

Compounds **1**, **18b–d** and **18g–i** were obtained in yields ranging from 56% to quantitative.

The thus obtained *N*-substituted 1,4-amino alcohols were finally employed as chiral ligands in the addition of Et_2Zn to benzaldehyde (Scheme 4). We applied the reaction conditions that worked best with the *N*-methyl ligand **1**,[6b] and the results are reported in Table 1.



Scheme 4. Catalysed addition of Et_2Zn to benzaldehyde.

Before starting to test all the chiral ligands synthesised in the present work, we ran a 'ligand-free' control experiment (entry 1). Surprisingly, racemic **20** was formed in 43% yield after 18 h, together with benzylic alcohol **21** (17%). It was clear that a competitive non-catalysed reaction was also occurring and since it has

Table 1
Distribution of products obtained by diethylzinc addition on benzaldehyde

Entry	L*	R	Time (h)	**19**[a] (%)	**20**[a] (%)	**21**[a] (%)	(*S*)-ee[b] (%)
1[c]	None		18	40	43	17	0
2[d]	None		18	83	14	3	0
3[d]	None		6	87	8	5	0
4[c]	**1**	Me	18	0	96	4	96
5[d]	**1**		18	8	88	4	96
6[d]	**1**		6	11	84	5	96
7[c]	**18b**	C_6H_5	18	45	48	7	0
8[c]	**18c**	4-MeO-C_6H_4	18	40	40	20	0
9[c]	**18d**	2-Me-C_6H_4	18	33	61	6	6
10[d]	**18d**		6	71	23	6	14
11[c]	**18e**	Ms	18	60	32	8	0
12[c]	**18f**	Ts	18	41	43	17	0
13[c]	**18g**	CH_2CH_2F	18	38	46	16	65
14[d]	**18g**		18	22	73	6	84
15[d]	**18g**		6	40	54	6	85
16[6a]	**22**	CH_2CH_3[e]	24	0	98	2	90
17[c]	**18h**	CH_2CF_3	18	20	64	16	2
18[c]	**18i**	Pr	18	4	90	6	73

[a] Determined by GC.
[b] Determined by GC using β DEX™ 120 column.
[c] Et_2Zn 1.0 M in hexanes, Batch S38116.
[d] Et_2Zn 1.0 M in hexanes, Batch S29515.
[e] Tested at 10% mol.

been well established that dialkylzinc itself does not add to carbonyl groups, we supposed that the commercial solutions of diethyl zinc used in our experiments contained trace amounts of impurities responsible for the side-addition.[21] Testing a different batch of diethyl zinc resulted in a noteworthy decrease in the amount of racemic **20** ('only' 14%, entry 2), that did not significantly changed when stopping the reaction after 6 h (8%, entry 3). Furthermore, the amount of **21** decreased (3–5%, entries 2 and 3). The same set of three experiments was carried out in the presence of *N*-methyl **1** (entries 4–6) and resulted in the important observation that the activity of the ligand was independent of the diethyl zinc batch used: (*S*)-**20** was always obtained with 96% ee, whereas the amount of **21** set to 4–5% and only the percentage of the remaining benzaldehyde was affected, increasing from 0 (entry 4) to 8–11% (entries 5 and 6). Based on these data, we could reasonably rely on the results obtained regardless of the commercial organozinc reagent quality, at least with the best ligand **1**.

In addition to the steric hindrance of the N-substituent, in *N*-phenyl **18b** (entry 7) the lone pair of the nitrogen atom conjugates with the π system of the aromatic ring and, therefore, is less inclined to complex zinc. MM2 calculations, performed on compound **18b** (Fig. 1), clearly showed the sp^2 nitrogen hybridisation (bond angles of 119.39°, 119.52° and 120.98°) and the resulting conformation of the *N*-phenyl substituent partially screened the coordination site, making the interaction of Et_2Zn with the ligand more difficult. For comparison, compound **1** was also analysed (Fig. 1): the sp^3 nitrogen hybridisation was evident (bond angles of 112.19°, 110.62° and 112.19°) and the *N*-methyl group was thus oriented far from the coordination site, allowing an easier access of the organozinc reagent for the ligand-metal complex formation (the X-ray structure of **1** hydrochloride was also determined,[22] and the ORTEP plot is depicted in Fig. 2).

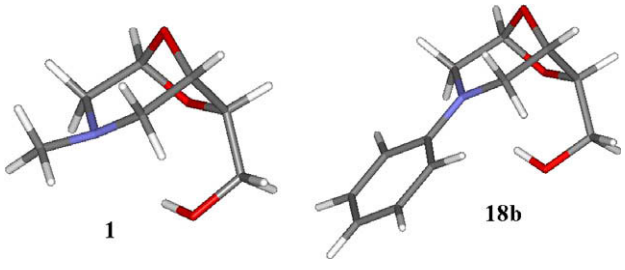


Figure 1. MM2 structures of ligands **1** and **18b**.

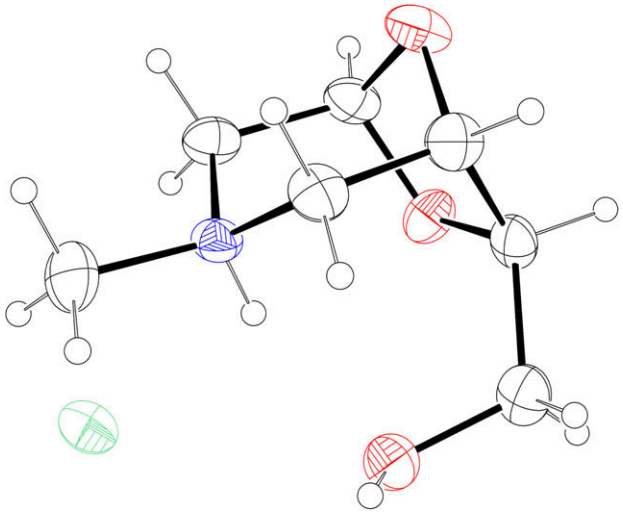


Figure 2. X-ray structure of **1**·HCl.

Consequently, only the competitive non-catalysed reaction occurred with ligand **18b**. In fact, racemic **20** formed (48%) and most of benzaldehyde **19** was left unreacted (45%). The presence of an electron-donating *p*-methoxy group on the *N*-aryl substituent (**18c**, entry 8) did not alter the outcome of the reaction; only the β-reduction reaction increased (20% of **21**), and racemic **20** and starting material **19** were obtained in an equal 40% amount.

Therefore, in order to restore the capability of the nitrogen lone pair for metal complexation, its conjugation with the π system had to be broken; this was possible by choosing an *o*-tolyl group for the next *N*-aryl **18d** ligand (entry 9), in which the presence of the *o*-methyl could force the aromatic ring to assume a skew

conformation. Actually, (*S*)-**20** formed in a higher amount (61%) and showed some optical activity (ee 6%); however, the *o*-tolyl group must be too hindered for rapid complex formation and the catalysed reaction proceeded too slowly to compete with the side non-catalysed addition. Since the presence of the latter could obviously weigh more on the cases of very low enantioselectivities, we ran a second experiment with the same ligand **18d**, using the best batch of Et_2Zn in our hands and stopping the reaction after 6 h (entry 10); most benzaldehyde was recovered unreacted (71% of **19**) but alcohol (*S*)-**20** was obtained with 14% ee. The result itself was not good in terms of enantioselectivity, but proved the hypothesis of the role of the *o*-tolyl substituent of the ligand.

Based on these results, we did not expect any enantioselectivity for the reactions conducted with *N*-solfonylamides **18e** and **18f** (entries 11 and 12), in which again the nitrogen lone pair was not available for N–Zn interactions. This was in fact the case, as we only obtained the racemic alcohol **20** (32% and 43%, respectively) and recovered the unreacted **19** (60% and 41%, respectively).

So far the *N*-alkyl ligands seemed to best complex the organozinc reagent. However, the literature[1,5] has reported countless examples of chiral amino alcohols able to afford, in shorter reaction times (2–3 h) and with minimal ligand amounts (1–2% mol), the same enantiopure products obtained by employing our 1,4-amino alcohols in higher amounts (15–20% mol) and over longer reaction times (18 h). The efficiency of a catalyst is usually explained in terms of turn over and, according to the reaction mechanism and to the transition state model proposed (Fig. 3),[6a] we thought that its rate could be influenced by the strength of the N-Zn interaction in complexes **A** and **B**.

