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Synthesis of new chiral hydroxy oxazolines and their use in the catalytic asymmetric phenyl transfer to aldehydes

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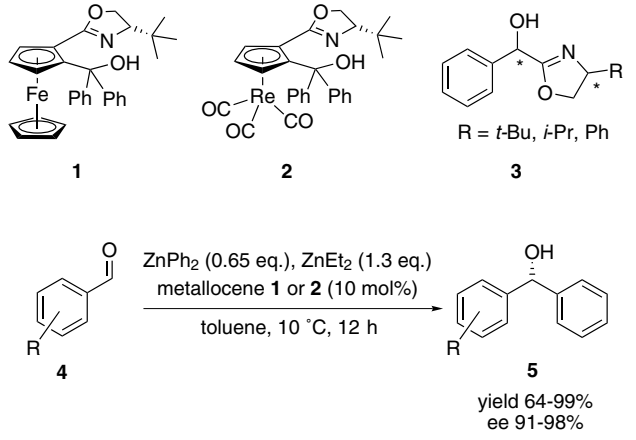
Abstract—Starting either from benzoylformic acid or ethyl oxamate and enantiopure β-amino alcohols, several chiral α-hydroxy oxazolines have been prepared by short synthetic routes. Subsequently, they have been employed in the catalytic asymmetric phenyl transfer to various aldehydes, using a mixture of triphenylborane and diethylzinc as the phenyl source. The corresponding secondary alcohols were obtained with good enantioselectivities (up to 81% ee) and up to 92% yield.

1. Introduction

Asymmetric catalysis is one of the most active research areas in organic chemistry.[1] Among the various reactions that can be conducted in a catalytic asymmetric manner, C–C bond forming processes have always attracted considerable attention due to their synthetic utility. One of the most studied enantioselective carbon–carbon single bond forming reactions is the addition of alkylzinc reagents to carbonyl compounds, in particular aldehydes.[2] On the other hand, the corresponding *aryl* transfer reactions have remained under-represented for a long time. Following the pioneering studies of Soai et al.[3] and Fu et al.,[4] major developments in the field have been recently reported, both by our group[5] and others.[6–8] The first catalytic systems, introduced by us for the enantioselective synthesis of diarylmethanols from aromatic aldehydes, utilized planar chiral metallocenyl hydroxy oxazolines **1** and **2** as pre-catalysts and a nucleophilic arylzinc species generated in situ from mixtures of $ZnEt_2$ and $ZnPh_2$ (Scheme 1).[5]

Despite its effectiveness, this approach still had some disadvantages: first, diphenylzinc is an air-sensitive and expensive compound, and its use limits the reaction scope to the transfer of simple phenyl groups. Second, the enantioselectivity of the process relies on the use of rather complex metallocenes **1** or **2**, which have to be applied in substantial amounts (usually 10 mol %). A solution for the first problem was provided by finding that



Scheme 1. Asymmetric catalytic phenyl transfer reaction to aromatic aldehydes employing a mixture of $ZnEt_2$ and $ZnPh_2$ as the phenyl source.

air-stable arylboronic acids could also be used as the aryl source, which furthermore allows the preparation of chiral diarylmethanols substituted on both aromatic rings with excellent enantioselectivities in high yields.[9] Later, triphenylborane was found to be an ideal substitute for diphenylzinc, due to its superior stability, easier handling and lower cost.[10] By using additives such as mono- or dimethylpolyethyleneglycol (MPEG and DiMPEG, respectively), a reduction of the catalyst loading became possible while maintaining high enantioselectivities.[11]

In light of these developments, which predominantly focus on the optimization of reagents and reaction

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conditions, the introduction of new, effective and more easily accessible catalysts for the asymmetric aryl transfer reaction has remained highly desirable. In our first attempt to meet this demand, we recently utilized mandelic acid for the synthesis of a series of hydroxy oxazolines **3** and applied those as N–O ligands for the same reaction.[12] Unfortunately, although reasonable yields of the products were generally obtained, the enantiomeric excesses remained low (ee_{max}: 35%) and the catalysts underwent partial or complete decomposition during the catalytic process. Following the same strategy and hoping for an improvement of the catalyst system, novel hydroxy oxazolines **11a–k** have now been prepared and tested in the phenyl transfer reaction. The results of these investigations are reported herein.

2. Results and discussion

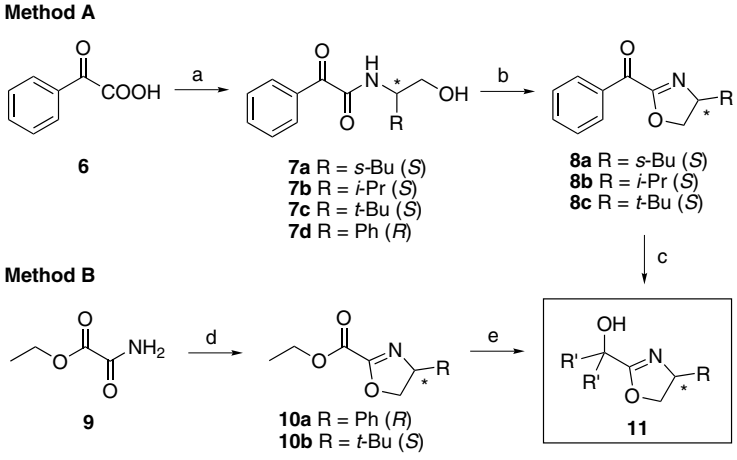
2.1. Synthesis of the ligands

A possible explanation for the poor enantioselectivity observed in the asymmetric phenyl transfer reaction with catalysts based on **3** could involve the destruction of the ligand by oxidation or epimerization at the benzylic position under the strongly basic reaction conditions. A solution to this problem was expected from the preparation of hydroxy oxazolines **11** containing a quaternary hydroxyl-bearing carbon. Although the loss of one stereogenic center, when compared to **3**, prevented the exploitation of possible match–mismatch effects, the resulting compounds should exhibit mproved stability, thus allowing better results to be obtained in the catalysis. The reagents and conditions that have been applied in the synthesis of **11** are depicted in Scheme 2.

In the first approach (method A),[13] commercially available benzoylformic acid **6** was reacted with enantiopure amino alcohols under standard peptide coupling conditions,[14] affording the corresponding hydroxy amides **7a–d**. After screening various oxazoline formation protocols, it was found that the reaction of hydroxy amides **7** with $SOCl_2$ followed by treatment of the resulting chloro amides with sodium carbonate in hot *N*,*N*′-dimethylformamide (DMF) furnished the highest yields of 2-benzoyl oxazolines **8a–c**. These products were finally converted into hydroxy oxazolines **11a–c** by reacting them with excess phenyl magnesium chloride.

Although this sequence was quite convenient, difficulties were encountered in the oxazoline formation starting from hydroxy amide **7d** derived from (*R*)-phenylglycinol (yield <20%). Furthermore, in order to prepare hydroxy oxazolines with different structural and electronic properties, the possibility of obtaining compounds with substituents other than simple phenyl groups at the α-position was desirable. After a brief survey of the literature, it was found that ethyl oxazoline-2-carboxylates **10** could be prepared in a single step starting from ethyl oxamate **9**, following a procedure reported by Pfaltz and co-workers.[15] This involved an activation of the starting material by a triethyloxonium salt, followed by transamidation and ring closure. Thus, compounds **10a** and **10b** bearing a phenyl and a *tert*-butyl group, respectively, on the oxazoline ring were readily synthesized. The ability to obtain the products in a single step from a simple starting material compensated for the drawback of the moderate yields (34–36%) obtained. Subsequent treatment of esters **10a** and **10b** with Grignard reagents used in excess afforded hydroxy oxazolines **11d–k** (Scheme 2, method B). Table 1 summarizes all structural data of the final products.

