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Synthesis of a new 1,4-aminoalcohol and its use as catalyst in the enantioselective addition of organozinc to aldehydes

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Abstract—The synthesis of a new enantiopure, conformationally constrained 1,4-aminoalcohol is reported, starting from commercially available reagents from the chiral pool. This 1,4-aminoalcohol was used as chiral ligand in the addition of Et_2Zn to aldehydes (best ee 98%) and in the synthesis of chiral propargylic alcohols (best ee 70%) by alkynylzinc species.

1. Introduction

The use of chiral ligands in asymmetric synthesis is a very well-known tool in organic chemistry and there are many examples of efficient catalysts, many of them commercially available. In organozinc chemistry the chiral ligands mostly belong to the class of 1,2-aminoalcohols,[1] whereas 1,4-aminoalcohols[2] are rarely used maybe because of their multi-step synthesis and, in order to guarantee good enantioselectivities, because they require complicated rigid structures that are less appealing than most simple and commercially available 1,2-aminoalcohols. Therefore, an efficient and easy-to-make chiral ligand, belonging to this neglected class, seemed a challenging goal.

2. Results and discussion

We recently[3] reported the synthesis of a few 1,4-aminoalcohols (Chart 1) and their application as chiral ligands in the asymmetric addition of diethylzinc on aldehydes. In this study, we verified that the less the *N*-substituent is hindered, is the higher the enantioselectivity of the reaction. This observation confirmed the hypothesis of the transition

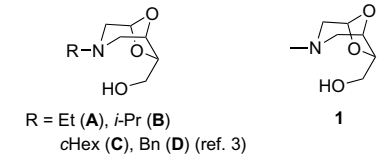

Chart 1. Structure of 1,4-aminoalcohols **A**–**D** and target *N*-methyl **1**.

state model elaborated on the basis of the one proposed by Noyori and Yamakawa.[4] We therefore proposed that most probably the *N*-methyl aminoalcohol **1** would have worked better than all the other structures and decided to synthesise it.

However, the synthetic strategy applied previously had the inconvenience of the Fmoc protection–deprotection steps that lower the yield and that did not follow the 'atom-economy' principle. We elaborated a new synthesis that affords the chiral ligand in only four steps, starting from commercially available compounds from the chiral pool. The synthesis can be easily extended to a multi-gram scale.

The synthesis starts with the formation of an aluminium amide[5] by mixing (methylamino)acetaldehyde dimethyl acetal **3** and $AlMe_3$ (Scheme 1). This species reacts with (−)-2,3-*O*-isopropylidene-D-erythronolactone **2** to give alcohol **4**, formed in 93% yield that required no purification for the next protection step. The corresponding acetate **5** (90% yield, prepared with Ac_2O in dry pyridine) was heated

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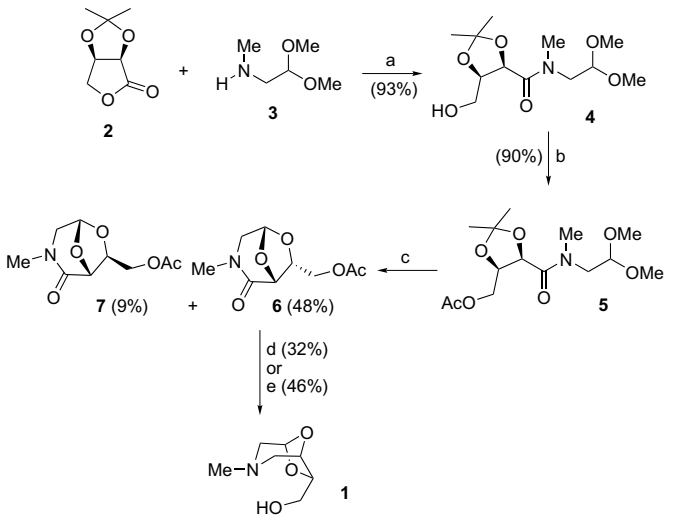
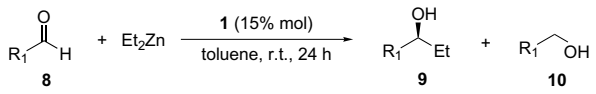