The modulation of the potency of this interaction could be realised by choosing either electron-donating or electron-withdrawing N-substituents. The *N*-fluoroalkyl **18g**, in which the electron-withdrawing fluorine caused a decrease of the nucleophilicity of the nitrogen, afforded (*S*)-**20** in 46% yield and with 65% ee (entry 13). The use of a second batch of Et_2Zn resulted in an increment of the enantiomeric excess of (*S*)-**20** to 84% (entry 14), showing how deeply the non-catalysed reaction could mislead in the evaluation of the efficiency of a ligand. Consistently, by reducing the reaction time from 18 to 6 h (entry 15), the amount of starting **19** increased (from 22% to 40%) but, as already seen in the case of **1** (entries 5 and 6), the enantiomeric excess held steady. The effect of the *N*-(2-fluoroethyl) group on the outcome of the reaction can be highlighted by the comparison with the results obtained with *N*-ethyl **22** (Fig. 4),[6a] tested at 10% mol over 24 h (entry 16): (*S*)-**20** was obtained in 98% yield and 90% ee. Hence the replacement of H with F lowered the reaction rate and the enantioselectivity, most probably because of a weakening of the N–Zn interaction. In this case, we could hardly ascribe this decrease in stereoselectivity to the difference in steric hindrance of the two atoms. This hypothesis seemed confirmed by the almost total loss of enantioselectivity (ee 2%, entry 17) in the reaction that used *N*-CH_2CF_3 **18h** as a chiral ligand, where the very poor nucleophilicity of the nitrogen, due to the presence of three F atoms, prevented the formation of a sufficiently strong N–Zn interaction in the metal-ligand complexes (**A** and **B**, Fig. 3).[23]

Finally, when employing *N*-propyl **18i**, the steric hindrance effect of the substituent caused, as expected, a decrease of the enantioselectivity and (*S*)-alcohol formed in 73% ee (entry 18); no significant change was obtained with the best Et_2Zn batch (ee 77%; data not shown).

Thus *N*-methyl **1** proved to be the best ligand belonging to this class of 1,4-amino alcohols. Therefore, assuming **1** as datum point, all data in our hands seemed to highlight that *N*-EWG ligands were less enantioselective because of the weakening of the N–Zn interaction in the TS. The effects of *N*-EDG ligands could only be verified with the introduction of EDGs at the α-position with respect to the nitrogen atom. The synthesis focussed on obtaining such structures, which required some less than trivial changes in the synthetic route; the results will be reported in due course.

3. Conclusions

Herein, we have reported on a new synthetic methodology tuned to the 1,4-amino alcohol scaffold **16** which is easily *N*-functionalisable with a wide variety of substituent (aryls, sulfonyls, alkyls and fluoroalkyls). The thus obtained chiral compounds **18b–i** were then used as chiral ligands in the addition of Et_2Zn to benzaldehyde. The results of these experiments gave an insight into the influence of the nature of the N-substituent on the stereoselectivity of the addition. However, the presence of a non-catalysed addition could not be neglected; in fact, depending on the diethyl zinc batch used, different amounts of racemic alcohol **20** formed and therefore the evaluation of the efficiency of a chiral ligand can be misleading at least when the catalysed reaction proceeds too slowly.

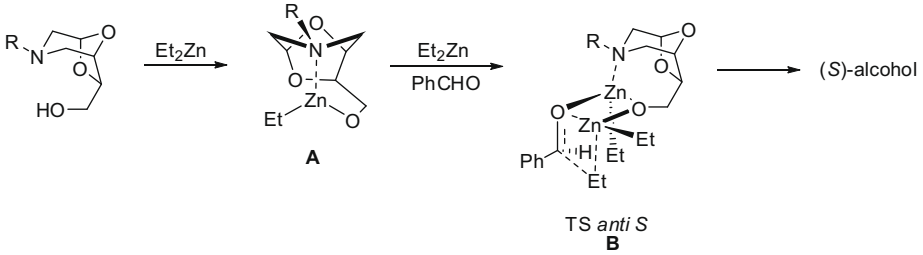
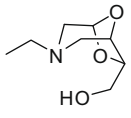


Figure 3. Model of transition state.



22

Figure 4. Structure of *N*-ethyl amino alcohol **22**.

Thus, a 'blank' experiment had to be carried out for every commercial batch purchased. The results in our hands showed that *N*-EWG ligands caused a decrease in the enantioselectivity, probably because of the weakening of the N–Zn interaction in the TS. The effect of the electron-donating substituent could only be evaluated by α-functionalised 1,4-amino alcohols, whose synthesis and application will be reported in due course.

4. Experimental

4.1. General

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.33 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. Mass spectra were carried out by EI at 70 eV, unless otherwise stated, on Shimadzu GC/MS QP5050 instruments. Microanalyses were carried out with a Perkin–Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument.

2,2,2-Trifluoroethyl trifluoromethanesulfonate[15] and 2-fluoroethyltosylate[14] were synthesised by published procedures. The 1.0 M Et_2Zn solution in hexanes was purchased from Aldrich (cat. No. 296112, batches S29515 and S38116).

4.1.1. (4*R*,5*R*)-5-Hydroxymethyl-2,2-dimethyl[1,3]dioxolane-4-carboxylic acid (2,2-dimethoxyethyl)amide 6

A solution of **5** (2.27 mL, 20.9 mmol) in anhydrous DCM (77 mL) was cooled at 0 °C; an $AlMe_3$ solution (2.0 M in hexane, 10.5 mL, 20.9 mmol) was added dropwise and, after 30 min, lactone **3** (3.0 g, 19.0 mmol) was added. After 1 h the ice bath was removed and the resulting solution was stirred for 19 h at room temperature. After cooling at 0 °C, concd HCl was added dropwise until a slurry formed; water (50 mL) and brine (25 mL) were then added and additional concd HCl until the slurry disappeared (pH ~ 2). After separation of the phases, the aqueous one was extracted with DCM (2 × 25 mL); the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **6** was obtained (4.78 g, 95%) and this was used in the next step without further purification. Compound **6**: $[\alpha]_D^{23} = +3.5$ (*c* 0.71, $CHCl_3$). ^{1}H NMR δ (ppm): 7.02–6.90 (br s, 1H), 4.64–4.49 (m, 2H), 4.38 (t, *J* 5.1 Hz, 1H), 3.85–3.77 (m, 1H), 3.64–3.52 (m, 2H), 3.40 (s, 6H), 3.38–3.25 (m, 1H), 1.55 (s, 3H), 1.39 (s, 3H). ^{13}C NMR δ (ppm): 170.6 (s), 110.0 (s), 102.3 (d), 77.6 (d), 76.8 (d), 61.5 (t), 54.5 (q), 54.4 (q), 40.4 (t), 29.6 (q), 24.7 (q). MS *m/z* (%): 263 (M^+, 5), 232 (27), 174 (100).

4.1.2. (4*R*,5*R*)-5-Benzyloxymethyl-2,2-dimethyl[1,3]dioxolane-4-carboxylic acid (2,2-dimethoxyethyl)amide 7

Freshly powdered KOH (917 mg, 16.3 mmol) was added to a solution of amido alcohol **6** (3.91 g, 14.8 mmol) in anhydrous THF (30 mL), followed by 18-C-6 ether (157 mg, 4% mol) and benzyl bromide (1.94 mL, 16.3 mmol). The suspension was left to stir at room temperature for 70 min. After this time, DCM (50 mL), water (30 mL) and 1 M HCl (10 mL) were added; the phases were separated and the organic one was washed with H_2O (2 × 40 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (eluent: EtOAc–petroleum ether, 1:1 + 0.5% Et_3N; R_f = 0.31) and pure **7** was obtained as a colourless oil (2.86 g, 55%). Compound **7**: $[\alpha]_D^{24} = +12.9$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 7.46–7.22 (m, 5H), 6.81–6.67 (br s, 1H), 4.62–4.48 (m, 4H), 4.26 (t, *J* 5.5 Hz, 1H), 3.83 (dd, *J* 10.6, 2.2 Hz, 1H), 3.45 (dd, *J* 10.6, 7.3 Hz, 1H), 3.39–3.22 (m, 2H), 3.34 (s, 3H), 3.32 (s, 3H), 1.58 (s, 3. H), 1.39 (s, 3H). ^{13}C NMR δ (ppm): 169.1 (s), 138.0 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.5 (d), 110.2 (s), 102.3 (d), 76.7 (d), 75.6 (d), 73.4 (t), 68.9 (t), 54.3 (q, 2C), 40.2 (t), 27.0 (q), 24.7 (q). MS *m/z* (%): 353 (M^+, 1), 234 (7), 91 (48). Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.44; H, 7.63; N, 4.03.