It is noteworthy that the developed synthetic routes (Scheme 2) allowed the introduction of a high degree of structural diversity in the products after a few synthetic steps. The choice of the amino alcohol determined the absolute configuration of the stereogenic center as well as the structure of the oxazoline ring, and by employing different Grignard reagents, several substituents could be easily placed at the α-position. Next,



Scheme 2. Reagents and conditions: (a) HOBt (1.0 equiv), amino alcohol (1.0 equiv), DMAP (0.1 equiv), DCC (1.1 equiv), CH_2Cl_2, 0 °C to rt, 16 h, 61–63%; (b) $SOCl_2$ (5.0 equiv), CH_2Cl_2, rt, 16 h, then Na_2CO_3 (5.0 equiv), DMF, 85 °C, 24 h, 62–71%; (c) PhMgCl (1.2 equiv), THF, rt, 2–12 h, 41–53%; (d) Et_3OBF_4 (1.2 equiv), 1,2-DCE, rt, 24 h, then amino alcohol (1.2 equiv), reflux, 24 h, 34–36%; (e) R′MgX (3.0 equiv), THF, rt, 16 h, 60–86%.

Table 1. Hydroxy oxazolines **11a–k** prepared in this study

Entry	Compound	Method	Config.	R	R′
1	**11a**	A	*S*	*s*-Bu	Ph
2	**11b**	A	*S*	*i*-Pr	Ph
3	**11c**	A	*S*	*t*-Bu	Ph
4	**11d**	B	*R*	Ph	Ph
5	**11e**	B	*S*	*t*-Bu	Me
6	**11f**	B	*S*	*t*-Bu	4-MeO–Ph
7	**11g**	B	*S*	*t*-Bu	3,5-$(CF_3)_2$Ph
8	**11h**	B	*S*	*t*-Bu	2-Me–Ph
9	**11i**	B	*S*	*t*-Bu	3,5-$(Me)_2$Ph
10	**11j**	B	*S*	*t*-Bu	2,4,6-$(Me)_3$Ph
11	**11k**	B	*S*	*t*-Bu	2-MeO–Ph

hydroxy oxazolines **11a–k** were employed in catalytic asymmetric phenyl transfer reactions to aldehydes.

2.2. Asymmetric phenyl transfer reactions

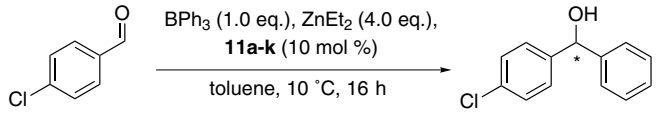
In order to study the capability of hydroxy oxazolines **11a–k** to yield catalysts for the title reaction, a series of experiments were carried out under the previously optimized reaction conditions[7,10–12] with 10 mol % of **11**, *p*-chlorobenzaldehyde **4a** as the test substrate and a mixture of triphenylborane and diethylzinc as the phenyl source. Furthermore, since a positive effect on the enantioselectivity had previously been observed upon the addition of polyethyleneglycols to the reaction mixture,[11] two series of experiments were performed. One involved reactions without the additive, the other utilized 13 mol % of DiMPEG (MW = 2000 g mol^{-1}) as additive. The results obtained are shown in Table 2.

Two general points became immediately clear: first, all hydroxy oxazolines led to active catalysts, furnishing products with varying enantioselectivities (up to 71% ee) in good to excellent yields (up to 92%). Second, the presence of DiMPEG had a beneficial effect on enantioselectivity, leading in most cases to an increased ee of the product. Unfortunately, however, this positive effect was generally accompanied by a decrease in yield.

In the first set of experiments, the impact of the substituent on the oxazoline ring was assessed, with all hydroxy oxazolines having two phenyl groups as substituents at the benzylic position (Table 2, entries 1–4). While **11a** and **11d** derived from (*S*)-leucinol and (*R*)-phenylglycinol, respectively, furnished only racemic products (entries 1 and 4), a low enantioselectivity (14% ee) was found in the catalysis with **11b**, derived from (*S*)-valinol (entry 2). The best result was obtained with hydroxy oxazoline **11c** bearing a *tert*-butyl group at the oxazoline ring, which led to the formation of diaryl methanol **5a** with 43% ee in 56% yield in the presence of the additive (entry 3). Although both ee and yield were still moderate, this result was already superior to those obtained in the same reaction with mandelic acid-derived ligands **3**.[12]

Having established the positive effect of the *tert*-butyl group on the enantioselectivity, several (*S*)-*tert*-leucinol-derived hydroxy oxazolines were then tested. When the phenyl groups at the hydroxyl-bearing carbon were changed to methyl substituents (hydroxy oxazoline **11e**), the racemic product was obtained in moderate yield (entry 5).[16] While the introduction of electron donating (entry 6) or electron withdrawing (entry 7) groups on the phenyl rings at the α-position had little effect on the enantioselectivity, a variation of the steric hindrance was more effective. Thus **11h**, having two 2-methylphenyl substituents, was in fact able to produce the final product with a promising 71% ee in 80% yield (entry 8; in the presence of DiMPEG). Unfortunately, using hydroxy oxazolines with more sterically hindered aryls did not lead to further improvements. For example, the introduction of two methyl groups at the *meta* positions of the aryl rings (hydroxy oxazoline **11i**) showed almost no effect on the enantioselectivity

Table 2. Asymmetric phenyl transfer reaction to 4-chlorobenzaldehyde **4a** catalyzed by hydroxy oxazolines **11a–k**



4a **5a**

Entry	Ligand	Without additive		With additive (13 mol % DiMPEG)	
		% Yield of **5a**[a]	% Ee of **5a** (config.)[b]	% Yield of **5a**[a]	% Ee of **5a** (config.)[b]
1	**11a**	74	*rac*	44	*rac*
2	**11b**	74	12 (*S*)	50	14 (*S*)
3	**11c**	91	27 (*S*)	56	43 (*S*)
4	**11d**	87	*rac*	48	*rac*
5	**11e**	43	*rac*	65	*rac*
6	**11f**	83	31 (*S*)	74	35 (*S*)
7	**11g**	92	17 (*S*)	80	30 (*S*)
8	**11h**	81	68 (*S*)	**80**	**71 (*S*)**
9	**11i**	84	24 (*S*)	72	39 (*S*)
10	**11j**	76	*rac*	72	*rac*
11	**11k**	80	26 (*R*)	70	20 (*R*)

[a] After column chromatography.
[b] Determined by chiral HPLC (see Experimental for details).

(entry 9) in comparison to the use of α,α-diphenyl compound **11c**. Applying α,α-dimesityl-substituted **11j** was even worse leading to racemic alcohol **5a** (entry 10). Presumably, the extreme bulk of the mesityl groups forced the ligand into a different conformation, which resulted in a lack of asymmetric induction.

