New Dihydroxy Bis(Oxazoline) Ligands for the Palladium-Catalyzed Asymmetric Allylic Alkylation: Experimental Investigations of the Origin of the Reversal of the Enantioselectivity

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Abstract: The origin of the reversal of the enantioselectivity in the palladium-catalyzed allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate anion using chiral dihydroxy bis(oxazoline) "BO" ligands derived from (*1S,2S*)-(+)-2-amino-1-phenyl-1,3-propanediol was investigated. To determine the structural effects of the dihydroxy BO ligand on this unique phenomenon, new homochiral dihydroxy BO ligands were prepared from L-threonine and L-serine and were assessed in the transformation. The results obtained with these novel BO ligands, compared with the one obtained by using the dihydroxy BO ligands derived from (*1S,2S*)-(+)-2-amino-1-phenyl-1,3-propanediol, reveal that the reversal in the enantioselectivity observed with the dihydroxy BO ligand depends on the structure of the ligand. The effect of different bases used to generate the dimethyl malonate anion was also examined. The results are discussed in terms of the interaction of one hydroxy group in the intermediate π-allyl palladium complex with the dimethyl malonate anion.

Keywords: allylic alkylation · asymmetric catalysis · enantioselectivity · N ligands · palladium

Introduction

We have recently been interested in the use of a new set of chiral bis(oxazoline)[1,2] "BO" **1** in the asymmetric transition-metal-catalyzed reactions. We have reported that a high level of enantioselectivity (up to 92% *ee*) was obtained in the palladium-catalyzed allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate anion. We have shown that the ligand structure has a dramatic impact on both the sense of the chiral induction and the level of enantioselectivity. Although ligands **1a** and **1b** possess identical chiral scaffolds, they produce opposite enantiomers of the alkylated product. The dibenzoyl BO **1a** gave the *R* product with a 90% *ee*, while the dihydroxy BO **1b** led unexpectedly to the *S* product with a 92% *ee* (Scheme 1).

Based on X-ray analysis of the palladium π-allyl complexes[2b] we assumed that an interaction of the nucleophile with one of the hydroxy groups located on the side chain of the oxazoline ring of ligand **1b** could reverse the enantioselection. However, this reversal of the enantioselectivity could also be explained by the presence of the o-protecting group.[3] To ascertain whether this reversal of enantioselectivity is due to steric hindrance or to the interaction between the OH group and the nucleophile, we decided to design new BOs with benzoyl or hydroxy groups on their side chains. Herein, we describe the synthesis of new BO ligands derived from L-threonine and L-serine (Scheme 2), with hydroxy or benzoyl groups on the side chain, and report their behavior in the Pd-catalyzed enantioselective allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (DMM). The role of the base was also studied to determine its impact on the observed shift of the enantioselectivity.

Results and Discussion

Ligands **2** and **3** (Scheme 2) were synthesized because we believed that they would impart good information on the role played by steric hindrance in influencing enantioselec-

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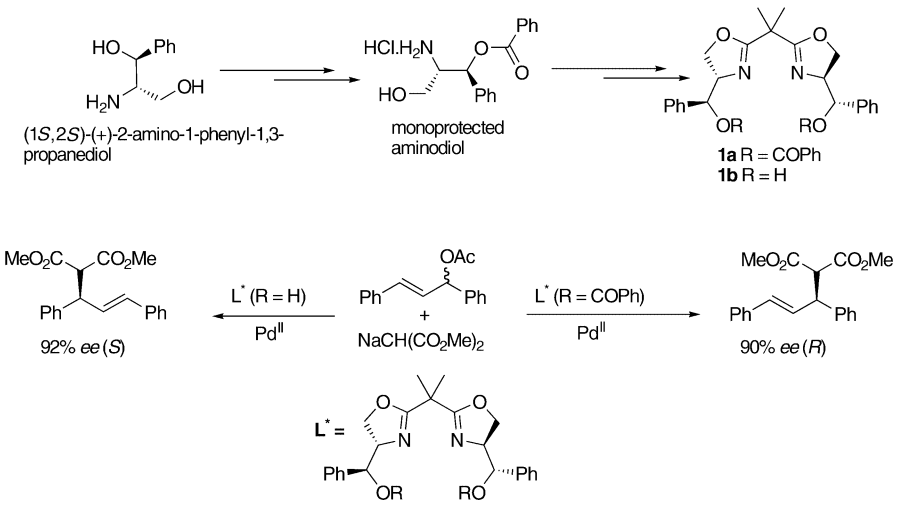
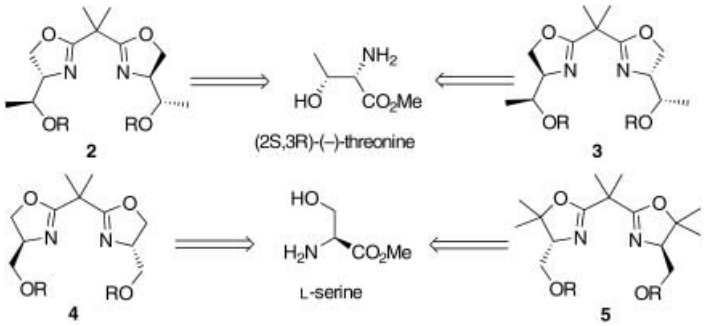


Scheme 1. Synthesis of BO ligand **1** and stereochemistry of the sodium dimethyl malonate (Nu^-) attack on the π-allyl palladium complex using BO **1a** (R = COPh) and BO **1b** (R = H).