4.1.3. (4*R*,5*R*)-(5-Benzyloxymethyl-2,2-dimethyl[1,3]dioxolane-4-carbonyl)-(2,2-dimethoxyethyl)carbamic acid methyl ester 8

A solution of amide **7** (995 mg, 2.81 mmol) in anhydrous THF (10 mL) was cooled to −70 °C. A *n*-BuLi solution (1.6 M in hexane, 1.8 mL, 2.81 mmol) was added dropwise, maintaining the temperature below −60 °C, and, after 30 min, a solution of methylchloroformate (217 μL, 2.81 mmol) in anhydrous THF (2 mL) was added. After 4 h at −70 °C, the mixture was allowed to warm at rt and quenched by addition of satd NH_4Cl (10 mL). The product was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (eluent: EtOAc–petroleum ether, 1:3 + 0.5% Et_3N; R_f = 0.29) and pure **8** was obtained as a colourless oil (746 mg, 65%). Compound **8**: $[\alpha]_D^{26} = +63.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 7.37–7.18 (m, 5H), 5.56 (d, *J* 7.0 Hz, 1H), 4.80 (q_{AB}, *J* 5.9 Hz, 1H), 4.47 (s, 2H), 4.49–4.42 (m, 1H), 3.85–3.62 (m, 2H), 3.73 (s, 3H), 3.57–3.43 (m, 2H), 3.30 (s, 3H), 3.26 (s, 3H), 1.60 (s, 3H), 1.40 (s, 3H). ^{13}C NMR δ (ppm): 170.8 (s), 154.4 (s), 137.8 (s), 128.1 (d, 2C), 127.4 (d, 3C), 109.9 (s), 101.5 (d), 100.9 (d), 77.5 (d), 76.5 (d), 73.2 (t), 69.1 (t), 54.4 (q), 54.3 (q), 53.8 (q), 45.1 (t), 27.4 (q), 25.4 (q). MS *m/z* (%): 411 (M^+, 0.3), 91 (90), 75 (100). Anal. Calcd for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10; N, 3.40. Found: C, 58.17; H, 6.87; N, 3.26.

4.1.4. (1*R*,5*R*,7*R*)-7-Benzyloxymethyl-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-3-carboxylic acid methyl ester (9)

Prepared as reported in the literature[6b] starting from **8** (721 mg, 1.75 mmol) and obtaining pure **9** (74 mg, 14%) as a white solid after FCC purification (eluent: EtOAc–petroleum ether, 2:3; R_f = 0.33). Compound **9**: mp 76–77 °C. $[\alpha]_D^{23} = -27.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR δ (ppm): 7.37–7.25 (m, 5H), 5.77 (d, *J* 2.6 Hz, 1H), 4.69 (d, *J* 4.8 Hz, 1H), 4.59–4.45 (m, 2H), 4.27 (q_{AB}, *J* 4.4 Hz, 1H), 3.82 (s, 3H), 3.75–3.53 (m, 4H). ^{13}C NMR δ (ppm): 165.8 (s), 153.3 (s), 137.3 (s), 128.3 (d, 2C), 127.7 (d, 3C), 98.3 (d), 78.5 (d), 77.6 (d), 73.7 (t), 67.4 (t), 54.1 (q), 51.7 (t). MS *m/z* (%): 307 (M^+, 1), 201 (M^+−OBn, 14), 172 (32), 91 (100). Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.57; H, 5.55; N, 4.28.

4.1.5. (4*S*,5*R*)-(5-Benzyloxymethyl-2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-(2,2-dimethoxyethyl)amine 11

Amidoalcohol **7** (1.0 g, 2.82 mmol) was dissolved into anhydrous THF (30 mL), and $BH_3{\cdot}SMe_2$ (10 M, 560 μL, 5.64 mmol) was added dropwise. The resulting solution was refluxed for 1 h; after cooling, abs EtOH (1.1 mL), 3 M NaOH (840 μL) and water (56 mL) were added dropwise and the resulting suspension was refluxed for 1 h. After this time, the mixture was cooled at room temperature and the product was extracted with EtOAc (2 × 75 mL); the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (eluent: DCM–MeOH, 30:1 + 0.5% Et_3N; R_f = 0.40) and pure **11** was obtained as a colourless oil (305 g, 32%). Compound **11**: $[\alpha]_D^{25} = -10.2$ (*c* 0.76, $CHCl_3$). ^{1}H NMR δ (ppm): 7.44–7.28 (m, 5H), 4.55 (q_{AB}, *J* 12.1 Hz, 2H), 4.44 (t, *J* 5.9 Hz, 1H), 4.38–4.27 (m, 2H), 3.57–3.45 (m, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 2.78–2.72 (m, 4H), 2.06–1.87 (br s, 1H), 1.43 (s, 3H), 1.35 (s, 3H). ^{13}C NMR δ (ppm): 137.7 (s), 128.3 (d, 2C), 127.7 (d, 2C), 127.6 (d), 108.3 (s), 103.7 (d), 76.5 (d), 75.7 (d), 73.5 (t), 68.6 (t), 54.0 (q), 51.4 (t), 49.2 (t), 28.1 (q), 25.5 (q). MS *m/z* (%): 324 (M^+−CH_3,

2), 264 (27), 91 (100). Anal. Calcd for $C_{18}H_{29}NO_5 \cdot H_2O$: C, 61.52; H, 8.70; N, 3.99. Found: C, 61.72; H, 8.75; N, 4.08.

4.1.6. (4*S*,5*R*)-(5-Benzyloxymethyl-2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-(2,2-dimethoxyethyl)carbamic acid methyl ester 10

From **11**: A solution of **11** (1.2 g, 3.5 mmol) in anhydrous DCM (60 mL) was cooled at 0 °C; Et_3N (630 μL, 4.6 mmol, 1.3 equiv) and methyl chloroformate (350 μL, 4.6 mmol, 1.3 equiv) were then added dropwise. The mixture was then allowed to warm to room temperature and was stirred for 1 h. The solution was then washed with water (40 mL), brine (40 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by FCC (eluent: EtOAc–petroleum ether, 1:2; $R_f = 0.35$) to afford pure **10** as a colourless oil (904 mg, 65%).

From **15**: A solution of **15** (1.72 g, 5.6 mmol) in anhydrous THF (56 mL) was cooled at 0 °C; NaH (60% suspension in mineral oil, 248 mg, 6.2 mmol) and tetrabutylammonium iodide (10% mol) were added, and the suspension was stirred under nitrogen for 30 min. Benzyl bromide (686 μL, 5.8 mmol) was then added and, after 30 min, the ice bath was removed and the suspension was stirred at room temperature for further 7 h. The reaction was then quenched by addition of satd NH_4Cl (28 mL) and water (56 mL); the product was extracted with EtOAc (3 × 70 mL) and the combined organic phases were washed with brine (56 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by FCC (eluent EtOAc–petroleum ether, 1:2; $R_f = 0.39$), affording pure **10** as a yellowish oil (1.5 g, 67%). Compound **10**: $[\alpha]_D^{23} = -54.4$ (*c* 0.87, $CHCl_3$). ^{1}H NMR δ (ppm): 7.34 (br s, 5H), 4.63–4.49 (m, 2H), 4.41–4.33 (m, 2H), 3.79–3.49 (m, 5H), 3.70 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 3.31–3.12 (m, 2H), 1.46 (s, 3H), 1.32 (s, 3H). ^{13}C NMR δ (ppm) [two rotamers]: 156.7 (s), 137.8 (s), 128.3 (d, 2C), 127.7 (d, 3C), 108.8 (s), 103.7 and 103.5 (d), 76.3 (d), 75.7 and 75.5 (d), 73.5 (t), 68.4 (t), 54.9 (q), 54.4 and 54.0 (q), 52.7 (q), 49.9 and 49.7 (t), 48.4 and 47.9 (t), 28.0 (q), 25.5 (q). MS *m/z* (%): 382 (M^+-CH_3, 4), 307 (4), 218 (14), 91 (74), 75 (100). Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.52. Found: C, 60.18; H, 7.91; N, 3.49.