Finally, we tried to combine steric and electronic effects by employing hydroxy oxazoline **11k** having two 2-MeO-substituted phenyl rings at the α-position. The result (entry 11) was unusual: first, the use of DiMPEG did not increase, but lowered the enantioselectivity, and second, the absolute configuration of the product was opposite to the ones obtained with all other ligands. Thus, the (*R*)-enantiomer of **5a** was formed in excess, whereas in the other cases, (*S*)-**5a** was predominantly obtained. It is most likely that a coordination of the metal by the methoxy groups on the phenyl rings played a key role in the reversal of enantioselectivity.

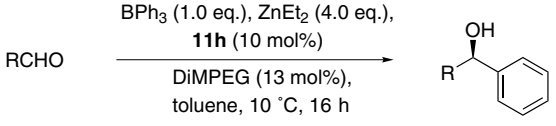
Since hydroxy oxazoline **11h** led to the best results in the test reaction, the scope of the asymmetric phenyl transfer to aldehydes was briefly examined (Table 3).

4-Methylbenzaldehyde **4b** reacted smoothly under the standard conditions giving the corresponding alcohol **5b** with 77% ee in 89% yield (Table 3, entry 2). 4-Methoxybenzaldehyde **4c** furnished the product in 81% ee with a slightly decreased yield (60%; entry 3). Unfortunately, when the 2-bromo-substituted aldehyde **4d**, which is known to be a challenging substrate for this kind of transformation, was subjected to the reaction, diarylmethanol **5d** was obtained with only 55% ee albeit in good yield (entry 4). Finally, as demonstrated with cyclohexyl carbaldehyde **4e**, aliphatic aldehydes also reacted, but in this case the enantioselectivity was very low (20% ee, entry 5).

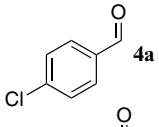
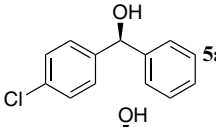
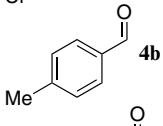
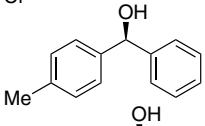
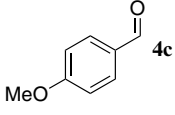
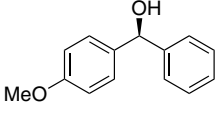
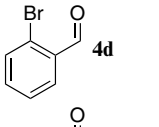
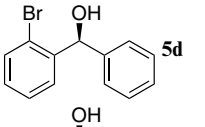
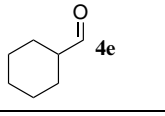
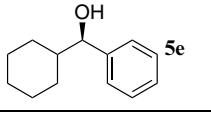
3. Conclusions

The synthesis of new hydroxy oxazolines **11a**–**k**, derived from chiral amino alcohols and benzoylformic acid or ethyl oxamate, and their application in the catalytic asymmetric phenyl transfer to aromatic and aliphatic aldehydes have been reported. Two synthetic pathways have been developed, which proved to be remarkably flexible, allowing the introduction of a high degree of structural diversity in very few steps. Although the results obtained in these reactions cannot compete with the best ones reported in the literature, promising enantioselectivities have been obtained with hydroxy oxazoline **11h** in the phenyl transfer to *para*-substituted benzaldehydes, with a maximum of 81% ee for 4-methoxybenzaldehyde **4c**. These results are far superior to those obtained with mandelic acid-derived hydroxy oxazolines **3**, thus confirming our initial assumption that a variation of the benzylic position of **11** would result in more active and selective catalysts. Considering the ease of preparation of the present class of hydroxy oxazolines, improvements are expected to arise from further optimization of ligand structure, as well as reaction conditions.

Table 3. Asymmetric phenyl transfer reaction to differently substituted aldehydes catalyzed by hydroxy oxazoline **11h**



4a-e **5a-e**

Entry	Starting material	Product	% Yield[a]	% Ee[b]
1	 **4a**	 **5a**	80	71 (*S*)
2	 **4b**	 **5b**	89	77 (*S*)
3	 **4c**	 **5c**	60	81 (*S*)
4	 **4d**	 **5d**	85	55 (*S*)
5	 **4e**	 **5e**	65	20 (*R*)

[a] After column chromatography.
[b] Determined by chiral HPLC (see Experimental for details).

4. Experimental

4.1. General remarks

Air sensitive manipulations were carried out under an argon atmosphere using either standard Schlenk techniques or a glovebox. THF and toluene were distilled from the sodium-benzophenone ketyl radical and CH_2Cl_2 from calcium hydride prior to use. Ethyl acetate, diethyl ether, petroleum ether (PE) and pentane for column chromatography were distilled before use. Dichloroethane and DMF were HPLC grade and used as received. ^1H and ^{13}C NMR spectra were recorded either on a Varian Gemini 300 spectrometer (300 and 75 MHz, respectively) or on a Varian Inova 400 spectrometer (400 and 100 MHz, respectively). IR spectra were measured on a Perkin–Elmer PE 1760 FT instrument as KBr pellets or neat (in case of liquid compounds); absorptions are given in wavenumbers (cm^{-1}). MS spectra were recorded on a Varian MAT 212 or on a Finnigan MAT 95 spectrometer with EI ionization. Optical rotation measurements were conducted at room temperature with a Perkin–Elmer PE 241 polarimeter at a wavelength of 589 nm. HPLC measurements were performed on a Merck-Hitachi HPLC apparatus (L-7400 UV-detector, L-7100 pump and D-7000 integrator) or on a Gynkotek HPLC system (Gina 50 autosampler, UVD 170S UV-detector, DG 503 degasser and M480G pump), using columns with chiral stationary phase purchased from Chiral Technologies Ltd. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Melting points were measured in open capillaries with a Buechi B-540 apparatus and are uncorrected.

4.2. General procedure for the condensation of benzoylformic acid 6 with amino alcohols to give oxo hydroxy amides 7

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, benzoylformic acid **6** (20.0 mmol, 3.00 g) was dissolved in dry CH_2Cl_2 (150 mL) and 1-hydroxybenzotriazol (HOBt, 20.0 mmol, 2.70 g) added in one portion. The mixture was stirred at room temperature for 30 min, and then 4-dimethylaminopyridine (DMAP, 2.0 mmol, 244 mg) and the appropriate amino alcohol (20 mmol) added. The resulting mixture was cooled to 0 °C and a solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC, 22.0 mmol, 4.54 g) in dry CH_2Cl_2 (100 mL) added dropwise. The reaction mixture was stirred for 1 h at 0 °C, and then allowed to warm to room temperature and stirred overnight. The solvent was then removed under reduced pressure and replaced with EtOAc (250 mL). The precipitate thus formed was filtered off on a short pad of Celite®, and the organic layer washed in sequence with aq HCl (1 M, 200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL) and finally dried over $MgSO_4$. Evaporation of the solvent afforded **7** as a crude product, which was purified by flash column chromatography.