Scheme 1. Reagents and conditions: (a) $AlMe_3$ 2.0 M in hexane (1.1 equiv), DCM, 0 °C → rt, 18 h; (b) Ac_2O, py, 0 °C → rt, 20 h; (c) $SiO_2{\cdot}H_2SO_4$, toluene, reflux, 10′; (d) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h, then H_2O (5 equiv), Amberlite IRA-743, rt, 12 h; (e) $LiAlH_4$, THF, 55 °C, 18 h, then KOH 0.4 M, H_2O, reflux, 30′.

in refluxing toluene under acid catalysis of H_2SO_4 absorbed on silica gel. Under these conditions, the C-7 stereocentre of compound **6** partially racemised and the crude mixture contained **6** and **7** in a 4:1 ratio. The two diastereoisomers were easily separated by chromatography, and compound **6** was obtained in 48% yield after purification. The one pot reduction and deprotection step was performed under two different conditions in order to explore more methods and increase the yield. Treatment of compound **6** with $BH_3{\cdot}SMe_2$ in dry THF under reflux was followed by the quench with water and Amberlite IRA-743[6] as boron scavenger.[7] Product **1** was obtained in 32% yield after purification. Alternatively, the same step was performed by employing $LiAlH_4$ in dry THF and heating the suspension at 55 °C for 18 h. After quenching the reaction by the addition of KOH 0.4 M and water, product **1** was recovered in 46% yield after purification. The overall yield of the synthesis was 13–18% over four steps.

Aminoalcohol **1** was then used as chiral ligand in the addition of Et_2Zn to aldehydes. We applied the reaction conditions that worked best with the *N*-ethyl ligand **A**[3] (Chart 1) but decreased the amount of ligand[8] from 20 to 15 mol % (Scheme 2). The results are reported in Table 1.



Scheme 2. Catalysed addition of Et_2Zn to aldehydes.

As hoped on the basis of our initial reasoning, the enantioselectivity increased with respect to the already reported ligands belonging to the same class of compounds. According to the transition state model proposed in our previous work,[3] the *Si* face of the carbonyl group was always attacked and therefore the (*S*)-alcohol was formed. The ee range generally was 92–98% employing **1** at 15 mol %,

Table 1. Distribution of products obtained by diethylzinc addition on aromatic and aliphatic aldehydes

Entry	R_1	**9**[a]	**10**[a]	ee[b] (%)	Configuration of **9**[c]
1	C_6H_5	98	2	97	*S*
2	2-Cl–C_6H_4	87	5	92	*S*
3	3-Cl–C_6H_4	96	2	96	*S*
4	4-Cl–C_6H_4	97	2	96	*S*
5	2-Me–C_6H_4	93	5	96	*S*
6	3-Me–C_6H_4	97	3	96	*S*
7	4-Me–C_6H_4	96	2	97	*S*
8	3-MeO–C_6H_4	96	3	98	*S*
9	4-MeO–C_6H_4	78[d]	0	80	*S*
10	4-MeS–C_6H_4	99	—	95	*S*
11	4-Biphenyl	94	4	92[e]	*S*
12	2-Naphthyl	94	4	88[e]	*S*
13	2-Thienyl	97	—	86	*S*
14	$CH_3(CH_2)_5$	42[f]	—	36[e]	*S*

[a] Determined by GC.
[b] Determined by GC using β DEX™ 120 column.
[c] Determined by the sign of the specific rotation.
[d] 1-Methoxy-4-propenylbenzene is formed during the reaction (22%).
[e] Determined by analysis of the corresponding Mosher ester ^1H NMR (400 MHz) spectrum.
[f] Isolated yield.