4.1.7. (2*R*,3*R*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol 13

A solution of **3** (1.95 g, 12.3 mmol) in water (100 mL) was cooled in an ice bath, and $NaBH_4$ (350 mg, 3 equiv) was added portion-wise over 2 h under stirring. The pH was monitored continuously and maintained between 4 and 7 by the addition of H_2SO_4 (3 N). When the reduction was complete (TLC; eluent: Et_2O–petroleum ether, 1:1), water was evaporated and CH_3OH was added to the residue and evaporated (3 × 40 mL). Finally, $CHCl_3$ (100 mL) was added to the residue and the solution was dried over Na_2SO_4. Filtration through a pad of Celite–silica gel and evaporation of the solvent provided crude **13** (1.68 g, 85%) as a colourless oil. This was used in the next reaction without further purification. Compound **13**: ^{1}H NMR δ (ppm): 5.42 (s, 1H), 4.84 (dd, *J* 6.2, 3.7 Hz, 1H), 4.58 (d, *J* 5.86 Hz, 1H), 4.12–3.99 (m, 2H), 2.64 (br s, 1H), 1.47 (s, 3H), 1.32 (s, 3H).

4.1.8. (4*S*,5*R*)-{5-[(2,2-Dimethoxyethylamino)methyl]-2,2-dimethyl[1,3]dioxolan-4-yl}methanol 14

A solution of **13** (1.68 g, 10.5 mmol) and **5** (1.26 mL, 11.6 mmol) in CH_3OH (53 mL) was cooled at 0 °C; $NaBH_3CN$ (726 mg, 11.6 mmol) was added, and the pH was adjusted to 6 with glacial CH_3CO_2H. The ice bath was removed after 15 min and the solution was stirred for 22 h at rt. After evaporation of the solvent, the residue was treated with satd Na_2CO_3 (25 mL) and the product was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **14** was purified by flash chromatography, eluting first with EtOAc and then with DCM–MeOH, 20:1 ($R_f = 0.50$), affording pure **14** (1.62 g, 62%) as a pale yellow oil. Compound **14**: $[\alpha]_D^{26} = -7.2$ (*c* 0.50, $CHCl_3$). ^{1}H NMR δ (ppm): 4.43 (t, *J* 5.5 Hz, 1H), 4.34–4.27 (m, 2H), 3.80–3.65 (m, 2H), 3.38 (s, 6H), 3.01–2.80 (m, 2H), 2.75 (d, *J* 5.5 Hz, 2H), 1.43 (s, 3H), 1.34 (s, 3H). ^{13}C NMR δ (ppm): 107.9 (s), 103.2 (d), 77.44 (d), 75.8 (d), 60.4 (t), 54.3 (q, 2C), 50.8 (t), 48.6 (t), 27.4 (q), 24.9 (q). MS *m/z* (%): 249 (M^+, 0.3), 174 (M^+–$CH(OCH_3)_2$, 34), 118 (74). Anal. Calcd for $C_{11}H_{23}NO_5 \cdot \frac{1}{4}H_2O$: C, 52.06; H, 9.33; N, 5.52. Found: C, 52.11; H, 9.64; N, 5.75.

4.1.9. (4*S*,5*R*)-(2,2-Dimethoxyethyl)-(5-hydroxymethyl-2,2-dimethyl[1,3]dioxolan-4-ylmethyl)carbamic acid methyl ester 15

A solution of **14** (1.62 g, 6.5 mmol) in anhydrous DCM (65 mL) was cooled at 0 °C; Et_3N (1.2 mL, 8.5 mmol, 1.3 equiv) and methyl chloroformate (657 μL, 8.5 mmol, 1.3 equiv) were added dropwise. A further 1.3 equiv of Et_3N and methyl chloroformate was added after 20 min, the ice bath was removed and the resulting solution was stirred at room temperature until **14** was consumed (TLC; eluent: EtOAc–petroleum ether, 2:1). The solution was then washed with water (2 × 40 mL), brine (60 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was taken up into methanol (15 mL) and anhydrous K_2CO_3 (5% mol) was added. The resulting solution was stirred at rt for 3.5 h; the solvent was then removed by evaporation and the crude was directly purified by FCC (eluent: DCM–MeOH, 30:1; $R_f = 0.11$) to afford pure **15** as a colourless oil (1.72 g, 86%). Compound **15**: $[\alpha]_D^{23} = -58.7$ (*c* 0.93, $CHCl_3$). ^{1}H NMR δ (ppm): 4.52–4.25 (m, 2H), 4.22–4.14 (m, 1H), 3.67 (s, 3H), 3.62–3.52 (m, 4H), 3.34 (s, 6H), 3.31–3.23 (m, 2H), 1.43 (s, 3H), 1.29 (s, 3H). ^{13}C NMR δ (ppm) [two rotamers]: 156.6 (s), 108.3 (s), 103.4 (d), 77.1 (d), 76.2 (d), 60.9 (t), 54.8 (q), 54.3 and 54.0 (q), 52.7 (q), 49.8 (t), 48.3 and 47.9 (t), 27.9 (q), 25.2 (q). MS *m/z* (%): 292 (M^+–CH_3, 2), 186 (5), 144 (8), 75 (100). Anal. Calcd for $C_{13}H_{25}NO_7 \cdot \frac{1}{4}H_2O$: C, 50.07; H, 8.24; N, 4.49. Found: C, 50.06; H, 8.65; N, 4.50.

4.1.10. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-3-carboxylic acid methyl ester 12

A solution of **10** (1.5 g, 3.8 mmol) in DCM (7.6 mL) was cooled at 0 °C and TFA (3.8 mL) was dropwise added. After 10 min, the ice bath was removed and the solution was stirred at rt overnight. The reaction was stopped by cautious addition of satd $NaHCO_3$ (15 mL) and Na_2CO_3 (s), under vigorous stirring, until pH was 7–8. The phases were then separated, the aqueous layer was extracted with DCM (2 × 8 mL). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by FCC (eluent: EtOAc–petroleum ether, 1:3; $R_f = 0.26$), affording pure **12** (736 mg, 66%) as a pale yellow oil. Compound **12**: $[\alpha]_D^{26} = -46.9$ (*c* 1.25, $CHCl_3$). ^{1}H NMR δ (ppm) [two rotamers]: 7.42–7.27 (m, 5H), 5.53 (s, 1H, minor rotamer), 5.49 (s, 1H; major rotamer), 4.66–4.52 (m, 2H), 4.48–4.34 (m, 1H), 4.25–4.15 (m, 1H), 3.97–3.83 (m, 1H), 3.82–3.71 (m, 2H), 3.70 (s, 3H, major rotamer), 3.67 (s, 3H, minor rotamer), 3.59–3.51 (m, 1H), 3.33–3.23 (m, 1H), 3.11–2.99 (m, 1H). ^{13}C NMR δ (ppm) [two rotamers]: 137.7 (s), 128.4 (d, 2C), 127.8 (d, 2C), 127.5 (d), 98.7 and 98.4 (d), 76.2 and 75.8 (d), 73.8 (t), 72.7 and 72.3 (d), 68.3 (t), 52.8 (q), 48.3 (t), 43.4 and 43.1 (t). MS *m/z* (%): 293 (M^+, 5), 202 (M^+–Bn, 6), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_3 \cdot H_2O$: C, 60.19; H, 6.62; N, 4.68. Found: C, 60.23; H, 6.30; N, 4.76.

4.1.11. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane 16

Powdered KOH (1.4 g, 25 mmol) was added to a solution of **12** (736 mg, 2.5 mmol) in MeOH (32 mL) and water (8 mL). The

resulting solution was refluxed for 48 h and a second portion of KOH (1.4 g, 25 mmol) was added after 24 h. After cooling at rt, the solvent was removed in vacuo, the residue was taken up into water (15 mL) and the product was extracted with $CHCl_3$ (3 × 15 mL). After filtration and evaporation of the solvent, amino alcohol **16** was obtained as a pale yellow oil (553 mg, 94%). Compound **16**: $[\alpha]_D^{24} = -52.0$ (*c* 1.03, $CHCl_3$). ^{1}H NMR δ (ppm): 7.40–7.30 (m, 5H), 5.40 (s, 1H), 4.61 (q_{AB}, *J* 12.1 Hz, 2H), 4.24–4.10 (m, 2H), 3.99–3.84 (m, 2H), 3.24–3.12 (m, 1H), 2.88 (q_{AB}, *J* 13.2 Hz, 2H), 2.66 (d, *J* 13.2 Hz, 1H). ^{13}C NMR δ (ppm): 137.3 (s), 128.2 (d, 2C), 127.6 (d), 127.5 (d, 2C), 100.7 (d), 77.0 (d), 74.5 (d), 73.6 (t), 67.5 (t), 49.0 (t), 45.2 (t). MS *m/z* (%): 144 (M^+−Bn, 38), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_3 \cdot H_2O$: C, 64.71; H, 7.38; N, 5.80. Found: C, 64.24; H, 7.37; N, 5.90.