4.2.1. (*S*)-*N*-(1-*sec*-Butyl-2-hydroxyethyl)benzoylformamide 7a. Prepared starting from (*S*)-leucinol (20.0 mmol, 2.34 g). Purification by flash column chromatography (PE–EtOAc 1:1) afforded pure **7a** as a colorless oil. Yield 3.03 g (12.2 mmol, 61%); $[\alpha]_D^{20} = -19.1$ (*c* 0.50, $CHCl_3$); IR (neat): 3339, 2956, 2872, 1662, 1529, 1251, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.28 (d, $J = 8.4$ Hz, 2H, H_{ar}), 7.61 (t, $J = 8.4$ Hz, 2H, H_{ar}), 7.46 (t, $J = 8.0$ Hz, 1H, H_{ar}), 7.22–7.27 (m, 1H, NH), 4.11–4.21 (m, 1H, CH), 3.76 (dd, $J = 9.3$ Hz, $J = 3.6$ Hz, 1H, CH_2), 3.63 (dd, $J = 9.3$ Hz, $J = 5.5$ Hz, 1H, CH_2), 2.80 (br s, 1H, OH), 1.67 (dsept, $J = 6.4$ Hz, $J = 2.1$ Hz, 1H, CH), 1.48–1.56 (m, 1H, CH_2), 1.38–1.47 (m, 1H, CH_2), 0.96 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 22.3, 23.2, 25.1, 40.1, 50.2, 65.5, 128.5, 131.1, 133.3, 134.4, 162.2, 187.9; MS (EI, 70 eV): *m*/*z* = 249 $[M]^+$, 218, 144, 105, 83, 77, 55; HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}NO_3$: 249.1365; found 249.1364.

4.2.2. (*S*)-*N*-(1-*iso*-Propyl-2-hydroxyethyl)benzoylformamide 7b. Prepared starting from (*S*)-valinol (20.0 mmol, 2.06 g). Purification by flash column chromatography (PE–EtOAc 1:1) afforded pure **7b** as a colorless oil. Yield 2.97 g (12.6 mmol, 63%); $[\alpha]_D^{20} = -13.7$ (*c* 0.18, $CHCl_3$); IR (neat): 3358, 2964, 2878, 1663, 1525, 1270, 1219 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.25–8.28 (m, 2H, H_{ar}), 7.57–7.65 (m, 1H, H_{ar}), 7.41–7.50 (m, 2H, H_{ar}), 7.29–7.39 (m, 1H, NH), 3.79–3.89 (m, 1H, CH), 3.73–3.78 (m, 2H, CH_2), 2.78 (br s, 1H, OH), 1.99 (sept, $J = 6.8$ Hz, 1H, CH), 1.01 (d, $J = 6.8$ Hz, 3H, CH_3), 0.98 (d, $J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 18.8, 19.6, 29.1, 57.2, 63.2, 128.5, 131.2, 133.3, 134.5, 162.6, 188.1. MS (EI, 70 eV): *m*/*z* = 235 $[M]^+$, 204, 130, 105, 87, 77, 69. HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}NO_3$: 235.1208; found 235.1208.

4.2.3. (*S*)-*N*-(1-*tert*-Butyl-2-hydroxyethyl)benzoylformamide 7c. Prepared starting from (*S*)-*tert*-leucinol (20.0 mmol, 2.34 g). Purification by flash column chromatography (PE–EtOAc 1:1) afforded pure **7c** as a colorless oil. Yield 2.78 g (12.0 mmol, 60%); $[\alpha]_D^{20} = -60.2$ (*c* 1.03, $CHCl_3$); IR (neat): 3257, 3170, 3095, 2958, 1661, 1325, 1234, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 8.24–8.28 (m, 2H, H_{ar}), 7.55–7.64 (m, 1H, H_{ar}), 7.40–7.48 (m, 2H, H_{ar}), 7.28–7.38 (m, 1H, NH), 3.86–3.97 (m, 2H, CH_2), 3.60–3.70 (m, 1H, CH), 2.78 (br s, 1H, OH), 1.00 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 26.9, 33.9, 59.9, 62.3, 128.5, 131.2, 133.3, 134.5, 163.0, 188.2. MS (EI, 70 eV): *m*/*z* = 249 $[M]^+$, 218, 164, 144, 105, 86, 77, 69, 57. HRMS (EI): *m*/*z* calcd for $C_9H_{10}NO_2$ [$C_{14}H_{19}NO_3$–C_5H_9O]: 164.0712; found 164.0711.

4.3. General procedure for the synthesis of 2-benzoyloxazolines 8

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, a solution of the appropriate oxo hydroxy amide **7** (2.0 mmol) in dry CH_2Cl_2 (20 mL) was prepared. The solution was cooled to 0 °C and $SOCl_2$ (10.0 mmol, 1.19 g, 0.73 mL) added dropwise over 10 min. The reaction mixture was warmed to room temperature and stirred overnight. The solvent and excess $SOCl_2$ were then evaporated and replaced with

DMF (20 mL). Solid Na_2CO_3 (10.0 mmol, 1.06 g) was added in one portion at room temperature and the reaction mixture heated to 85 °C and stirred for 24 h. The heterogeneous mixture was then diluted with AcOEt (20 mL) and the organic phase washed with water (5 × 20 mL). The aqueous phase was extracted with AcOEt (20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **8**, which was then purified by flash column chromatography.

4.3.1. (*S*)-2-Benzoyl-4-*sec*-butyloxazoline 8a. Prepared starting from **7a** (2.0 mmol, 0.499 g). Purification by flash column chromatography (PE–EtOAc 4:1) afforded pure **8a**. Yield 0.329 g (1.42 mmol, 71%); colorless oil; $[\alpha]_D^{20} = -31.0$ (*c* 1.06, $CHCl_3$); IR (neat): 3257, 3170, 2958, 1661, 1326, 1233, 1064 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.25–8.32 (m, 2H, H_{ar}), 7.57–7.66 (m, 1H, H_{ar}), 7.43–7.52 (m, 2H, H_{ar}), 4.40–4.58 (m, 2H, CH_2), 4.03 (t, *J* = 7.3 Hz, 1H, CH), 1.70–1.92 (m, 2H, CH_2), 1.40–1.52 (m, 1H, CH), 1.00 (d, *J* = 6.4 Hz, 3H, CH_3), 0.98 (d, *J* = 6.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 22.7, 22.8, 25.6, 45.2, 66.3, 73.0, 128.5, 130.7, 134.2, 134.9, 159.1, 183.7. MS (EI, 70 eV): *m*/*z* = 231 $[M]^+$, 174, 105, 77, 51.

4.3.2. (*S*)-2-Benzoyl-4-*iso*-propyloxazoline 8b. Prepared starting from **7b** (2.0 mmol, 0.471 g). Purification by flash column chromatography (PE–EtOAc 3:1) afforded pure **8b**. Yield 0.270 g (1.24 mmol, 62%); colorless oil; $[\alpha]_D^{20} = +112.7$ (*c* 0.97, $CHCl_3$); IR (neat): 2964, 1739, 1607, 1194, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.27–8.32 (m, 2H, H_{ar}), 7.58–7.65 (m, 1H, H_{ar}), 7.45–7.52 (m, 2H, H_{ar}), 4.46 (dd, *J* = 9.6 Hz, *J* = 8.3 Hz, 1H, CH_2), 4.21–4.30 (m, 1H, CH), 4.17 (t, *J* = 8.3 Hz, 1H, CH_2), 1.85–199 (m, 1H, CH), 1.06 (d, *J* = 6.9 Hz, 1H, CH_3), 0.98 (d, *J* = 6.9 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 18.6, 19.1, 32.8, 70.2, 73.7, 128.5, 130.7, 134.2, 134.9, 159.1, 183.7; MS (EI, 70 eV): *m*/*z* = 217 $[M]^+$, 173, 144, 104, 77, 70, 55. HRMS (EI): *m*/*z* calcd for $C_{13}H_{15}NO_2$: 217.1103; found 217.1103.