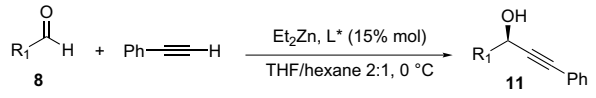
whereas with *N*-ethyl **A** at 20 mol % the ee was 90–95%. In most cases a small amount of alcohol **10** also formed. The substituent on the aromatic ring did not generally influence the stereochemical outcome of the reaction, as the chiral alcohols were obtained in 96–98% ee with the exceptions represented by the cases of the 2-chlorobenzaldehyde (entry 2, ee 92%)—probably due to the steric hindrance of the *ortho* position—and the 4-methoxybenzaldehyde (entry 9, ee 80%)—mainly because of the increased competition of the noncatalysed reaction,[9] that is probably due to electronic effects of the substituent. In fact, the substitution of the methoxy group with a thiomethyl (entry 10) improved the enantioselectivity to the average values (ee 95%); the same effect was obtained by the methoxy group in the *meta* position (entry 8, ee 98%).

The ligand was also tested on a few more aromatic (entries 11 and 12) and heteroaromatic substrates (entry 13). In all three cases, the enantioselectivity slightly decreased (ee 92%, 88%, 86%, entries 11, 12 and 13, respectively), but not significantly.

Unfortunately, performing the Et_2Zn addition on an aliphatic aldehyde resulted in a poor enantioselectivity (entry 7, ee 36%). However, this result is consistent with some analogous experiments reported in the literature for non-aromatic aldehydes.[10]

Encouraged by these results, we decided to explore an interesting reaction that has been very widely studied over the last few years: the synthesis of chiral propargylic alcohols by addition of alkynylzinc species to aromatic and aliphatic aldehydes (Scheme 3).[11]

The organometallic reagent is usually prepared in situ by mixing Et_2Zn and the desired alkyne (in our case, phenyl-



Scheme 3. Catalysed addition of alkynylzinc to aldehydes.

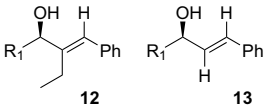


Chart 2. By-products of the synthesis of propargylic alcohols.

acetylene), in a stoichiometric ratio, in order to obtain the corresponding ethyl-alkynylzinc reactant. Therefore, the main problem can be the side reaction of the Et_2Zn addition to the aldehydes to give alcohol **9** (and by-product **10**) instead of propargylic alcohol **11**. For this reason, the use of a co-ordinating solvent[11b–d] or an additive[11e] in the reaction mixture is advised, or even the change of strategy by employing $Zn(OTf)_2$ and a base (Et_3N or DIPEA).[12] We decided to use the solvent mixture THF/hexane ~2:1 and study the reaction first on benzaldehyde. The experiments are summarised in Table 2.

Racemic propargylic alcohol **11** (28%) was formed through the competitive noncatalysed reaction[13] (entry 1), together with alcohols **9** and **10** that derive from the Et_2Zn addition reaction, and alcohol **12** (Chart 2) that derives from a carbozincation side reaction. The reaction catalysed by *N*-methyl **1** (entry 2) afforded an increased amount of alcohol **11**, but all by-products still formed. When the less efficient ligand **B** was used (entry 3), alcohol **13** also formed. Interestingly, in analogy with Et_2Zn addition, the enantioselectivity of the reaction drastically decreased by increasing the hindrance of the *N*-substituent of the ligand (ee 52%, entry 2, vs ee 8%, entry 3).

In order to limit the amount and number of by-products, the reaction was stopped after 6 h: by that time, the competitive noncatalysed reaction could be neglected (only 4% conversion, entry 4) and no carbozincation occurred. In the presence of chiral ligand **1**, alcohol **11** was obtained with higher ee (68%, entry 5) and the percentages of alcohols **9** and **10**, the only by-products, did not increase significantly (12%, entry 5, vs 9%, entry 2). The use of a different solvent (entry 6) resulted in a worse ee (33%) and in an increase of the number of by-products (**9**, **10** and **13**), whereas the slow addition of the substrate to the organozinc mixture (entry 7) did not significantly improve either the yield (44%) or the ee (67%) with respect to the easier to manage experiment carried out over 6 h (entry 5). We therefore applied these conditions (entry 5) to a few more aldehydes and the results are reported in Table 3.