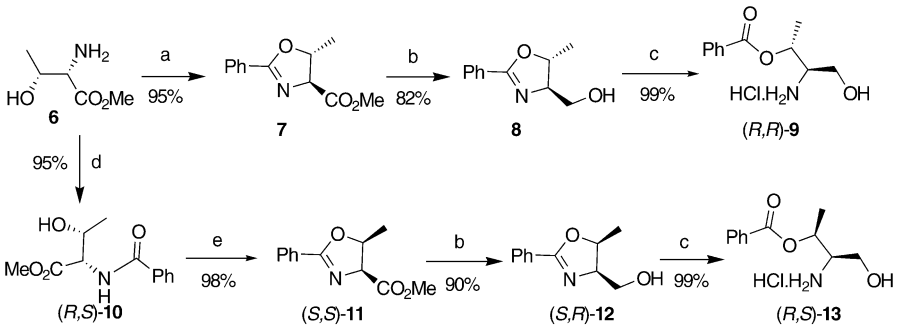


Scheme 2. BO ligands **2** and **3** derived from L-threonine and BO **4** and **5** derived from L-serine.

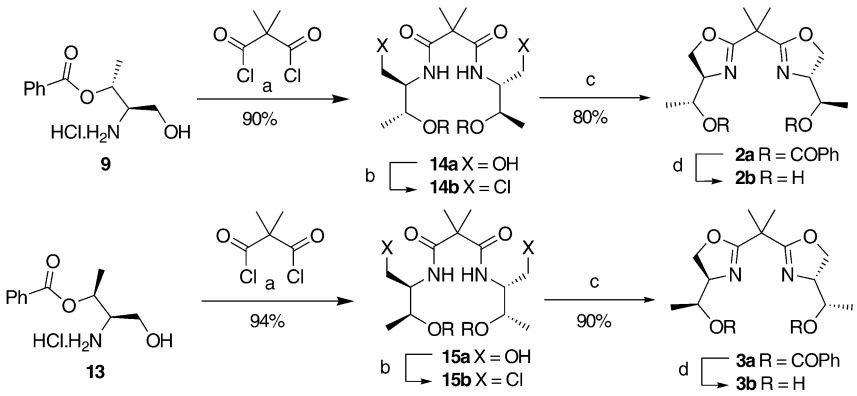
tivity in the palladium-catalyzed allylic alkylation. As can be seen from Scheme 2, ligands **2** and **3** are diastereomers of each other and differ from ligands **1** in that they posses methyl, rather than phenyl substituents at the stereocenter on the side chain. Thus, the results obtained by the use of BO ligands **2** and **3** in the palladium-catalyzed allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate compared to the BO **1** ones (Scheme 1) will be very informative on the role of the steric hindrance and the effect of the relative stereochemistry of the stereogenic center located on the side chain. On the other hand, ligands **4** and **5** contain no stereocenter on the side chain and were synthesized so that we could determine whether a stereocenter at this position was necessary for the control of the chiral induction sense.

Synthesis of BO ligands 2 and 3: We had previously reported the synthesis of (*S*,*S*)-BO ligand **1** through the monoprotected aminodiol intermediate from (*1S*,*2S*)-(+)-2-amino-1-phenyl-1,3-propanediol (Scheme 1)[2a] and used the same approach to synthesize (*R*,*R*)-BO ligands **2** and (*R*,*S*)-BO ligands **3** from L-threonine and (*R*)-BO ligands **4** and **5** from L-serine. For the synthesis of BO **2** and **3**, L-threonine methyl ester was transformed to monoprotected aminodiols (*2R*,*3R*)-**9** and (*2R*,*3S*)-**13** by using two different pathways (Scheme 3). Condensation of L-threonine with ethyl benzimidate hydrochloride led to the (*S*,*R*)-oxazoline **7** in excellent yield.[4]

Treatment of **7** with $LiAlH_4$ in diethyl ether,[5] followed by selective hydrolysis of the oxazoline ring with HCl in THF[6] gave the monoprotected aminodiol (*R*,*R*)-**9** in 81% yield in two steps and an overall yield of 77%. Compound (*2R*,*3S*)-**13** was prepared in four steps with 83% overall yield from L-threonine. Reaction of L-threonine methyl ester with the benzoyl chloride yielded the amide **10**, which underwent cyclization in the presence of thionyl chloride to form the oxazoline product **11** with inversion of configuration at carbon C3.[7] Treatment of **11** with $LiAlH_4$ in diethyl ether followed by a selective cleavage of the oxazoline ring under acidic conditions afforded (*2R*,*3S*)-**13** in a high yield. Compounds **9** and **13** were then independently used to synthesize **2** and **3**, respectively (Scheme 4). The coupling of the monoprotected aminodiols (*R*,*R*)-**9** and (*R*,*S*)-**13** with 2,2′-dimethylpropane-1,3-dioyl chloride[8] gave the dihydroxy diamides **14a** and **15a** in high yields (95 and 94%, respectively).[2a] These dihydroxy diamides were transformed to their corresponding dichloro diamides **14b** and **15b** by treatment with $SOCl_2$. Refluxing **14b** and **15b** in toluene in the presence of triethylamine produced **2a** in 85% yield and **3a** in 90% yield, respectively.[9] Saponification of the dibenzoyl derivatives **2a** and **3a** with sodium hydroxide in methanol gave the dihydroxy BOs **2b** in 88% and **3b** in 95% yield.



Scheme 3. Synthesis of the monoprotected aminodiols **9** and **13**: a) Ethyl benzimidate hydrochloride, Et_3N, CH_2Cl_2, room temperature, 48 h; b) $LiAlH_4$, Et_2O, reflux; c) THF, 2 M HCl, room temperature; d) benzoyl chloride, Et_3N, CH_2Cl_2; e) thionyl chloride, 0 °C, 16 h.