4.3.3. (*S*)-2-Benzoyl-4-*tert*-butyloxazoline 8c. Prepared starting from **7c** (2.0 mmol, 0.499 g). Purification by flash column chromatography (PE–EtOAc 3:1) afforded pure **8c**. Yield 0.315 g (1.36 mmol, 68%); colorless oil; $[\alpha]_D^{20} = +219.8$ (*c* 0.80, $CHCl_3$); IR (neat): 2960, 2907, 1741, 1608, 1476, 1176, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 8.28–8.35 (m, 2H, H_{ar}), 7.58–7.66 (m, 1H, H_{ar}), 7.43–7.53 (m, 2H, H_{ar}), 4.34–4.46 (m, 1H, CH), 4.16–4.29 (m, 2H, CH_2), 1.01 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 26.1, 34.0, 68.7, 77.4, 128.5, 130.8, 134.2, 135.0, 159.2, 183.7; MS (EI, 70 eV): *m*/*z* = 231 $[M]^+$, 175, 158, 130, 104, 84, 77, 69, 57; HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_2$: 231.1259; found 231.1260.

4.4. General procedure for the addition of phenylmagnesium chloride to 2-benzoyloxazolines 8

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, a solution of the appropriate 2-benzoyloxazoline **8** (1.0 mmol) in dry THF (15 mL) was prepared. The solution was cooled to 0 °C and PhMgCl (2.0 M solution in THF, 1.1 mmol, 0.55 mL) then added dropwise over 5 min. The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction was quenched with satd aq NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (25 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **11**, which was then purified either by recrystallization or flash column chromatography.

4.4.1. (*S*)-2-(Diphenylhydroxy)methyl-4-*sec*-butyloxazoline 11a. Prepared starting from **8a** (1.0 mmol, 0.231 g). Purification by flash column chromatography (PE–EtOAc 4:1) afforded pure **11a**. Yield 0.144 g (0.47 mmol, 47%); colorless oil; $[\alpha]_D^{20} = -57.2$ (*c* 0.67, $CHCl_3$); IR (neat): 3065, 2953, 2892, 2792, 1655, 1450, 1224, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.38–7.49 (m, 4H, H_{ar}), 7.25–7.37 (m, 6H, H_{ar}), 4.90 (s, 1H, OH), 4.49 (dd, *J* = 8.9 Hz, *J* = 7.9 Hz, 1H, CH_2), 4.06–4.19 (m, 1H, CH), 4.02 (t, *J* = 7.9 Hz, 1H, CH_2), 1.68–1.83 (m, 1H, CH_2), 1.50–1.66 (m, 1H, CH_2), 1.24–1.35 (m, 1H, CH), 0.93 (d, *J* = 6.4 Hz, 3H, CH_3), 0.91 (d, *J* = 6.4 Hz, 3H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$): 22.7, 22.8, 25.4, 45.3, 63.8, 75.6, 77.3, 127.3, 127.4, 127.6, 127.9, 128.0, 128.1, 142.9, 143.1, 170.1. MS (EI, 70 eV): *m*/*z* = 309 $[M]^+$, 232, 183, 165, 105, 77. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.60; H, 7.44; N, 4.20.

4.4.2. (*S*)-2-(Diphenylhydroxy)methyl-4-*iso*-propyloxazoline 11b. Prepared starting from **8b** (1.0 mmol, 0.217 g). Purification by recrystallization from *n*-hexane/CH_2Cl_2 afforded pure **11b**. Yield 0.120 g (0.41 mmol, 41%); colorless crystals; mp 91–92 °C; $[\alpha]_D^{20} = -58.9$ (*c* 0.95, $CHCl_3$); IR (KBr): 3093, 2959, 2893, 2870, 1659, 1451, 1228, 1181 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.40–7.48 (m, 4H, H_{ar}), 7.25–7.37 (m, 6H, H_{ar}), 5.00 (br s, 1H, OH), 4.38–4.47 (m, 1H, CH_2), 4.13–4.20 (m, 1H, CH_2), 3.80–3.90 (m, 1H, CH), 1.68–1.81 (m, 1H, CH), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3), 0.86 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 18.4, 18.9, 32.8, 71.0, 73.0, 77.4, 127.3, 127.4, 127.8, 128.0, 143.0, 143.1, 170.2. MS (EI, 70 eV): *m*/*z* = 295 $[M]^+$, 222, 218, 165, 105, 77. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.42; H, 7.34; N, 4.52.

4.4.3. (*S*)-2-(Diphenylhydroxy)methyl-4-*tert*-butyloxazoline 11c. Prepared starting from **8c** (1.0 mmol, 0.231 g). Purification by recrystallization from *n*-hexane afforded pure **11c**. Yield 0.166 g (0.54 mmol, 54%); colorless needles; mp 130–131 °C; $[\alpha]_D^{20} = -59.7$ (*c* 0.87, $CHCl_3$); IR (KBr): 3062, 2957, 2895, 2868, 1657, 1451, 1227, 1181, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.38–7.49 (m, 4H, H_{ar}), 7.25–7.36 (m, 6H, H_{ar}), 4.98 (br s, 1H, OH), 4.36–4.44 (m, 1H, CH_2), 4.28 (t, *J* = 8.5 Hz, 1H, CH_2), 3.89 (dd, *J* = 10.1 Hz, *J* = 8.4 Hz, 1H, CH), 0.89 (s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 26.0, 34.0, 71.7, 74.4, 77.1, 127.3, 127.4, 127.8, 127.8, 128.0, 128.0, 142.7, 143.0, 170.6. MS (EI, 70 eV): *m*/*z* = 309

$[M]^+$, 232, 222, 183, 105, 77. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.89; H, 7.71; N, 4.21.

4.5. General procedure for the synthesis of ethyl oxazoline-2-carboxylates 10 from ethyl oxamate 9

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, a solution of triethyloxonium tetrafluoroborate (15.1 mmol, 2.87 g) in 1,2-dichloroethane (DCE, 80 mL) was prepared. To this solution, ethyl oxamate **9** (15.1 mmol, 1.77 g) was added in one portion at room temperature. The reaction mixture was stirred at room temperature for 24 h and then the appropriate amino alcohol (17.1 mmol) added in one portion. The reaction mixture was heated to reflux and stirred for an additional 24 h. It was then cooled to room temperature and poured into ice-cold satd aq NH_4Cl (25 mL). Dichloromethane was added (80 mL) and the organic layer washed with satd aq NH_4Cl (2×25 mL), and brine (25 mL), and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **10**, which was then purified by flash column chromatography.