4.2. General procedure for arylation with arylboronic acids

To a solution of amino alcohol **16** (118 mg, 0.5 mmol) in anhydrous DCM (3.2 mL) were added the desired aryl boronic acid (1.0 mmol), anhydrous $Cu(AcO)_2$ (0.5 mmol) and Et_3N (1.0 mmol). The resulting blue suspension was stirred under an oxygen atmosphere (balloon) at room temperature for 5 h. The dark green suspension was then diluted with DCM (12 mL) and washed with 10% aq NH_4OH (3 × 10 mL). The aqueous phases were extracted once with DCM (10 mL) and the combined organic layers were washed with water (2 × 10 mL), brine (15 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was straightly purified by FCC (eluent: EtOAc–petroleum ether, 1:7 + 0.5% Et_3N) to afford pure *N*-aryl compounds **17b–d**.

4.2.1. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-3-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane 17b

White solid (50%). R_f = 0.38. mp 64–65 °C. $[\alpha]_D^{23} = -59.1$ (*c* 0.75, $CHCl_3$). ^{1}H NMR δ (ppm): 7.38–7.30 (m, 5H), 7.28–7.22 (m, 2H), 6.82 (t, *J* 7.0 Hz, 1H), 6.69–6.64 (m, 2H), 5.65 (s, 1H), 4.59–4.55 (m, 1H), 4.53 (q_{AB}, *J* 12.1 Hz, 2H), 4.31–4.22 (m, 1H), 3.91–3.83 (m, 1H), 3.75–3.66 (m, 1H), 3.54–3.47 (m, 2H), 3.15 (dd, *J* 12.5, 2.9 Hz, 1H), 2.94 (dd, *J* 11.7, 1.5 Hz, 1H). ^{13}C NMR δ (ppm): 149.1 (s), 137.8 (s), 129.2 (d, 3C), 128.4 (d, 2C), 127.8 (d, 2C), 118.3 (d), 112.5 (d, 2C), 99.1 (d), 75.7 (d), 73.6 (t), 73.1 (d), 68.4 (t), 51.2 (t), 46.0 (t). MS *m/z* (%): 311 (M^+, 7), 220 (M^+−Bn, 46), 105 (100), 91 (71). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.19; H, 6.98; N, 4.69.

4.2.2. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-3-(4-methoxyphenyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane 17c

Pale pink solid (43%). R_f = 0.34. mp 91–92 °C. $[\alpha]_D^{23} = -61.5$ (*c* 0.92, $CHCl_3$). ^{1}H NMR δ (ppm): 7.39–7.31 (m, 5H), 6.92–6.82 (m, 2H), 6.68–6.60 (m, 2H), 5.65 (s, 1H), 4.57 (q_{AB}, *J* 12.1 Hz, 2H), 4.58–4.53 (m, 1H), 4.35–4.25 (m, 1H), 3.98–3.90 (m, 1H), 3.83–3.75 (m, 1H), 3.79 (s, 3H), 3.44 (d, *J* 11.4 Hz, 2H), 3.12 (dd, *J* 12.1, 2.6 Hz, 1H), 2.90 (dd, *J* 11.4, 1.1 Hz, 1H). ^{13}C NMR δ (ppm): 152.5 (s), 143.3 (s), 137.7 (s), 128.2 (d, 2C), 127.7 (d, 2C), 127.6 (d), 114.5 (d, 2C), 114.0 (d, 2C), 99.1 (d), 75.8 (d), 73.5 (t), 73.1 (d), 68.2 (t), 55.6 (q), 52.0 (t), 47.0 (t). MS *m/z* (%): 341 (M^+, 41), 250 (M^+−Bn, 64), 135 (100), 120 (32), 91 (39). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.55; H, 6.73; N, 4.14.

4.2.3. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-3-*o*-tolyl-6,8-dioxa-3-azabicyclo[3.2.1]octane 17d

Yellow oil (10%). R_f = 0.48. $[\alpha]_D^{26} = -123.7$ (*c* 0.5, $CHCl_3$). ^{1}H NMR δ (ppm): 7.33–7.02 (m, 9H), 5.56 (d, *J* 1.5 Hz, 1H), 4.57 (q_{AB}, *J* 11.7 Hz, 2H), 4.49–4.45 (m, 1H), 4.40–4.31 (m, 1H), 4.22–4.14 (m, 1H), 4.01–3.94 (m, 1H), 3.58 (dd, *J* 12.1, 2.2 Hz, 1H), 3.15 (d, *J* 11.4 Hz, 1H), 2.88 (d, *J* 12.5 Hz, 1H), 2.68 (d, *J* 11.7 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR δ (ppm): 149.0 (s), 137.8 (s), 132.8 (s), 131.4 (d), 128.3 (d, 2C), 127.7 (d, 2C), 127.6 (d), 126.7 (d), 123.8 (d), 120.1 (d), 99.9 (d), 77.1 (d), 74.0 (d), 73.5 (t), 68.2 (t), 55.5 (t), 49.6 (t), 18.2 (q). MS *m/z* (%): 325 (M^+, 7), 234 (M^+−Bn, 94), 118 (100), 91 (93). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.95; H, 7.46; N, 4.26.

4.2.4. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-3-methanesulfonyl-6,8-dioxa-3-azabicyclo[3.2.1]octane 17e

At first, Et_3N (62 μL, 0.44 mmol) and CH_3SO_2Cl (50 mg, 0.44 mmol) were added to a solution of **16** (80 mg, 0.34 mmol) in anhydrous DCM (7 mL), stirred at room temperature and under nitrogen atmosphere. The reaction was monitored by TLC (eluent: DCM–MeOH, 20:1) and, after 28 h, DCM was added (8 mL) and the organic phase was washed with 1 M HCl (10 mL), satd $NaHCO_3$ (10 mL), water (2 × 10 mL), brine (10 mL) and finally dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by FCC (eluent: DCM–MeOH, 60:1; R_f = 0.65), affording pure **17e** as a white solid (86 mg, 81%). Compound **17e**: mp 90–91 °C. $[\alpha]_D^{26} = -47.4$ (*c* 0.74, $CHCl_3$). ^{1}H NMR δ (ppm): 7.36–7.28 (m, 5H), 5.59 (s, 1H), 4.59 (s, 2H), 4.51–4.45 (m, 1H), 4.30–4.21 (m, 1H), 4.03–3.83 (m, 2H), 3.69 (d, *J* 11.9 Hz, 1H), 3.52 (d, *J* 11.4 Hz, 1H), 3.16 (dd, *J* 12.1, 2.9 Hz, 1H), 2.92 (d, *J* 11.4 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR δ (ppm): 137.7 (s), 128.4 (d, 2C), 127.9 (d, 2C), 127.8 (d), 98.3 (d), 76.3 (d), 73.8 (t), 72.5 (d), 68.0 (t), 49.1 (t), 44.7 (t), 34.5 (q). MS *m/z* (%): 313 (M^+, 1), 234 (M^+−Ms, 8), 128 (8), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.95; H, 6.46; N, 4.86.

4.2.5. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-3-(toluene-4-sulfonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane 17f

Prepared as reported for **17e**. Starting from **16** (89 mg, 0.38 mmol) and TsCl (95 mg, 0.50 mmol) and obtaining, after purification by FCC (eluent: EtOAc–petroleum ether, 1:1; R_f = 0.26), pure **17f** (100 mg, 71%) as a white solid. Compound **17f**: mp 145–146 °C. $[\alpha]_D^{26} = +4.6$ (*c* 0.85, $CHCl_3$). ^{1}H NMR δ (ppm): 7.63 (d, *J* 8.4 Hz, 2H), 7.38–7.27 (m, 7H), 5.51 (s, 1H), 4.60 (s, 2H), 4.41–4.38 (m, 1H), 4.27–4.18 (m, 1H), 4.08–3.89 (m, 2H), 3.68 (d, *J* 12.1 Hz, 1H), 3.57 (d, *J* 11.0 Hz, 1H), 2.79 (dd, *J* 11.7, 2.2 Hz, 1H), 2.58 (d, *J* 11.4 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR δ (ppm): 143.8 (s), 137.7 (s), 132.1 (s), 129.6 (d, 2C), 128.3 (d, 2C), 127.7 (d, 2C), 127.6 (d), 127.4 (d, 2C), 98.3 (d), 76.2 (d), 73.7 (t), 72.4 (d), 68.1 (t), 49.2 (t), 44.8 (t), 21.6 (q). MS *m/z* (%): 389 (M^+, 0.4), 298 (M^+−Bn, 12), 234 (22), 128 (21), 91 (100). Anal. Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.46; H, 5.91; N, 3.50.