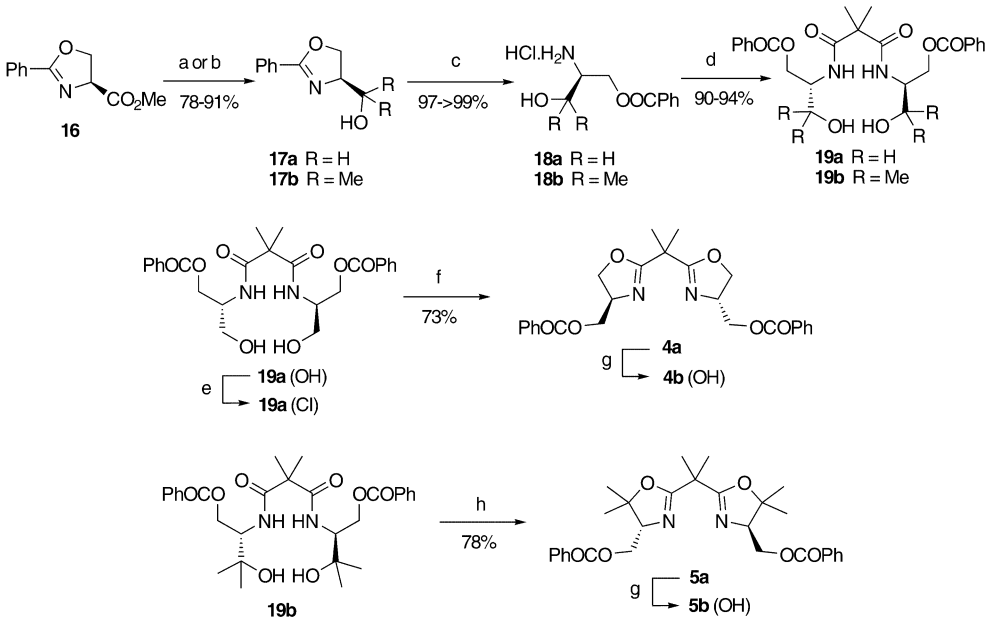


Scheme 4. Synthesis of BO (*R*,*R*)-**2** and (*R*,*S*)-**3** from the monoprotected aminodiols **9** and **13**: a) Et_3N, CH_2Cl_2; b) thionyl chloride, reflux, 6 h; c) toluene, Et_3N, reflux 6 or 16 h; d) 1% sodium hydroxide in methanol, room temperature.

BO ligands from L-serine:[10] The key intermediates for the synthesis of **4** and **5**, monoprotected aminodiols **18a** and **18b**, were obtained in four steps from L-serine methyl ester (Scheme 5). Condensation of L-serine methyl ester and ethyl benzimidate in dichloromethane in the presence of triethylamine at room temperature resulted in the formation of 2-phenyloxazoline **16**.[11] This oxazoline ester was then transformed to its corresponding hydroxyl oxazoline, either by treatment with diisobutylaluminum hydride (DIBAH)[6] giving **17a** in 91% yield, or by reaction with methyl magnesium iodide[12] leading to **17b** in 78% yield. The selective cleavage of the oxazoline ring by HCl in THF led to the monoprotected aminodiols **18a** and **18b** in quasi-quantitative yields. Condensation of **18a** and **18b** with 2,2′-dimethyl propane-1,3-dioyl chloride provided the diamide **19a** in 90% yield, and **19b** in 89% yield. **19a** and **19b** were then converted to **4** and **5** through separate synthetic routes. The dihydroxy diamide **19a** was then transformed to the bis(oxazoline) **4a** by the cyclization of its corresponding dichloride diamide **19a** (Cl) in toluene in the presence of triethylamine.[8] BO **4a** was then saponified with sodium hydroxide in methanol to give **4b** in good yield. The cyclization of the diamide **19b** under acidic conditions[10b] led to the bis(oxazoline) **5a**, which was in turn saponified to give the dihydroxy BO **5b**.

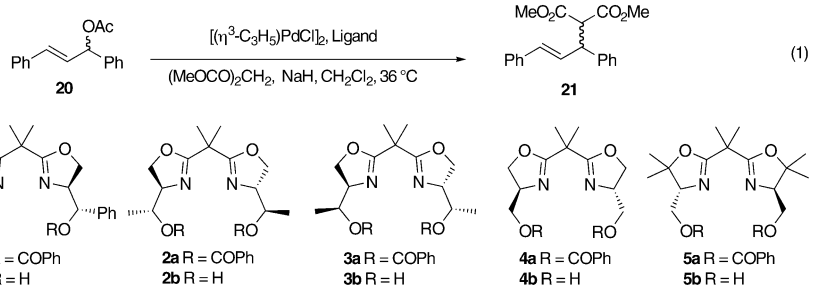
Asymmetric allylic alkylation: Allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **20** was performed in dichloromethane at 36 °C in the presence of a (π-allyl)-palladium–ligand complex generated in situ from 1 mol% of bis[(π-allyl)palladium chloride] and 4 mol% of the appropriate BO ligand. The nucleophile was generated from dimethyl malonate (DMM) in the presence of sodium hydride [Eq. (1)].[13,14] The data collected is summarized in Table 1.

Our attention was focused on comparing the sense of the chiral induction produced by different BO ligands possessing the same chiral scaffold to extract the structural futures that affect the regiochemistry of the nucleophilic attack on the palladium allyl intermediate. We had previously reported that with sodium hydride as the base, (*S*,*S*)-BO **1a** led to



Scheme 5. Synthesis of BO **4** and **5** from L-serine: a) DIBAH, **17a**; b) MeMgI, Et_2O, reflux, **17b**; c) 2 M HCl, room temperature, **18a** and **18b**; d) Et_3N, $ClCOC(Me)_2COCl$, CH_2Cl_2, 0 °C to room temperature, **19a** and **19b**; e) $SOCl_2$, reflux, 6 h; f) toluene, Et_3N, reflux; g) 1% NaOH in methanol, room temperature; h) methanesulfonic acid, CH_2Cl_2, reflux, see reference [10b].