4.5.1. Ethyl (*R*)-4-phenyloxazoline-2-carboxylate 10a. Prepared starting from (*R*)-phenylglycinol (17.1 mmol, 2.35 g). Purification by flash column chromatography (PE–EtOAc 4:3) afforded pure **10a**. Yield 1.141 g (5.2 mmol, 34%); yellow oil; $[\alpha]_D^{20} = -38.3$ (*c* 0.48, $CHCl_3$); IR (neat): 3358, 1745, 1697, 1529, 1306, 1188 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.29–7.41 (m, 2H, H_{ar}), 7.23–7.29 (m, 3H, H_{ar}), 5.41 (dd, $J = 10.5$ Hz, $J = 9.0$ Hz, 1H, CH_2), 4.83 (dd, $J = 10.6$ Hz, $J = 8.9$ Hz, 1H, CH_2), 4.36–4.46 (m, 2H, CH_2), 4.32–4.38 (t, $J = 8.9$ Hz, 1H, CH), 1.40 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 63.0, 70.3, 75.4, 126.6, 127.9, 128.7, 140.1, 156.5, 157.3. MS (EI, 70 eV): *m/z* = 219 $[M]^+$, 189, 144, 117, 90, 77.

4.5.2. Ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate 10b. Prepared starting from (*S*)-*tert*-leucinol (17.1 mmol, 2.00 g). Purification by flash column chromatography (PE–EtOAc 3:2) afforded pure **10b**. Yield 1.050 g (5.3 mmol, 36%); colorless oil; $[\alpha]_D^{20} = -74.7$ (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 4.40 (dd, $J = 10.6$ Hz, $J = 1.9$ Hz, 1H, CH), 4.34–4.42 (m, 2H, CH_2), 4.25 (t, $J = 8.8$ Hz, 1H, CH_2), 4.09 (dd, $J = 10.6$ Hz, $J = 8.8$ Hz, 1H, CH_2), 1.39 (t, $J = 7.3$ Hz, 3H, CH_3), 0.95 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 26.0, 33.9, 62.9, 69.8, 76.7, 155.4, 157.6. All the other data are in agreement with those previously reported in the literature.[15]

4.6. General procedure for the addition of Grignard reagents to ethyl oxazoline-2-carboxylates 10

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, a solution of the appropriate ethyl oxazoline-2-carboxylate **10** (1.0 mmol) in dry THF (10 mL) was prepared. The solution was cooled to 0 °C and a solution of the appropriate Grignard reagent ($\geqslant 3.0$ mmol) in THF or Et_2O added dropwise over 5 min. The reaction mixture was warmed to room temperature and stirred for 16–24 h. The reaction was quenched by the addition of satd aq NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude **11**, which was then purified either by recrystallization or flash column chromatography.

4.6.1. (*R*)-2-(Diphenylhydroxy)methyl-4-phenyloxazoline 11d. Prepared starting from ethyl (*R*)-4-phenyloxazoline-2-carboxylate **10a** (1.0 mmol, 0.219 g) and PhMgCl (2.0 M solution in THF, 3.0 mmol, 1.5 mL). Purification by flash column chromatography (PE–EtOAc 7:2) afforded pure **11d**. Yield 0.284 g (0.86 mmol, 86%); white solid; mp 84–85 °C; $[\alpha]_D^{20} = +113.9$ (*c* 0.99, $CHCl_3$); IR (KBr): 3062, 3027, 1736, 1655, 1494, 1450, 1220, 1172, 1057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.46–7.54 (m, 4H, H_{ar}), 7.25–7.40 (m, 9H, H_{ar}), 7.16–7.22 (m, 2H, H_{ar}), 5.16–5.25 (m, 1H, CH_2), 4.88 (s, 1H, OH), 4.77–4.86 (m, 1H, CH_2), 4.26–4.33 (m, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 68.3, 77.1, 77.4, 126.3, 127.1, 127.2, 127.6, 127.8, 127.8, 127.9, 127.9, 128.6, 141.2, 142.4, 142.6, 171.5. MS (EI, 70 eV): *m/z* = 329 $[M]^+$, 252, 183, 105, 77. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.16; H, 5.55; N, 3.98.

4.6.2. (*S*)-2-(Dimethylhydroxy)methyl-4-*tert*-butyloxazoline 11e. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and MeMgCl (3.0 M solution in Et_2O, 3.0 mmol, 1.0 mL). Purification by recrystallization from *n*-hexane afforded pure **11e**. Yield 0.110 g (0.60 mmol, 60%); white solid; mp 86–87 °C; $[\alpha]_D^{20} = -28.9$ (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 4.15–4.35 (m, 2H, CH_2), 3.86 (dd, $J = 9.9$ Hz, $J = 7.4$ Hz, 1H, CH), 3.40 (s, 1H, OH), 1.44 (s, 6H, CH_3), 0.90 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 25.6, 27.7, 28.1, 33.7, 68.8, 70.6, 75.0, 172.4. All the other data are in agreement with those previously reported in the literature.[16]

4.6.3. (*S*)-2-[Di-(4′-methoxyphenyl)hydroxy]methyl-4-*tert*-butyloxazoline 11f. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and [4-(MeO)Ph]MgBr (0.5 M solution in THF, 3.0 mmol, 6.0 mL). Purification by double recrystallization from Et_2O afforded pure **11f**. Yield 0.320 g (0.86 mmol, 86%); light brown solid; mp 136–137 °C; $[\alpha]_D^{20} = -48.3$ (*c* 0.78, $CHCl_3$); IR (KBr): 3175, 2956, 2898, 1650, 1508, 1466, 1247, 1175, 1075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.29–7.41 (m, 4H, H_{ar}), 6.80–6.89 (m, 4H, H_{ar}), 4.90 (br s, 1H, OH), 4.40 (dd, $J = 10.0$ Hz, $J = 8.8$ Hz, 1H, CH_2), 4.27 (t, $J = 8.5$ Hz, 1H, CH_2), 3.90 (dd, $J = 10.0$ Hz, $J = 8.5$ Hz, 1H, CH), 3.795 (s, 3H, CH_3), 3.790 (s, 3H, CH_3), 0.90 (s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 26.0, 33.9, 55.35, 55.37, 71.7, 74.4, 77.1, 113.29, 113.31, 128.5, 128.6, 135.1, 135.3, 159.0, 159.1, 171.0. MS (EI, 70 eV): *m/z* = 369 $[M]^+$, 262, 151, 135, 107, 77. Anal. Calcd for

$C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.22; H, 7.09; N, 3.54.

4.6.4. (*S*)-2-[Di-(3′,5′-di(trifluoromethyl)phenyl)hydroxy]methyl-4-*tert*-butyloxazoline 11g. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and 3,5-$(CF_3)_2$PhMgBr (approx. 1.0 M solution in THF, 5.0 mmol, 5.0 mL, prepared according to the literature[17]). Purification by flash column chromatography (PE–EtOAc 4:1) afforded pure **11g**. An analytical sample was obtained by recrystallization from *n*-hexane. Yield 0.510 g (0.88 mmol, 88%); white solid; mp 121–122 °C; $[\alpha]_D^{20} = -28.5$ (*c* 1.06, $CHCl_3$); IR (KBr): 3420, 2968, 1660, 1372, 1283, 1176, 1137 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.97 (s, 2H, H_{ar}), 7.86–7.92 (m, 4H, H_{ar}), 5.27 (br s, 1H, OH), 3.92–4.02 (m, 1H, CH_2), 4.46–4.54 (m, 1H, CH_2), 4.36–4.44 (m, 1H, CH), 0.90 (s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 25.7, 34.0, 72.6, 74.6, 76.0, 122.6, 122.6, 123.04 (q, $J = 70.8$ Hz), 123.08 (q, $J = 70.9$ Hz), 127.2, 127.4, 131.8 (q, $J = 33.0$ Hz), 131.9 (q, $J = 33.4$ Hz), 143.6, 144.4, 167.5. MS (EI, 70 eV): *m*/*z* = 581 $[M]^+$, 562, 525, 455, 241, 213, 163, 70, 57. Anal. Calcd for $C_{24}H_{19}NO_2F_{12}$: C, 49.58; H, 3.29; N, 2.41. Found: C, 49.97; H, 3.49; N, 2.40.