4.2.6. (1*S*,5*S*,7*R*)-7-Benzyloxymethyl-3-(2-fluoroethyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane 17g

In a 5-mL flask equipped with a reflux condenser and magnetic stirrer were placed amino alcohol **16** (124 mg, 0.53 mmol), 2-fluoroethyltosylate (127 mg, 0.58 mmol), $NaHCO_3$ (89 mg, 1.06 mmol) and dry DMF (1.6 mL). The mixture was heated at 80 °C for 19 h and, after cooling, aqueous NH_4OH 10% (16 mL) was added and the product was extracted with Et_2O (4 × 10 mL). The combined organic phases were washed with water (3 × 10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the thus obtained crude was purified by FCC (eluent: EtOAc–petroleum ether, 1:6 + 0.5% Et_3N; R_f = 0.29) to afford pure **17g** as a colourless oil (104 mg, 70%). Compound **17g**: $[\alpha]_D^{23} = -68.4$ (*c* 1.38, $CHCl_3$). ^{1}H NMR δ (ppm): 7.37–7.27 (m, 5H), 5.45 (s, 1H), 4.58 (q_{AB}, *J* 11.7 Hz, 2H), 4.56–4.50 (m, 1H), 4.36–4.28 (m, 2H), 4.27–4.18 (m, 1H), 4.12–4.04 (m, 1H), 3.98–3.90 (m, 1H), 2.86–2.80 (m, 2H), 2.72–2.50 (m, 3H), 2.39 (d, *J* 11.0 Hz, 1H). ^{13}C NMR δ (ppm): 137.9 (s), 128.2 (d, 2C), 127.7 (d, 2C), 127.5 (d), 99.6 (d), 81.7 (dt, J_{CF} 167.9 Hz), 76.6 (d), 73.7 (d), 73.4 (t), 68.0 (t), 56.7 (dt, J_{CF} 19.8 Hz), 56.7 (t), 52.0 (t). MS

m/z (%): 281 (M^+, 0.3), 190 (M^+−Bn, 70), 91 (100). Anal. Calcd for $C_{15}H_{20}FNO_3 \cdot \frac{1}{4}H_2O$: C, 63.03; H, 7.23; N, 4.90. Found: C, 63.28; H, 7.09; N, 4.87.

4.2.7. (1*S*,5*S*,7*S*)-7-Benzyloxymethyl-3-(2,2,2-trifluoroethyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane 17h

In a 5-mL flask equipped with a reflux condenser and magnetic stirrer were placed amino alcohol **16** (136 mg, 0.58 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (134 mg, 0.58 mmol), $NaHCO_3$ (97 mg, 1.16 mmol) and absolute ethanol (1.7 mL). The mixture was heated at reflux for 17 h and, after cooling, the solvent was removed under vacuum. Aqueous NH_4OH 10% (10 mL) was added to the residue and the product was extracted with DCM (4 × 5 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the thus obtained crude was purified by FCC (eluent: EtOAc–petroleum ether, 1:7 + 0.5% Et_3N; R_f = 0.42), affording pure **17h** as a colourless oil (120 mg, 65%). Compound **17h**: $[\alpha]_D^{24} = -59.1$ (*c* 0.99, $CHCl_3$). ^1H NMR δ (ppm): 7.36–7.28 (m, 5H), 5.45 (s, 1H), 4.57 (q_{AB}, *J* 12.1 Hz, 2H), 4.34–4.30 (m, 1H), 4.27–4.18 (m, 1H), 4.09–4.01 (m, 1H), 3.95–3.87 (m, 1H), 2.97–2.83 (m, 5H), 2.64 (d, *J* 10.6 Hz, 1H). ^{13}C NMR δ (ppm): 137.8 (s), 128.2 (d, 2C), 127.8 (d, 2C), 127.6 (d), 125.3 (qs, J_{CF} 280.8 Hz), 99.4 (d), 76.5 (d), 73.6 (d), 73.5 (t), 68.0 (t), 57.1 (qt, J_{CF} 30.5 Hz), 56.5 (t), 51.9 (t). MS *m/z* (%): 317 (M^+, 2), 226 (M^+−Bn, 77), 166 (34), 91 (100). Anal. Calcd for $C_{15}H_{18}F_3NO_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.44; H, 5.55; N, 4.62.

4.2.8. (1*S*,5*S*,7*S*)-7-Benzyloxymethyl-3-propyl-6,8-dioxa-3-azabicyclo[3.2.1]octane 17i

Amino alcohol **16** (166 mg, 0.71 mmol) was dissolved into CH_3OH (3.6 mL) and propionaldehyde (56 μL, 0.78 mmol) was added dropwise followed by $NaBH_3CN$ (49 mg, 0.78 mmol) and few drops of glacial acetic acid (pH ∼ 6). The mixture was left to stir at room temperature for 18 h. After evaporation of the solvent, $NaHCO_3$ satd (5 mL) was added (pH ∼ 8) to the residue and the product was extracted with $CHCl_3$ (3 × 5 mL); the combined organic phases were washed with water (8 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the thus obtained crude was purified by FCC (eluent: EtOAc–petroleum ether, 1:7; R_f = 0.56), affording pure **17i** as a thick colourless oil (104 mg, 53%).

Compound **17i**: $[\alpha]_D^{24} = -71.7$ (*c* 1.0, $CHCl_3$). ^1H NMR δ (ppm): 7.36–7.27 (m, 5H), 5.44 (s, 1H), 4.58 (q_{AB}, *J* 12.1 Hz, 2H), 4.34–4.29 (m, 1H), 4.25–4.17 (m, 1H), 4.12–4.05 (m, 1H), 3.98–3.90 (m, 1H), 2.82–2.72 (m, 2H), 2.43 (dd, *J* 11.7, 2.2 Hz, 1H), 2.29–2.09 (m, 3H), 1.41–1.25 (m, 2H), 0.84 (t, *J* 7.3 Hz, 3H). ^{13}C NMR δ (ppm): 138.0 (s), 128.2 (d, 2C), 127.7 (d, 2C), 127.5 (d), 99.9 (d), 76.7 (d), 74.0 (d), 73.5 (t), 68.3 (t), 59.3 (t), 56.7 (t), 52.1 (t), 19.7 (t), 11.9 (q). MS *m/z* (%): 187 (M^+−Bn, 14), 158 (100), 142 (43). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.32; H, 8.46; N, 4.86.

4.2.9. (1*S*,5*S*,7*S*)-7-Benzyloxymethyl-3-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane 17l

Amino alcohol **16** (240 mg, 1.02 mmol) was dissolved into CH_3CN (14 mL), and HCHO (36.5%, 387 μL, 5.10 mmol) was added dropwise followed by $NaBH_3CN$ (83 mg, 1.33 mmol). A white precipitate was formed; after 10 min, a few drops of glacial AcOH were added (pH ∼ 7) and more precipitate formed. The suspension was left under stirring at room temperature for 4 h. After evaporation of the solvent, water (10 mL) and Na_2CO_3 (s) were added (pH ∼ 8) to the residue, and the product was extracted with $CHCl_3$ (4 × 12 mL) and the combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, the thus obtained crude was purified by FCC (eluent: EtOAc–*n*-hexane, 1:6 + 0.5% Et_3N; R_f = 0.30), affording pure **17l** as a colourless oil (113 mg, 44%). Compound **17l**: $[\alpha]_D^{26} = -73.1$ (*c* 1.50, $CHCl_3$). ^1H NMR δ (ppm): 7.30–7.18 (m, 5H), 5.35 (s, 1H), 4.50 (q_{AB}, *J* 12.1 Hz, 2H), 4.23–4.19 (m, 1H), 4.17–4.08 (m, 1H), 4.03–3.95 (m, 1H), 3.88–3.80 (m, 1H), 2.71–2.57 (m, 2H), 2.36 (dd, *J* 11.7, 2.2 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR δ (ppm): 137.9 (s), 128.1 (d, 2C), 127.6 (d, 2C), 127.4 (d), 99.6 (d), 76.7 (d), 73.7 (d), 73.3 (t), 68.1 (t), 58.3 (t), 53.9 (t), 44.4 (q). MS *m/z* (%): 249 (M^+, 1), 158 (M^+−Bn, 89), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.32; H, 7.46; N, 5.86.