Table 1. Palladium-catalyzed enantioselective allylic alkylation of *rac*-**20** using BO **1**–**5** and sodium hydride procedure.[a]



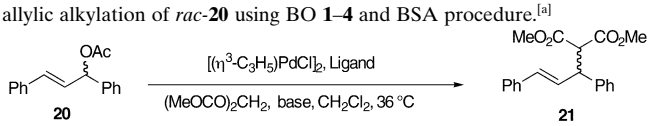
Run	L	*t* [h]	*ee*[b] [%]	Config.[c]	Yield[d] [%]
1	(*S*,*S*)-**1a**	24	90	*R*	98
2	(*S*,*S*)-**1b**	2	92	*S*	98
3	(*R*,*R*)-**2a**	24	68	*S*	90
4	(*R*,*R*)-**2b**	24	63	*R*	90
5	(*R*,*S*)-**3a**	16	97	*S*	95
6	(*R*,*S*)-**3b**	24	72	*S*	90
7	(*R*)-**4a**	15	80	*S*	100
8	(*R*)-**4b**	24	80	*S*	100
9	(*R*)-**5a**	144	85	*S*	80
10	(*R*)-**5b**	72	77	*S*	88

[a] *rac*-**20** (1 equiv), DMM (3 equiv), NaH (3 equiv), [{Pd(C_3H_5)Cl}$_2$] (1 % mol), L = Ligand (4 % mol), CH_2Cl_2, 36 °C. [b] The *ee* values were determined by HPLC using a chiral column (Pharmacir 7C, flow rate 0.7 mL min^{-1}, *n*-BuOH/*n*-hexane 1:9). [c] The absolute stereochemistry of the product was determined by comparison of the optical rotation with the literature values.[15] [d] Yields refer to purified product after column chromatography.

(*R*)-**21**, whereas (*S*,*S*)-BO **1b** gave (*S*)-**21**, with high degrees of enantioselectivity in both cases (Table 1, entries 1 and 2).[16] The level of enantioselectivity was lower with (*R*,*R*)-BO **2a** and **2b**, but we observed parallel behavior concerning the chiral induction sense, since BO ligand **2a** gave (*S*)-**21**, whereas BO **2b** led to (*R*)-**21** (Table 1, entries 3 and 4). The difference in the level of induction between (*S*,*S*)-BO **1** and (*R*,*R*)-BO **2** is presumably to be due to the difference in the steric environment of BO **1** and BO **2** (Ph versus Me). In stark contrast, dihydroxy (*R*,*S*)-BO **3b**, a diastereoisomer of dihydroxy BO **2b**, did not reverse the chiral induction of **21**, and produce the same enantiomer of **21** as ligand **3a**, albeit with lower *ee* (Table 1, entries 4 and 5). The results obtained with (*R*,*S*)-BO **3** point out the huge impact of the relative stereochemistry of the stereogenic center located on the side chain on both the sense of the chiral induction and the regioselectivity of the nucleophilic attack on the palladium π-allyl intermediate. The behavior of BO **2** and BO **3** in this transformation clearly demonstrates that the reversal of the enantioselectivity occurs when the two stereogenic centers (the one on the oxazoline ring and the one on the side chain) of the dihydroxy BO ligand have the same absolute configuration. This phenomena is presumably due to a more pronounced steric interaction between the oxazoline substituents and one of the phenyl substituents on the allyl moiety. No reversal of the enantioselectivity occurred upon employing BO ligands **4a**/**4b**, with the *S* product being obtained with 80 % ee in both cases (Table 1, entries 7 and 8). The lower enantioselectivities obtained with **4** with respect to **3** could be explained by the lack of a stereocenter with a defined stereochemistry on the side chain of the oxazoline ring in BO **4**. The same result was obtained with the BO ligands **5a**/**5b** (Table 1, entries 9 and 10). The levels of the enansiolectivity obtained by BO **4** and BO **5** are similar to each other showing that the increase of the steric hindrance at the C-5 position of the oxazoline ring has no significant impact on the asymmetric induction.[17] More importantly, these results obtained with BO **4** and **5** prove clearly that a specific structure of the dihydroxy BO ligand is required to induce a reversal of the sense of the chiral induction. Hence, the presence of a stereogenic center on the side chain indeed has a crucial impact on the selectivity. We further investigated the effect that the base [Eq. (2)] had on the enantioselectivity and the reactivity. First, a soft anionic nucleophile was produced by using DMM in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate (KOAc).[18,19] To our surprise, by switching from sodium dimethyl malonate (Table 1, entry 2) to BSA/KOAc (Table 2, entry 2) with ligand **1b**, the chirality of the reaction product is inverted ((*R*) instead of (*S*)). The same trend was also observed with BO **2b**, but with a lower level of enantiomeric excess under these conditions (Table 1, entry 4, and Table 2, entry 4). Additionally, very high levels of enantioselectivity (up to >99 %) were obtained with BO **3a** and **3b** (Table 2, entries 5 and 6), although the sense of asymmetric induction did not reverse. A similar trend was also observed with BO **4** (Table 2, entries 7 and 8).