As already seen for the addition of Et_2Zn to the aldehydes, there is no significant influence of the substituents on the aromatic ring on the enantioselectivity of the reaction (entries 1–5): the ee range narrowed to 68–70% and dropped, as expected, to 40–47% in the case of aliphatic substrates (entries 8 and 9). The exceptions to this apparent rule are represented by 4-methoxybenzaldehyde (entry 6) that was recovered almost unreacted, and 4-nitrobenzaldehyde (entry 7) that reacted slower than all other substrates and afforded the poorest ee (7%). As for the absolute configuration of alcohol **11**, this can easily be explained by the same transition state model used in the former application: also in this case, the *Si* face of the carbonyl group is attacked and therefore the (*R*)-alcohol is formed.

Table 3. Distribution of products obtained by phenylacetylene Et_2Zn-catalysed addition on aromatic and aliphatic aldehydes

Entry	R_1	**9**[a]	**10**[a]	**11**[a]	ee[b] (%)	Configuration of **11**[b]
1	C_6H_5	11	1	32	68	*R*
2	2-Cl–C_6H_4	15	2	36	70	*R*
3	3-Cl–C_6H_4	13	5	25	70	*R*
4	3-Me–C_6H_4	27	16	42	69	*R*
5	4-Me–C_6H_4	19	6	32	68	*R*
6	4-MeO–C_6H_4	4	1	4	n.d.	—
7	4-NO_2–C_6H_4	11	5	25	7	*R*
8	$CH_3(CH_2)_5$	—	—	15[c]	47	*R*
9	$C(CH_3)_3$	—	—	12[c]	40	*R*

[a] Determined by ^{1}H NMR.
[b] Determined by analysis of the corresponding Mosher ester ^{1}H NMR (400 MHz) spectrum.
[c] Isolated yield.

Table 2. Distribution of products obtained by phenylacetylene Et_2Zn-catalysed addition on benzaldehyde (R_1 = Ph)

Entry	L* ([a])	Time (h)	**8**[b]	**9**[b]	**10**[b]	**11**[b]	**12**[b]	**13**[b]	ee[c] (%)	Configuration of **11**[c]
1	None	20	44	5	2	28	21	—	—	—
2	**1**	20	29	6	3	50	12	0	52	*R*
3	**B**[d]	20	0	3	3	58	19	17	8	*R*
4	None	6	96	1	—	3	—	—	—	—
5	**1**	6	56	11	1	32	0	0	68	*R*
6[e]	**1**	6	53	19	2	15	0	11	33	*R*
7[f]	**1**	24	45	8	3	44	0	0	67	*R*

[a] 15 mol %.
[b] Determined by ^{1}H NMR.
[c] Determined by analysis of the corresponding Mosher ester ^{1}H NMR (400 MHz) spectrum.
[d] Chart 1, R = *i*-Pr.
[e] DCM/hexane ~ 2.2:1 was used as a solvent.
[f] Slow addition of the aldehyde over 20 h.

3. Conclusion

In conclusion, in the present work a new chiral 1,4-aminoalcohol was synthesised. The results obtained in the Et_2Zn addition to aromatic aldehydes confirm the influence of the *N*-substituent of the ligand on the stereoselectivity of the reactions. With this new conformationally constrained 1,4-aminoalcohol ee's comparable to those obtained with 1,2-aminoalcohols are achieved. A second application, that is, the synthesis of propargylic alcohols, proved less successful both in yield and ee. However, to the best of our knowledge, this is the first example of a 1,4-aminoalcohol employed as a catalyst for the synthesis of chiral propargylic alcohols. Furthermore, the narrow range of the enantiomeric excesses obtained in both applications on the same aromatic aldehydes (92–98% and 68–70%) seems to indicate the maximum asymmetric induction obtainable by this chiral rigid bicyclic system.

Further investigations employing ligand **1** in other catalysed reactions are currently in progress.

4. Experimental

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. ^1H NMR (200 MHz) and ^{13}C NMR (50.33 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. NMR spectra of Mosher esters were performed on a Varian MercuryPlus 400 spectrometer operating at 400 MHz for ^1H. Mass spectra were carried out by EI at 70 eV, unless otherwise stated, on Shimadzu GC/MS QP5050 instruments. GC analyses were performed on a HP5890 Series II instrument supported with a Supelco β DEX™ 120, 30 m × 0.25 mm, 0.25 μm film column. Microanalyses were carried out with a Perkin–Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument.