4.3. General procedures for O-debenzylation of substrates 12 and 17b–l

Method A: The substrate (1 mmol) was dissolved into EtOAc (10 mL), under a nitrogen atmosphere, and 10% Pd/C (0.1 mmol Pd) was added. The mixture was flushed first with nitrogen then with hydrogen and finally left under a hydrogen atmosphere (balloon) at room temperature for 18 h. The catalyst was removed by filtration through a Celite pad, washed with EtOAc and the solvent was removed under vacuum. The crude was purified by FCC with the specified eluent.

Method B: In a 50-mL flask equipped with a reflux condenser and magnetic stirrer the substrate (1 mmol) was dissolved into absolute ethanol (14 mL), and cyclohexene (14 mL) and 20% $Pd(OH)_2$/C (0.68 mmol Pd) were added. The mixture was refluxed under nitrogen atmosphere for 4–7.5 h (TLC) and, after cooling, the catalyst was removed by filtration through a Celite pad, washed with methanol and the solvent was removed under vacuum. The crude was purified by FCC with the specified eluent.

4.3.1. (1*S*,5*S*,7*R*)-7-Hydroxymethyl-6,8-dioxa-3-azabicyclo-[3.2.1]octane-3-carboxylic acid methyl ester 18a

Prepared according to Method A, starting from **12** (148 mg, 0.5 mmol) and obtaining **18a** (86 mg, 84%). Compound **18a**: EtOAc; R_f = 0.34. Colourless oil. $[\alpha]_D^{26} = -44.2$ (*c* 0.51, $CHCl_3$). ^1H NMR δ (ppm): 5.52 (br s, 1H), 4.40 (br s, 1H), 4.18–4.09 (m, 1H), 3.95–3.86 (m, 2H), 3.73 (s, 3H), 3.79–3.64 (m, 2H), 3.38–3.22 (m, 1H), 3.08 (d, *J* 13.2 Hz, 1H). ^{13}C NMR δ (ppm) [two rotamers]: 98.7 and 98.4 (d), 77.9 (d), 72.3 and 71.9 (d), 61.2 (t), 52.9 (q), 48.3 (t), 43.4 and 43.2 (t). MS *m/z* (%): 203 (M^+, 8), 126 (18). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.56; H, 7.11; N, 6.62.

4.3.2. (1*S*,5*S*,7*R*)-(3-Phenyl-6,8-dioxa-3-azabicyclo[3.2.1]oct-7-yl) methanol 18b

Prepared according to Method B, starting from **17b** (78 mg, 0.25 mmol) and obtaining **18b** (55 mg, quantitative). Compound **18b**: EtOAc–*n*-hexane, 2:3 + 0.5% Et_3N ; R_f = 0.12. White solid. mp 102–103 °C. $[\alpha]_D^{26} = -33.1$ (*c* 0.82, $CHCl_3$). ^1H NMR δ (ppm): 7.36–7.24 (m, 2H), 6.90–6.78 (m, 3H), 5.68 (s, 1H), 4.58–4.52 (m, 1H), 4.19 (q_{AB}, *J* 5.5 Hz, 1H), 4.06–3.85 (m, 2H), 3.63–3.51 (m, 2H), 3.21 (dd, *J* 12.1, 2.9 Hz, 1H), 2.98 (dd, *J* 11.7, 1.5 Hz, 1H). ^{13}C NMR δ (ppm): 149.0 (s), 129.2 (d, 2C), 119.3 (d), 113.3 (d, 2C), 99.0 (d), 77.9 (d), 73.0 (d), 60.8 (t), 51.6 (t), 47.0 (t). MS *m/z* (%): 221 (M^+, 41), 144 (M^+−Ph,11), 105 (100), 77 (29). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.46; H, 7.18; N, 6.26.

4.3.3. (1*S*,5*S*,7*R*)-(3-(4-Methoxyphenyl)-6,8-dioxa-3-azabicyclo [3.2.1]oct-7-yl)methanol 18c

Prepared according to Method B, starting from **17c** (86 mg, 0.25 mmol) and obtaining **18c** (55 mg, 88%). Compound **18c**: DCM–MeOH, 30:1 + 0.5% Et_3N; R_f = 0.31. Pale pink solid. mp 123–124 °C. $[\alpha]_D^{24} = -41.8$ (*c* 0.58, $CHCl_3$). ^1H NMR δ (ppm): 6.87–6.75 (m, 4H), 5.64 (s, 1H), 4.52–4.47 (m, 1H), 4.04–3.93 (m, 2H), 3.75 (s, 3H), 3.53 (s, 1H), 3.44 (d, *J* 12.1 Hz, 2H), 3.15 (dd, *J* 12.1, 2.9 Hz, 1H), 2.92 (dd, *J* 11.4, 0.7 Hz, 1H). ^{13}C NMR δ (ppm): 153.4 (s),

143.0 (s), 115.5 (d, 2C), 114.6 (d, 2C), 99.0 (d), 78.1 (d), 73.4 (d), 60.4 (t), 55.7 (q), 52.9 (t), 48.5 (t). MS *m/z* (%): 252 (M^++1, 10), 251 (M^+, 61), 135 (100), 120 (37). Anal. Calcd for $C_{13}H_{17}NO_4 \cdot H_2O$: C, 60.69; H, 6.92; N, 5.44. Found: C, 60.71; H, 6.70; N, 5.67.

4.3.4. (1*S*,5*S*,7*R*)-(3-*o*-Tolyl-6,8-dioxa-3-azabicyclo[3.2.1]oct-7-yl) methanol 18d

Prepared according to Method B, starting from **17d** (30 mg, 92 μmol) and obtaining **18d** (14 mg, 65%). Compound **18d**: DCM–MeOH, 30:1 + 0.5% Et_3N; R_f = 0.18. Pale yellow oil. $[\alpha]_D^{26} = -90.2$ (*c* 1.2, $CHCl_3$). ^1H NMR δ (ppm): 4H), 5.57 (d, *J* 1.8 Hz, 1H), 4.49–4.46 (m, 1H), 4.28–4.03 (m, 3H), 3.66 (dd, *J* 11.7, 2.2 Hz, 1H), 3.24 (d, *J* 11.7 Hz, 1H), 3.01 (d, *J* 12.1 Hz, 1H), 2.69 (d, *J* 12.1 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR δ (ppm): 148.4 (s), 132.6 (s), 131.7 (d), 126.8 (d), 124.3 (d), 120.0 (d), 99.6 (d), 78.8 (d), 74.0 (d), 60.4 (t), 55.9 (t), 50.0 (t), 18.3 (q). MS *m/z* (%): 235 (M^+, 30), 118 (100). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.48; H, 7.50; N, 5.82.

4.3.5. (1*S*,5*S*,7*S*)-(3-Methanesulfonyl-6,8-dioxa-3-azabicyclo [3.2.1]oct-7-yl)methanol 18e

Prepared according to Method A, starting from **17e** (67 mg, 0.21 mmol) and obtaining **18e** (44 mg, 94%). Compound **18e**: EtOAc; R_f = 0.36. White solid. mp 179–180 °C. $[\alpha]_D^{26} = -40.4$ (*c* 0.70, CH_3OH). ^1H NMR (CD_3OD) δ (ppm): 5.61 (s), 4.53–4.49 (m, 1H), 4.18–4.02 (m, 2H), 3.95–3.83 (m, 1H), 3.65 (d, *J* 12.1 Hz, 1H), 3.42 (d, *J* 11.4 Hz, 1H), 3.23 (dd, *J* 12.1, 2.6 Hz, 1H), 2.98 (dd, *J* 11.0, 0.7 Hz, 1H), 2.88 (s, 3H). ^{13}C NMR (CD_3OD) δ (ppm): 99.7 (d), 80.0 (d), 73.4 (d), 61.0 (t), 50.3 (t), 45.7 (t), 34.1 (q). MS *m/z* (%): 222 (M^+−1, 2), 144 (M^+−Ms, 100). Anal. Calcd for $C_7H_{13}NO_5S$: C, 37.66; H, 5.87; N, 6.27. Found: C, 38.38; H, 5.82; N, 6.09.