In our previous study,[2b] we demonstrated that the use of BO **1b** under NaH conditions proceed via a change in the stereochemical attack of the nucleophile on the palladium π-allyl complex in direct contrast with BO **1a** (Scheme 1). An interaction between one of the hydroxy groups located on the side chain of the oxazoline ring was assumed to govern the regioselectivity of the attack of the nucleophile on the palladium π-allyl intermediate.[20] Using the BSA procedure suggests that such an interaction was suppressed under these reactions conditions. We propose that BSA works not only as a base, but also as a silylating agent for the dimethyl malonate salt to produce a ketene silyl acetal [Eq. (3)].[21] To confirm this hypothesis we decided to use a pre-formed ketene silyl acetal as a masked nucleophile in this reaction. Silyl ketene acetals have been successfully used in the allylic alkylations as alternative nucleophiles to the "harder" anionic species.[22] Thus, the use of ketene silyl acetal of dimethyl malonate gave, under our conditions, the *R* product with both BO ligands **1a** and **1b** in 80 and 78 %

Table 2. Results of enantioselective allylic alkylation of *rac*-**20** using BO **1**–**4** and BSA procedure.[a]

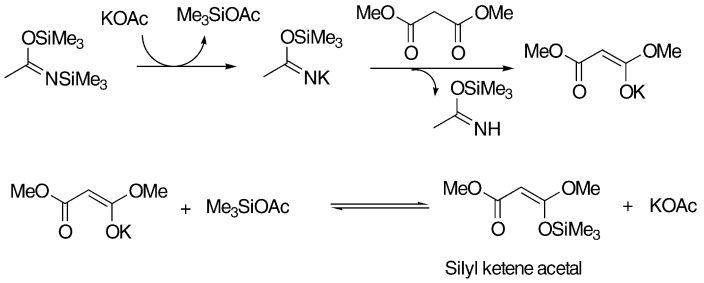


Run	Base	L	t [h]	ee[b] [%]	Config.[c]	Yield[d] [%]
1	KOAc	(*S*,*S*)-**1a**	72	90	*R*	75
2	KOAc	(*S*,*S*)-**1b**	72	91	*R*	70
3	KOAc	(*R*,*R*)-**2a**	72	55	*S*	70
4	KOAc	(*R*,*R*)-**2b**	72	50	*S*	81
5	KOAc	(*R*,*S*)-**3a**	44	98	*S*	98
6	KOAc	(*R*,*S*)-**3b**	44	>99	*S*	95
7	KOAc	(*R*)-**4a**	124	78	*S*	75
8	KOAc	(*R*)-**4b**	124	81	*S*	72
9	NBu_4F	(*S*,*S*)-**1a**	36	65	*R*	80
10	NBu_4F	(*S*,*S*)-**1b**	36	52	*S*	75

[a] *rac*-**20** (1 equiv), DMM (2 equiv), BSA (2 equiv), KOAc (3% mol), NBu_4F (2 equiv), [{Pd(C_3H_5)Cl}$_2$] (1% mol), L = Ligand (4% mol), CH_2Cl_2, 36 °C. [b] The *ee* values were determined by HPLC using a chiral column (Pharmacir 7C, flow rate 0.7 mL min^{-1}, *n*BuOH/*n*-hexane 1:9). [c] The absolute stereochemistry of the product was determined by comparison of the optical rotation with the literature values.[15] [d] Yields refer to purified product after column chromatography.

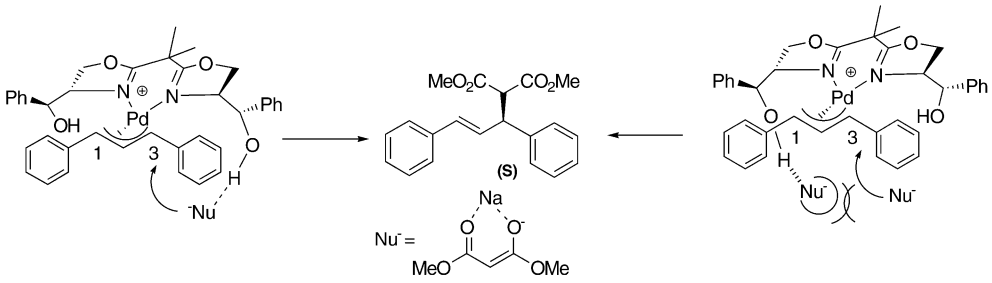
ee confirming that BSA is probably acting as a silylating reagent of the nucleophile.

The stereochemistry of the nucleophilic attack observed when BO **1b** was used with ketene silyl acetal or employing the BSA/KOAc procedure is may be due to the reaction mode of the silylated nucleophile with the palladium π-allyl intermediate. It was proposed that this reaction probably proceeds by the nucleophilic attack of ketene silyl acetal on the π-allyl complex through an interaction of π-orbital between the π-allyl and the carbon-carbon double bond of ketene silyl acetal.[22c] This reaction pathway prevents any interaction between the nucleophile and the side chain of the dihydroxy BO ligand in the π-allyl intermediate. Interestingly, the opposite trend was observed when BSA was employed with an equimolar amount of tetrabulylammoniun fluoride (TBAF), in which the fluorine trapped the trimethyl silyl group (Table 2, entries 7 and 8).[23] These results clearly confirm the impact that the interaction of the nucleophile with one of the hydroxy groups plays on the regioselection of the nucleophilic attack on the π-allyl intermediate. Thus, with the sodium dimethyl malonate salt, the selectivity observed with the dihydroxy BO **1b** and BO **2b** ligands originates from a hydrogen bond interaction between the hydroxy group and the nucleophile. As shown in Scheme 6, two different pathways are suggested to rationalize the nucleophilic attack of the sodium malonate on the π-allylpalladium intermediate including BO ligand **1b**. The attack of the nucleophile on C3 yielding the *S* product is likely favored by the hydrogen bond involving either the hydroxy group close to C3, which could drags the nucleophile to attack this carbon on the side opposite the palladium, or by the H bond of the nucleophile with the hydroxy group close to C1, which prevents the attack on C1 by increasing the steric hindrance at this position which in turn will favor the attack of the nucleophile on C3 from the opposite side to the palladium. However, at this stage, we have no experimental evidence to favor any of these two pathways.