4.6.5. (*S*)-2-[Di-(2′-methylphenyl)hydroxy]methyl-4-*tert*-butyloxazoline 11h. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and 2-MePhMgCl (1.0 M solution in THF, 3.0 mmol, 3.0 mL). Purification by recrystallization from *n*-hexane afforded pure **11h**. Yield 0.266 g (0.79 mmol, 79%); white solid; mp 188–189 °C; $[\alpha]_D^{20} = -52.3$ (*c* 0.96, $CHCl_3$); IR (KBr): 3167, 2957, 1654, 1483, 1461, 1218, 1049 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.06–7.30 (m, 8H, H_{ar}), 4.94 (br s, 1H, OH), 4.38–4.49 (m, 1H, CH_2), 4.21–4.32 (m, 1H, CH_2), 3.87–3.99 (m, 1H, CH), 2.15 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 0.92 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5, 21.7, 26.1, 33.8, 71.6, 74.5, 79.4, 125.4, 125.5, 127.4, 127.6, 127.8, 127.9, 132.3, 132.3, 137.9, 137.9, 140.7, 140.8, 171.4. MS (EI, 70 eV): *m*/*z* = 337 $[M]^+$, 304, 231, 192, 128, 119, 91, 65, 57. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 77.92; H, 8.22; N, 3.91.

4.6.6. (*S*)-2-[Di-(3′,5′-dimethylphenyl)hydroxy]methyl-4-*tert*-butyloxazoline 11i. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and 3,5-$(Me)_2$PhMgBr (approx. 1.0 M solution in THF, 5.0 mmol, 5.0 mL, prepared according to the literature[18]). Purification by recrystallization from PE afforded pure **11i**. Yield 0.256 g (0.70 mmol, 70%); white solid; mp 115–116 °C; $[\alpha]_D^{20} = -33.8$ (*c* 1.06, $CHCl_3$); IR (KBr): 3152, 2957, 2867, 1660, 1602, 1467, 1218, 1151, 1100, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 6.84–7.13 (m, 6H, H_{ar}), 4.81 (br s, 1H, OH), 4.35–4.46 (m, 1H, CH_2), 4.23–4.34 (m, 1H, CH_2), 3.89 (dd, $J = 10.0$ Hz, $J = 8.3$ Hz, 1H, CH), 2.29 (s, 6H, CH_3), 2.27 (s, 6H, CH_3), 0.92 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 21.4, 21.5, 25.9, 33.9, 71.6, 74.4, 77.4, 125.18, 125.21, 129.5, 129.5, 137.3, 137.4, 142.5, 143.1, 170.9. MS (EI, 70 eV): *m*/*z* = 365 $[M]^+$, 347, 278, 260, 133, 105, 77, 57. Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.87; H, 8.55; N, 3.83. Found: C, 78.66; H, 8.83; N, 3.58.

4.6.7. (*S*)-2-[Di-(2′,4′,6′-trimethylphenyl)hydroxy]methyl-4-*tert*-butyloxazoline 11j. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and 2,4,6-$(Me)_3$PhMgBr (1.0 M solution in THF, 3.0 mmol, 3.0 mL). Purification by flash column chromatography (PE–EtOAc 13:1) afforded pure **11j**. Yield 0.223 g (0.57 mmol, 57%); yellow oil; $[\alpha]_D^{20} = -157.7$ (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 3429, 2958, 2870, 1646, 1477, 1382, 1220, 1057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 6.73 (s, 2H, H_{ar}), 6.70 (s, 2H, H_{ar}), 5.05 (br s, 1H, OH), 4.40 (dd, $J = 10.0$ Hz, $J = 8.9$ Hz, 1H, CH_2), 4.15 (t, $J = 9.1$ Hz, 1H, CH_2), 3.84 (t, $J = 10.0$ Hz, 1H, CH), 2.21 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.12 (s, 6H, CH_3), 2.10 (s, 6H, CH_3), 0.88 (s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 22.0, 23.5, 26.3, 27.1 33.8, 71.6, 74.4, 79.7, 131.4, 131.5, 136.0, 136.1, 136.2, 136.9, 138.3, 139.8, 172.8. MS (EI, 70 eV): *m*/*z* = 393 $[M]^+$, 360, 259, 202, 147, 119, 91, 57. Anal. Calcd for $C_{26}H_{35}NO_2$: C, 79.35; H, 8.96; N, 3.56. Found: C, 79.65; H, 9.24; N, 3.35.

4.6.8. (*S*)-2-[Di-(2′-methoxyphenyl)hydroxy]methyl-4-*tert*-butyloxazoline 11k. Prepared starting from ethyl (*S*)-4-*tert*-butyloxazoline-2-carboxylate **10b** (1.0 mmol, 0.199 g) and 2-MeO–PhMgBr (1.0 M solution in THF, 3.0 mmol, 3.0 mL). Purification by flash column chromatography (PE–EtOAc 4:1, then 2:1) afforded pure **11k**. Yield 0.235 g (0.64 mmol, 64%); pale yellow oil; $[\alpha]_D^{20} = -14.7$ (*c* 0.96, $CHCl_3$); IR ($CHCl_3$): 3495, 2956, 1662, 1488, 1464, 1243, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.27–7.39 (m, 2H, H_{ar}), 6.83–7.05 (m, 6H, H_{ar}), 5.52 (br s, 1H, OH), 4.14–4.32 (m, 2H, CH_2), 3.98 (dd, $J = 10.2$ Hz, $J = 7.8$ Hz, 1H, CH), 3.81 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 0.93 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 26.0, 33.9, 55.6, 55.7, 69.8, 75.4, 84.1, 111.4, 111.6, 120.8, 120.8, 128.6, 129.1, 129.3, 129.3, 130.0, 130.2, 157.3, 157.5, 171.2. MS (EI, 70 eV): *m*/*z* = 369 $[M]^+$, 338, 262, 238, 135, 121, 91, 77. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.60; H, 7.44; N, 3.63.

4.7. General procedure for the phenyl transfer reaction on aldehydes catalyzed by compounds 11a–k

4.7.1. General procedure without additive. In a glovebox under an inert atmosphere of argon, BPh_3 (0.25 mmol, 60 mg) was sealed in a flame-dried reaction vessel (18 × 50 mm). Toluene (2 mL) was added and the resulting solution treated with Et_2Zn (1.0 M solution in heptane, 1.0 mmol, 1.0 mL). After stirring at room temperature for 30 min, the appropriate hydroxy oxazoline **11** (0.025 mmol) was added as toluene solution (1.0 mL) and stirring continued for further 45–60 min at room temperature. The resulting clear solution was cooled to 10 °C and the appropriate aldehyde **4** (0.25 mmol), dissolved in toluene (1.0 mL), was slowly added. After stirring at 10 °C for 12–18 h, the reaction mixture was quenched with water (10 mL). Aqueous

AcOH (10%) was added (10 mL) and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. Evaporation of the solvent furnished crude alcohols **5**, which were then purified by flash column chromatography.