4.3.6. (1*S*,5*S*,7*R*)-(3-(Toluene-4-sulfonyl)-6,8-dioxa-3-azabicyclo [3.2.1]oct-7-yl)methanol 18f

Prepared according to Method A, starting from **17f** (66 mg, 0.17 mmol) and obtaining **18f** (29 mg, 56%). Compound **18f**: DCM–MeOH, 30:1 + 0.5% Et_3N; R_f = 0.34. Colourless oil. $[\alpha]_D^{26} = -7.1$ (*c* 1.0, $CHCl_3$). ^1H NMR δ (ppm): 7.60 (d, *J* 8.1 Hz, 2H), 7.32 (d, *J* 8.4 Hz, 2H), 5.51 (s, 1H), 4.41 (s, 1H), 4.26–4.12 (m, 2H), 4.03–3.90 (m, 1H), 3.60 (q_{AB}, *J* 12.1 Hz, 2H), 2.76 (dd, *J* 12.1, 2.6 Hz, 1H), 2.54 (d, *J* 11.0 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR δ (ppm): 144.1 (s), 131.8 (s), 129.8 (d, 2C), 127.5 (d, 2C), 98.3 (d), 78.2 (d), 72.0 (d), 60.7 (t), 49.2 (t), 44.8 (t), 21.6 (q). MS *m/z* (%): 299 (M^+, 1), 184 (18), 155 (29), 144 (M^+−Ts, 100). Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68. Found: C, 52.32; H, 6.01; N, 4.63.

4.3.7. (1*S*,5*S*,7*R*)-(3-(2-Fluoroethyl)-6,8-dioxa-3-azabicyclo[3.2.1] oct-7-yl)methanol 18g

Prepared according to Method B, starting from **17g** (104 mg, 0.37 mmol) and obtaining **18g** (61 mg, 86%). Compound **18g**: DCM–MeOH + 0.5% Et_3N; R_f = 0.31. Colourless oil. $[\alpha]_D^{26} = -73.8$ (*c* 0.48, $CHCl_3$). ^1H NMR δ (ppm): 6.30–6.20 (br s, 1H), 5.50 (s, 1H), 4.66 (t, *J* 4.8 Hz, 1H), 4.42 (t, *J* 4.8 Hz, 1H), 4.35–4.30 (m, 1H), 4.19–4.08 (m, 2H), 3.93–3.84 (m, 1H), 3.10–3.00 (m, 2H), 2.82–2.64 (m, 3H), 2.48 (d, *J* 11.0 Hz, 1H). ^{13}C NMR δ (ppm): 98.8 (d), 80.9 (dt, J_{CF} 168.5 Hz), 78.4 (d), 74.3 (d), 59.2 (t), 56.6 (dt, J_{CF} 19.8 Hz), 56.4 (t), 53.1 (t). MS *m/z* (%): 191 (M^+, 6). Anal. Calcd for $C_8H_{14}FNO_3$: C, 50.25; H, 7.38; N, 7.33. Found: C, 49.95; H, 7.46; N, 7.14.

4.3.8. (1*S*,5*S*,7*R*)-(3-(2,2,2-Trifluoroethyl)-6,8-dioxa-3-azabicyclo[3.2.1]oct-7-yl)methanol 18h

Prepared according to Method B, starting from **17h** (100 mg, 0.32 mmol) and obtaining **18h** (69 mg, 95%). Compound **18h**: DCM–MeOH, 30:1 + 0.5% Et_3N; R_f = 0.22. Pale yellow oil. $[\alpha]_D^{24} = -67.8$ (*c* 0.12, $CHCl_3$). ^1H NMR δ (ppm): 5.50 (s, 1H), 4.36–4.30 (m, 1H), 4.18–4.10 (m, 1H), 4.10–4.03 (m, 2H), 3.78–3.68 (br s, 1H), 3.10–2.90 (m, 5H), 2.68 (d, *J* 11.0 Hz, 1H). ^{13}C NMR δ (ppm): 125.0 (qs, J_{CF} 280.2 Hz), 99.0 (d), 78.6 (d), 73.7 (d), 60.0 (t), 57.3 (qt, J_{CF} 31.1 Hz), 56.5 (t), 52.7 (t). MS *m/z* (%): 227 (M^+, 9), 182 (56), 112 (100). Anal. Calcd for $C_8H_{12}F_3NO_3 \cdot {}^1\!/_4H_2O$: C, 41.47; H, 5.44; N, 6.05. Found: C, 41.17; H, 5.17; N, 6.02.

4.3.9. (1*S*,5*S*,7*R*)-(3-Propyl-6,8-dioxa-3-azabicyclo[3.2.1]oct-7-yl) methanol 18i

Prepared according to Method B, starting from **17i** (88 mg, 0.32 mmol) and obtaining **18i** (50 mg, 84%). Compound **18i**: DCM–MeOH, 40:1; R_f = 0.36. Thick colourless oil. $[\alpha]_D^{24} = -68.5$ (*c* 0.20, $CHCl_3$). ^1H NMR δ (ppm): 7.12 (br s, 1H), 5.52 (s, 1H), 4.37–4.31 (m, 1H), 4.24–4.08 (m, 2H), 3.85 (d, *J* 11.8 Hz, 1H), 3.08–2.98 (m, 1H), 2.62 (dd, *J* 11.9, 2.3 Hz, 1H), 2.41–2.30 (m, 3H), 1.49 (qt, *J* 8.0 Hz, 2H), 0.89 (t, *J* 7.4 Hz, 3H). ^{13}C NMR δ (ppm): 99.0 (d), 78.3 (d), 74.7 (d), 59.1 (t, 2C), 56.0 (t), 53.4 (t), 19.2 (t), 11.7 (q). MS *m/z* (%): 187 (M^+, 18), 158 (100), 142 (45). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.52; H, 8.71; N, 7.05.

4.3.10. (1*S*,5*S*,7*R*)-(3-Methyl-6,8-dioxa-3-azabicyclo[3.2.1]oct-7-yl) methanol 1

Prepared according to Method B, starting from **17l** (61 mg, 0.24 mmol) and obtaining **1** (32 mg, 84%). Compound **1**: DCM–MeOH, 30:1; R_f = 0.28. Colourless oil. $[\alpha]_D^{24} = -92.4$ (*c* 0.95, $CHCl_3$). [lit.[1b] $[\alpha]_D^{22} = -91.2$ (*c* 0.89, $CHCl_3$)]. ^1H NMR δ (ppm): 5.51 (s, 1H), 4.39–4.26 (m, 1H), 4.19–4.08 (m, 2H), 3.84 (d, *J* 11.7 Hz, 1H), 3.07–2.88 (m, 2H), 2.67–2.55 (m, 1H), 2.39 (d, *J* 11.0 Hz, 1H), 2.29 (s, 3H), 1.77–1.46 (br s, 1H). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.95; H, 8.46; N, 8.86.

4.4. General procedure for addition reaction of diethylzinc to aldehydes

Diethylzinc (1.0 M solution in hexanes, 1.5 mmol) was added to a solution of ligand **18** (0.15 mmol) in anhydrous toluene (1.5 mL). After 30 min, the aldehyde (1 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 18 h. The reaction was quenched by 1 M aqueous HCl solution (5 mL) and the product was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude alcohol was obtained and directly analysed by GC to determine product composition and ee.

Acknowledgements

Mr Maurizio Passaponti and Mrs Brunella Innocenti are acknowledged for their technical support; Dr Cristina Faggi is acknowledged for X-ray structure determination. The authors wish to thank Dr S. Zhao for advice.

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21. Traces of metal halides, acting as Lewis acids themselves or in situ generating ethylzinc halides, could be responsible for the non-enantioselective addition.
22. Crystallographic data (excluding structure factors) for structure **1**·HCl have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC711875. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK (fax: +44(0)-1223-336033 or e-mail:deposit@ccdc.cam.ac.uk).
23. It should be mentioned that in the case of the CF_3 group, the steric effect E_S makes it more comparable to a *sec*-butyl rather than to a CH_3. However, the E_S should be less pronounced in the case of a single H–F substitution. See Ref. 1b and also: Taft, R. W. In *Steric effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, NY, 1956; pp 556–675.