(3)

In summary, this study provides a clear explanation of the shift of the enantioselectivity observed in the Pd-catalyzed allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with the sodium dimethyl malonate anion in the presence of BO ligands **1b** and **2b**. The comparison of the behavior of the dihydroxy BO ligands obtained from L-serine and L-threonine and BO **1b** revealed the importance of the structure of



Scheme 6. Change of the stereochemistry of the nucleophilic attack caused by the OH–Nu hydrogen bonding.

the ligand in the selectivity of this reaction. We have determined that the presence of a hydroxyl group on the side chain of the oxazoline ring is not in itself sufficient to change the stereochemistry of the nucleophilic attack on the palladium π-allyl intermediate. A defined structure of the dihydroxy BO ligand is needed to orient the nucleophilic attack. Both stereogenic centers (the one on the oxazoline ring and the one on the side chain bearing the hydroxyl group) must have the same absolute configuration for true influence on the sense of the chiral induction. The investigation of the effect of the base used to generate the nucleophile was very revealing. The reversal of the enantioselectivity observed using **1b** and **2b** employing NaH as the base was suppressed when BSA/KOAc was used as the base system. We have also confirmed that BSA acts as silylating agent for the dimethyl malonate anion under the reaction conditions. These results demonstrate the impact exerted by the H bond interaction between the hydroxyl group and the nucleophile on the chiral sense of induction, which confirms our previously postulated hypothesis concerning the origin of the shift of the enantioselectivity observed with BO **1b** ligand. This study prompted us to develop a series of BO ligands, which are able to impart very high levels of asymmetric induction. We are currently exploring the possibility of employing these ligands in other asymmetric catalytic processes.

Experimental Section

All reactions were carried out under an inert argon atmosphere. Melting points were taken on a Stuart scientific apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker AM-250 (250 MHz) and AC-200 (200 MHz) spectrometers for ^{1}H and ^{13}C, and chemical shifts are reported in ppm downfield from Me_4Si. Optical rotations were measured on Perkin-Elmer 241 MC. DCI mass spectra were recorded with a quadripolar Nermag R 10-10H instrument. Elemental analyses were performed by LCC (Laboratoire de Chimie de Coordination) Microanalytical Service. Column chromatography was performed using Merck alumina (70–230 mesh ASTM), deactivated with 8% of water or Merck silica gel (230–400 mesh). High pressure liquid chromatography (HPLC) analyses were performed with an analytical chiral chromatography column (Pharmacir 7C, 4.6 mmx 250 mm) eluted with *n*BuOH/*n*-hexane (10 : 90); flow rate 0.7 mL min^{-1} using a Waters 600 pump and a Waters 486 detector operating at 254 nm.

(4*S*,5*R*)-4-carbomethoxy-5-methyl-2-phenyloxazoline (7): L-Threonine methyl ester (33.46 g, 197.0 mmol) and ethyl benzimidate hydrochloride (36.52 g, 197 mmol) were mixed in CH_2Cl_2 (200 mL). Triethylamine (27.6 mL, 197.0 mmol) was added and the mixture was stirred for 24 h. The insoluble salts were filtered off and the filtrate was washed with an $NaHCO_3$ saturated aqueous solution, dried over $MgSO_4$ and filtered. Evaporation of the solvent afforded **7** (39.98 g, 182.0 mmol) as a clear oil. Yield = 92%. $[\alpha]_D^{20} = +96.7$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.50$ (d, $J = 6.3$ Hz, 3H; C*H*$_3$), 3.80 (s, 3H; O–C*H*$_3$), 4.50 (d, $J = 7.4$ Hz, 1H; C*H*–COOC*H*$_3$), 5.00 (dq, $J = 7.4$ Hz and 6.3 Hz, 1H; C*H*–CH$_3$), 7.45 (m, 3H; Ar–*H*), 8.00 ppm (m, 2H; Ar–*H*); ^{13}C NMR ($CDCl_3$): $\delta = 20.7$, 52.3, 74.8, 78.5, 126.6, 126.9, 128.0, 129.2, 130.9, 131.5, 165.2, 171.3 ppm; elemental analysis calcd (%) for $C_{12}H_{13}NO_3$ (219.25): C 65.74, H 5.98, N 6.39; found: C 65.85, H 5.80, N 6.25.

(4*R*,5*R*)-4-hydroxymethyl-5-methyl-2-phenyloxazoline (8):A solution of oxazoline ester **7** (19.7 g, 90 mmol) in diethyl ether (200 mL) was added dropwise to a cold suspension of $LiAlH_4$ (3.54 g, 90.0 mmol) in diethyl ether (250 mL). The mixture was stirred for 4 h at 0°C. The reaction was quenched with water and the insoluble salts were filtered off. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The product was purified by chromatography on silica gel (ethyl acetate) to give **8** (14.13 g, 74 mmol) as a white solid. Yield = 85%. M.p. 97–98°C; $[\alpha]_D^{20} = +80.7$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (d, $J = 6.3$ Hz, 3H; C*H*$_3$), 3.75 (dd, $J = 4.0$ Hz and 11.4 Hz, 1H; N–C*H*), 4.05 (m, 2H; C*H*$_2$–OH), 4.90 (m, 3H; O–C*H*$_3$), 7.50 (m, 3H; Ar–*H*), 8.00 ppm (m, 2H; Ar–*H*); ^{13}C NMR ($CDCl_3$): $\delta = 20.5$, 63.2, 74.8, 78.0, 127.1, 128.0, 128.2, 131.0, 131.2, 164.7 ppm; elemental analysis calcd (%) for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32; found: C 68.80, H 6.85, N 7.30.