Before use, Amberlite IRA-743 (Aldrich) was washed with methanol (three times), dichloromethane (three times), diethyl ether (three times) and dried to constant mass under vacuum.

4.1. (4*R*,5*R*)-5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid (2,2-dimethoxy-ethyl)-methyl-amide 4

To a solution of **3** (2.3 mL, 17.9 mmol) in dry CH_2Cl_2 (64 mL), cooled at 0 °C under nitrogen, was added $AlMe_3$ (2 M in hexane, 8.96 mL, 17.9 mmol) and, after 30 min, **2** (2.58 g, 16.3 mmol). The reaction mixture was allowed to warm to room temperature and after 18 h was cooled to 0 °C and quenched with HCl (1 M, 40 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, **4** was obtained (4.2 g, 93%) as a white solid.

Compound **4**. Mp 65–66 °C. $[\alpha]_D^{27} = +35.4$ (*c* 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm) (3:1 mixture of two rotamers): 5.04 (d, *J* 6.2 Hz, 1H, minor rotamer), 4.99 (d, *J* 6.4 Hz, 1H, major rotamer), 4.55–4.32 (m, 2H), 3.84 (dd, *J* 13.4, 5.5 Hz, 1H, major rotamer), 3.75–3.48 (m, 2H+1H, minor rotamer), 3.42 (s, 6H, minor rotamer), 3.38 (s, 6H, major rotamer), 3.22 (dd, *J* 13.9, 4.7 Hz, 1H, major rotamer), 3.14 (s, 3H, major rotamer), 3.03 (s, 3H, minor rotamer), 1.57 (s, 3H, major rotamer), 1.55 (s, 3H, minor rotamer), 1.40 (s, 3H, major rotamer), 1.33 (s, 3H, minor rotamer). ^{13}C NMR ($CDCl_3$) δ (ppm) (3:1 mixture of two rotamers): 169.1 (s, minor rotamer), 168.3 (s, major rotamer), 109.7 (s, major rotamer), 109.6 (s, minor rotamer), 103.4 (d, minor rotamer), 102.5 (d, major rotamer), 78.2 (d, minor rotamer), 77.3 (d, major rotamer), 74.8 (d, minor rotamer), 74.6 (d, major rotamer), 62.3 (t, minor rotamer), 61.9 (t, major rotamer), 55.5 (q, minor rotamer), 55.0 (q, minor rotamer), 54.8 (q, major rotamer), 54.5 (q, major rotamer), 52.1 (t, minor rotamer), 50.0 (t, major rotamer), 36.7 (q, major rotamer), 35.5 (q, minor rotamer), 27.1 (q), 25.3 (q). MS *m*/*z* (%) 262 (M^+-CH_3, 3), 185 (15), 75 (100). Anal. Calcd for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 52.06; H, 9.00; N, 5.03.

4.2. (4*R*,5*R*)-Acetic acid 5-[(2,2-dimethoxy-ethyl)-methyl-carbamoyl]-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester 5

To a solution of **4** (4.2 g, 15.1 mmol) in dry pyridine (20 mL), cooled at 0 °C under nitrogen, was added acetic anhydride (2.9 mL, 30.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 h. Then the solution was cooled to 0 °C, quenched with HCl (1 M, 20 mL), and diluted with DCM (50 mL). The organic phase was washed with HCl (1 M, 2 × 20 mL) and brine (20 mL), and then dried over Na_2SO_4. After filtration and evaporation of the solvent, product **5** (4.34 g, 90%) was obtained without further purification as a colourless oil.