4.7.2. General procedure with additive. In a glovebox under an inert atmosphere of argon, BPh_3 (0.25 mmol, 60 mg) and DiMPEG ($M = 2000$ g mol^{-1}, 0.032 mmol, 63 mg) were sealed in a flame-dried reaction vessel (18×50 mm). Toluene (2 mL) was added, and the resulting solution treated with Et_2Zn (1.0 M solution in heptane, 1.0 mmol, 1.0 mL), to give a clear solution containing a small quantity of precipitate. After stirring at room temperature for 30 min, hydroxy oxazoline **11** (0.025 mmol) was added as a toluene solution (1.0 mL) and stirring continued for further 45–60 min at room temperature. The resulting mixture was cooled to 10 °C and the appropriate aldehyde **4** (0.25 mmol) dissolved in toluene (1.0 mL) slowly added. From hereon, the protocol followed the procedure reported above for the reactions performed without additive.

4.7.3. (*S*)-(4-Chlorophenyl)phenylmethanol 5a. Obtained from 4-chlorobenzaldehyde **4a** (0.25 mmol, 35 mg). Purification by flash column chromatography (pentane–Et_2O 85:15) furnished pure **5a** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): 7.23–7.45 (m, 9H, H_{ar}), 5.78 (s, 1H, CH), 2.50 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): 75.7, 126.6, 127.9, 127.9, 128.7, 128.8, 133.3, 142.3, 143.5. HPLC separation conditions: Chiralcel OB-H, 230 nm, heptane/*i*-PrOH 90:10, 0.5 mL/min; t_r = 24.1 min (*R*), 30.4 min (*S*).

4.7.4. (*S*)-(4-Methylphenyl)phenylmethanol 5b. Obtained from 4-methylbenzaldehyde (**4b**, 0.25 mmol, 30 mg). Purification by flash column chromatography (pentane–Et_2O 8:2) furnished pure **5b** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.08–7.39 (m, 9H, H_{ar}), 5.79 (s, 1H, CH), 2.32 (s, 3H, CH_3), 2.30 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 76.0, 126.2, 126.3, 127.2, 128.2, 129.0, 137.0, 140.8, 143.8. HPLC separation conditions: Chiralcel OD, 230 nm, heptane/*i*-PrOH 98:2, 0.9 mL/min; t_r = 27.2 min (*S*), 30.8 min (*R*).

4.7.5. (*S*)-(4-Methoxyphenyl)phenylmethanol 5c. Obtained from 4-methoxybenzaldehyde **4c** (0.25 mmol, 34 mg). Purification by flash column chromatography (pentane–Et_2O 85:15) furnished pure **5c** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.21–7.38 (m, 7H, H_{ar}), 6.81–6.88 (m, 2H, H_{ar}), 5.77 (s, 1H, CH), 3.76 (s, 3H, CH_3), 2.35 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): 55.4, 75.9, 113.9, 126.4, 127.3, 127.9, 128.4, 136.2, 144.0, 159.0. HPLC separation conditions: Chiralcel OJ, 230 nm, heptane/*i*-PrOH 90:10, 1.0 mL/min; t_r = 30.6 min (*R*), 33.7 min (*S*).

4.7.6. (*S*)-(2-Bromophenyl)phenylmethanol 5d. Obtained from 2-bromobenzaldehyde **4d** (0.25 mmol, 46 mg). Purification by flash column chromatography (pentane–Et_2O 8:2) furnished pure **5d** as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.50–7.60 (m, 2H, H_{ar}), 7.19–7.47 (m, 7H, H_{ar}), 6.18 (s, 1H, CH), 2.81 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): 74.8, 122.8, 127.1, 127.8, 128.5, 128.6 129.1, 129.6, 132.8, 142.2, 142.6. HPLC separation conditions: Chiralcel OD, 230 nm, heptane/*i*-PrOH 90:10, 0.8 mL/min; t_r = 10.3 min (*R*), 13.2 min (*S*).

4.7.7. (*R*)-Cyclohexylphenylmethanol 5e. Obtained from cyclohexylcarbaldehyde **4e** (0.25 mmol, 28 mg). Purification by flash column chromatography (pentane–Et_2O 8:2) furnished pure **5e** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): 7.17–7.37 (m, 5H, H_{ar}), 4.34 (d, 1H, J = 7.2 Hz, CH), 2.85 (br s, 1H, OH), 1.93–2.04 (m, 1H, H_{al}), 1.53–1.80 (m, 4H, H_{al}), 0.85–1.42 (m, 6H, H_{al}). ^{13}C NMR (75 MHz, $CDCl_3$): 26.1, 26.1, 26.5, 28.9, 29.3, 45.0, 79.5, 126.7, 127.3, 128.2, 143.6. HPLC separation conditions: Chiralcel OD, 254 nm, heptane/*i*-PrOH 95:5, 0.5 mL/min; t_r = 14.2 min (*R*), 15.6 min (*S*).

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References

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (c) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; (d) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004.
2. (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Soai, K.; Shibata, T. in Ref. 1b; pp 911–922; (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
3. Soai, K.; Kawase, Y.; Oshio, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1613–1615.
4. Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445.
5. (a) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295–1296; (b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467; (c) Bolm, C.; Kesselgruber, M.; Grenz, A.; Hermanns, N.; Hildebrand, J. P. *New J. Chem.* **2001**, *25*, 13–15; (d) Bolm, C.; Hermanns, N.; Kesselgruber, M.; Hildebrand, J. P. *J. Organomet. Chem.* **2001**, *624*, 157–161; (e) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488–1490; For theoretical studies, see: (f) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem., Int. Ed.* **2003**, *42*, 3002–3005; (g) Rudolph, J.; Bolm, C.; Norrby, P.-O. *J. Am. Chem. Soc.*, in press.
6. (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940–7956; (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145–149.
7. Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543.
8. For catalytic enantioselective arylations of ketones, see: (a) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957; (b) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641–3644; (c) Anaya de Parrodi, C.;

Walsh, P. J. *Synlett* **2004**, 2417–2420; Review: (d) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284–287.
9. (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; (b) Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis*, in press.
10. Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867–872.
11. Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997–4000.
12. Bolm, C.; Zani, L.; Rudolph, J.; Schiffers, I. *Synthesis* **2004**, 2173–2180.
13. For the exploitation of this strategy in the synthesis of enantioenriched α-hydroxy acids, see: Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785–2791.
14. (a) Klausner, Y. S.; Bodanszky, M. *Synthesis* **1972**, 453–463; (b) Bodanszky, M. *Principles of Peptide Synthesis*; Springer: Berlin, 1984.
15. Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *84*, 3178–3196.
16. Compound **11e** has already been prepared. However, to the best of our knowledge, it has only been employed as an intermediate, not as ligand in asymmetric catalysis. (a) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814–1816; (b) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023–2026; For the preparation and catalytic application of related compounds, see: (c) Pridgen, L. N.; Miller, G. *J. Heterocycl. Chem.* **1983**, *20*, 1223–1230; (d) Allen, J. V.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 277–282.
17. Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882.
18. RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012–6028.