(2*R*,3*R*)-2-amino-3-benzoyloxybutan-1-ol (9): To a solution of the hydroxy oxazoline **8** (11.7 g, 61.4 mmol) in THF (400 mL) a 2M aqueous solution of HCl (45.0 mL) was added. The mixture was stirred for 24 h at room temperature. Evaporation of the solvent and drying under reduced pressure left the monoprotected aminodiol **9** (14.8 g, 60.0 mmol) as a white solid, which was used without further purification in the next step. Yield = 99%. M.p. 144–145°C; $[\alpha]_D^{20} = -35.7$ ($c = 1.7$ in CH_3OH); ^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (d, $J = 6.3$ Hz, 3H; C*H*$_3$), 3.60 (m, 1H; C*H*–NH$_2$), 3.90 (m, 2H; C*H*$_2$–OH), 5.50 (dq, $J = 6.3$ Hz and 7.4 Hz, 1H; C*H*–CH$_3$), 7.55 (m, 2H; Ar–*H*), 7.75 (m, 1H; Ar–*H*), 8.20 ppm (m, 2H; Ar–*H*); ^{13}C NMR ($CDCl_3$): $\delta = 16.6$, 56.4, 58.7, 68.6, 128.0, 128.9, 129.8, 133.0, 165.5 ppm; MS (CI, NH_3): *m*/*z* (%): 210 (100) [*M* + H].

Methyl (2*R*,3*S*)-*N*-2-benzoylamide-3-hydroxybutanoate (10): A solution of benzoyl chloride (11.2 mL, 96.6 mmol) in CH_2Cl_2 (100 mL) was added dropwise to a mixture of L-threonine methyl ester (18.0 g, 106.0 mmol) and triethylamine (27.1 mL, 212.0 mmol) in CH_2Cl_2 (200 mL) at 0°C. The reaction was stirred for 12 h at 0°C and quenched with water. After warming to room temperature, the organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuum* to give the amide **10** (23.6 g, 99.5 mmol) as a white solid. Yield = 95%. M.p. 95–96°C; $[\alpha]_D^{20} = +22.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) $\delta = 1.30$ (d, $J = 6.4$ Hz, 3H; CH–C*H*$_3$), 2.74 (s, 1H; O*H*),=3.75 (s, 3H; COOC*H*$_3$), 4.45 (dq, $J = 6.4$ Hz and 4.0 Hz, 1H; C*H*–OH), 4.80 (dd, $J = 3.5$ Hz and 6.3 Hz, 1H; C*H*–NH), 7.05 (d, $J = 8.7$Hz, 1H; N*H*), 7.45 (m, 3H; Ar–*H*), 7.80 ppm (m, 2H; Ar–*H*); ^{13}C NMR ($CDCl_3$): $\delta = 19.7$, 52.1, 57.9, 67.4, 126.9, 127.9, 129.5, 131.6, 132.7, 133.1, 168.2, 171.0 ppm; elemental analysis calcd (%) for $C_{12}H_{15}NO_4$ (237.25): C 60.75, H 6.37, N 5.90; found: C 60.80, H 6.05, N 5.70.

(4*S*,5*S*)-4-carboxymethoxy-5-methyl-2-phenyloxazoline (11): A large excess of thionyl chloride (56.0 mL) was added to a solution of amide **10** (19.8 g, 83.0 mmol) in CH_2Cl_2 (200 mL) at 0°C. The resulting mixture was stirred at the same temperature overnight. Excess thionyl chloride was removed by distillation under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with a 10% Na_2CO_3 aqueous solution (100 mL) and water (3×100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (ethyl acetate/pentane; 3:2) to afford the oxazoline **11** (17.8 g, 81.0 mmol) as a clear oil. Yield = 98%. $[\alpha]_D^{20} = +69.4$ ($c = 8.5$ in EtOH). ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (d, $J = 6$ Hz, 3H; CH–C*H*$_3$), 3.75 (s, 3H; COOC*H*$_3$), 5.00 (m, 2H; C*H*–C*H*), 7.50 (m, 3H; Ar–*H*), 7.95 (m, 2H; Ar–*H*); elemental analysis calcd (%) for $C_{12}H_{13}NO_3$ (219.24): C 65.74, H 5.98, N 6.39; found: C 65.50, H 6.25, N 6.43.

(4*R*,5*S*)-4-hydroxymethyl-5-methyl-2-phenyloxazoline (12): Following the procedure used for the synthesis of alcohol **8**, ester **11** (14.0 g, 64.1 mmol) in of diethyl ether (200 mL) was reacted with $LiAlH_4$ (2.5 g, 64.1 mmol) in diethyl ether (150 mL) to give, after purification by chromatography on silica gel (ethyl acetate), **12** (11.0 g, 57.7 mmol) as a white solid. Yield = 90%. M.p. 98–99°C; $[\alpha]_D^{20} = +105.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.45$ (d, $J = 6.6$ Hz, 3H; CH–C*H*$_3$), 3.65 (s, 1H; O*H*), 3.75 (dd, $J = 5.6$ Hz and 6.3 Hz, 2H; C*H*$_2$–OH), 4.30 (ddd, $J = 5.1$ Hz, 4.7 Hz and 3.9 Hz, 1H; C*H*-N), 4.90 (dq, $J = 6.6$ Hz and 3.9Hz, 1H; C*H*–O), 7.40 (m, 3H; Ar–*H*), 7.80 ppm (m, 2H; Ar–*H*); ^{13}C NMR ($CDCl_3$): $\delta =$ 14.7, 61.1, 69.1, 78.2, 127.3, 128.0, 131.2, 164.4 ppm; MS (CI, NH_3): *m*/*z* (%): 192 [100, *M* + H]; elemental analysis calcd (%) for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32; found: C 68.85, H 6.60, N 7.10.