Compound **5**. $[\alpha]_D^{26} = +23.6$ (*c* 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm) (3:1 mixture of two rotamers): 5.08 (d, *J* 6.6 Hz, 1H, minor rotamer), 5.00 (d, *J* 7.0 Hz, 1H, major rotamer), 4.62–4.44 (m, 2H), 4.23–4.03 (m, 2H), 3.53–3.27 (m, 2H), 3.40 (s, 6H), 3.12 (s, 3H, major rotamer), 3.00 (s, 3H, minor rotamer), 2.08 (s, 3H, major rotamer), 2.07 (s, 3H, minor rotamer), 1.61 (s, 3H, major rotamer), 1.59 (s, 3H, minor rotamer), 1.40 (s, 3H, major rotamer), 1.39 (s, 3H, minor rotamer). ^{13}C NMR ($CDCl_3$) δ (ppm) (3:1 mixture of two rotamers): 170.2 (s), 167.7 (s, minor rotamer), 167.1 (s, major rotamer), 110.4 (s, major rotamer), 110.3 (s, minor rotamer), 103.2 (d, minor rotamer), 102.6 (d, major rotamer), 75.2 (d, minor rotamer), 74.5 (d, major rotamer), 74.0 (d, major rotamer), 73.8 (d, minor rotamer), 63.5 (t, minor rotamer), 63.4 (t, major rotamer), 55.3 (q, minor rotamer), 55.2 (q, minor rotamer), 54.7 (q, major rotamer), 54.6 (q, major rotamer), 51.7 (t, minor rotamer), 50.5 (t, major rotamer), 36.5 (q, major rotamer), 35.3 (q, minor rotamer), 27.1 (q), 25.3 (q), 20.7 (q). MS *m*/*z* (%) 304 (M^+-CH_3, 3), 115 (13), 75 (100). Anal. Calcd for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.59; H, 8.17; N, 4.43.

4.3. (1*R*,5*R*,7*R*)-Acetic acid 3-methyl-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]oct-7-yl ester 6

A solution of **5** (2.16 g, 6.78 mmol) in toluene (90 mL) was quickly added, under nitrogen, to a refluxing suspension of H_2SO_4/SiO_2 (1.24 g) in toluene (250 mL). When 100 mL of the solvent was distilled off (10 min), the hot solution was filtered through a short pad of $NaHCO_3$, and the pad was washed with EtOAc (2×40 mL). The combined organic phases were concentrated in vacuo and the crude contained a mixture of **6** and **7**. The compounds were separated by chromatography (EtOAc–petroleum ether, 3:1 + 0.5% Et_3N) yielding **6** (0.70 g, 48%) as a pale yellow oil and **7** (0.26 g, 9%) as an orange solid.

Compound **6**. $R_f = 0.33$. $[\alpha]_D^{28} = -39.7$ (*c* 0.63, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 5.71 (d, *J* 2.6 Hz, 1H), 4.65 (d, *J* 4.4 Hz, 1H), 4.33–4.24 (m, 2H), 4.06 (dd, *J* 12.8, 8.4 Hz, 1H), 3.49 (dd, *J* 12.0, 2.6 Hz, 1H), 3.18 (d, *J* 12.0 Hz, 1H), 2.92 (s, 3H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.9 (s), 164.7 (s), 96.6 (d), 77.2 (d), 75.3 (d), 62.1 (t), 54.1 (t), 32.0 (q), 20.4 (q). MS *m*/*z* (%) 216 (M^++1, 5), 197 (17), 155 (30), 84 (100). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.14; H, 6.30; N, 6.85.

Compound **7**. $R_f = 0.22$. Mp 134–135 °C. $[\alpha]_D^{24} = -51.3$ (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 5.37 (d, *J* 5.1 Hz, 1H), 4.85 (s, 1H), 4.49 (s, 1H), 4.15 (dd, *J* 13.2, 2.9 Hz, 1H), 3.94 (d, *J* 13.2 Hz, 1H), 3.79 (dd, *J* 13.6, 5.1 Hz, 1H), 3.38 (d, *J* 13.6 Hz, 1H), 3.03 (s, 3H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.9 (s), 165.0 (s), 90.0 (d), 72.6 (d), 67.1 (d), 61.8 (t), 52.0 (t), 33.3 (q), 21.0 (q). MS *m*/*z* (%) 215 (M^+, 36), 142 (48), 71 (100). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.55; H, 6.37; N, 6.52.

4.4. (1*S*,5*R*,7*R*)-(3-Methyl-6,8-dioxa-3-aza-bicyclo[3.2.1]-oct-7-yl)-methanol 1

4.4.1. Method A. To a suspension of **6** (423 mg, 1.97 mmol) in dry THF (20 mL), under nitrogen, was slowly added a 10 M solution of $BH_3{\cdot}SMe_2$ (590 μL). The reaction mixture was refluxed for 2 h, cooled to rt and Amberlite IRA-743 (4.2 g) was slowly added to the solution, immediately followed by H_2O (532 μL, 29.5 mmol). The suspension was stirred at rt for 12 h. The resin was then filtered off and washed with Et_2O (5×15 mL), and the combined organic phases were concentrated in vacuo to give the crude that was purified by chromatography (eluent: CH_2Cl_2–MeOH, 20:1 + 0.5% Et_3N, $R_f = 0.14$) yielding **1** (100 mg, 32%) as a colourless oil.

4.4.2. Method B. A solution of **6** (746 mg, 3.47 mmol) in dry THF (13 mL) was added, under nitrogen, to a suspension of $LiAlH_4$ (527 mg, 13.9 mmol) in dry THF (40 mL), cooled at 0 °C. The ice bath was removed and the mixture was heated at 55 °C. After 18 h, the mixture was cooled to 0 °C, quenched with KOH (0.4 M, 3 mL) and water (2 mL) and, after 5′, refluxed for 30′. The white salts were eliminated by filtration on a short Celite pad that was washed with EtOAc (3×15 mL). The combined organic phases were concentrated in vacuo to give the crude that was purified by chromatography (eluent: CH_2Cl_2–MeOH, 20:1 + 0.5% Et_3N, $R_f = 0.14$) yielding **1** (255 mg, 46%) as a colourless oil.

Compound **1**. $[\alpha]_D^{22} = -91.2$ (*c* 0.89, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 7.13 (br s, 1H), 5.51 (s, 1H), 4.34–4.33 (m, 1H), 4.17–4.10 (m, 2H), 3.84 (d, *J* 11.7 Hz, 1H), 3.01–2.92 (m, 2H), 2.65–2.59 (m, 1H), 2.39 (d, *J* 11.0 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 98.6 (d), 78.1 (d), 74.3 (d), 58.8 (t), 57.8 (t), 54.4 (t), 43.5 (q). MS *m*/*z* (%) 159 (M^+, 28), 114 (49), 100 (17), 86 (47), 57 (100). Anal. Calcd for $C_7H_{13}NO_3{\cdot}1/3\,H_2O$: C, 50.90; H, 8.14; N, 8.48. Found: C, 50.85; H, 8.48; N, 8.69.

4.5. General procedure for addition reaction of diethylzinc to aldehydes

Diethylzinc (1.0 M solution in hexane, 1.5 mmol) was added to a solution of ligand **1** (0.15 mmol) in anhydrous toluene (1.5 mL). After 30 min, the aldehyde (1 mmol) was added dropwise and the resulting mixture stirred for 24 h. The reaction was quenched by 1 M aqueous HCl solution (5 mL) and the product 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. In the case of chiral 3-nonanol, the ee and the absolute configuration were determined by ^1H NMR of the corresponding Mosher ester.

The chiral ligand can be recovered as follows: the aqueous layer was neutralised with NaOH (s) until the pH was 8–9 (zinc hydroxides precipitate) and compound **1** was extracted five times with $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and, after filtration and evaporation of the solvent, pure **1** was recovered (69%).

4.6. General procedure for alkynylation reactions

Diethylzinc (1.0 M solution in hexane, 1.05 mmol) was added to a solution of ligand **1** (0.15 mmol) in anhydrous THF (2.2 mL). After 1 h, phenylacetylene (1.05 mmol) was added and after one more hour, the solution was cooled at 0 °C and the aldehyde (1 mmol) was added dropwise. After 6 h, the ice bath was removed and the reaction quenched by saturated NH_4Cl solution (5 mL) and the product extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and after filtration and evaporation of the solvent, the crude alcohol was purified by chromatography (eluent: EtOAc–petroleum ether, 1:6 + 0.5% Et_3N; $R_f = 0.20$–0.32). The ee and the absolute configuration were determined by ^1H NMR of the corresponding Mosher ester.

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