(2*R*,3*S*)-2-amino-3-benzoyloxybutan-1-ol (13): Following the procedure used for the preparation of **9**, the oxazoline **12** (11.7 g, 61.4 mmol) was allowed to react with aqueous HCl 2M (45.0 mL, 90.0 mmol) in THF (400 mL) to give **13** (14.9g, 60.85 mmol) as a colorless oil. Yield = 99%. M.p.

125–127 °C; $[\alpha]_D^{20} = -45.5$ ($c = 1.25$ in CH_3OH); ^{1}H NMR ($CDCl_3$): $\delta =$ 1.55 (d, $J = 6.4$ Hz, 3H; CH–CH_3), 3.70 (m, 1H; CH–NH_2), 3.90 (dd, $J =$ 4.2 Hz and 7.5 Hz, 1H; CH_2–OH), 4.10 (dd, $J = 4.2$ Hz and 7.2 Hz, 1H; CH_2–OH), 5.50 (dq, $J = 6.4$ Hz and 7.5 Hz, 1H; CH–O), 7.70 (m, 3H; Ar–H), 8.15 ppm (m, 2H; Ar–H); ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 56.6, 58.3, 69.3, 128.7, 129.9, 133.7, 166.1 ppm; elemental analysis calcd (%) for $C_{11}H_{16}NO_3Cl$ (245.70): C 53.77, H 6.56, N 5.70; found: C 53.50, H 6.80, N 5.45.

(2*R*,3*R*)-*N*,*N*′-Bis-[(3-phenylcarboxy-3-methyl-1-hydroxypropyl)]-2,2-1,3-propanamide (14a): Triethylamine (16.2 mL, 115.6 mmol) was added dropwise to a solution of dimethyl malonic chloride (4.85 g, 29.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was then added to a suspension of **9** (9.5 g, 30.8 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred at room temperature for 3 h. The solution was then concentrated under reduced pressure. The crude product was triturated in acetone (200 mL) and the insoluble salts were filtered off and the filtrate was concentrated. The residue was purified by chromatography on silica gel (ethyl acetate) to afford the bis-amide **14a** (14.18 g, 27.6 mmol) as a colorless oil. Yield = 95 %. $[\alpha]_D^{20} = +40.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.0$ (d, $J = 6.2$ Hz, 6H; CH–CH_3), 1.35 (s, 6H; C–CH_3), 3.60 (m, 4H; CH_2–OH), 4.20 (m, 2H; N–CH), 5.40 (m, 2H; CH–OCOPh), 6.90 (d, $J = 9.1$ Hz, 1H; NH), 7.40 (m, 6H; Ar–H), 8.00 ppm (m, 4H; Ar–H); ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 23.3, 49.8, 55.4, 61.9, 69.8, 128.3, 129.5, 129.6, 133.1, 166.0, 174.0 ppm; elemental analysis calcd (%) for $C_{27}H_{34}N_2O_8$ (514.58): C 63.02, H 6.66, N 5.44; found: C 63.60, H 6.62, N 5.40.

(2*R*,3*S*)-*N*,*N*′-Bis-[(3-phenylcarboxy-3-methyl-1-hydroxypropyl)]-2,2-1,3-propanamide (15a): Following the procedure used for the synthesis of the bisamide **14a**, a solution of triethylamine (16.2 mL, 115.6 mmol) and dimethyl malonic chloride (4.8 g, 29.0 mmol) in CH_2Cl_2 was reacted with a suspension of amino ester **13** (9.5 g, 30.8 mmol) in CH_2Cl_2 to give, after work up and purification by chromatography on silica gel (ethyl acetate), the bisamide **15a** (14.0 g, 27.26 mmol) as a white solid. Yield = 94 %. M.p. 85–86 °C; $[\alpha]_D^{20} = +3.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.40$ (d, $J = 7.5$ Hz, 6H; CH–CH_3), 1.55 (s, 6H; C–CH_3), 2.95 (s, 2H; OH), 3.70 (m, 4H; CH_2–OH), 4.25 (m, 2H; CH–NH), 5.20 (m, 2H; CH–OCOPh), 7.10 (d, $J = 7.5$Hz, 2H; NH), 7.40–7.65 (m, 6H; Ar–H), 8.05 ppm (m, 4H; Ar–H); ^{13}C NMR ($CDCl_3$): $\delta = 17.1$, 23.6, 50.1, 54.8, 60.9, 70.3, 128.4, 129.6, 133.2, 166.3, 174.1 ppm; elemental analysis calcd (%) for $C_{27}H_{34}N_2O_8$ (514.58): C 63.02, H 6.66, N 5.44; found: C 63.50, H 6.40, N 5.40.

(2*R*,3*R*)-*N*,*N*′-Bis-[(3-phenylcarboxy-3-methyl-1-chloropropyl)]-2,2-1,3-propanamide (14b): To a suspension of bisamide **14a** (9.65 g, 19.2 mmol) in 1,2-dichloroethane (180 mL), freshly distilled thionyl chloride (13.9 mL, 192 mmol) was added. The resulting mixture was kept at reflux for 3 h. The solvent and the excess of thionyl chloride were removed by distillation under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), washed with 2 M K_2CO_3 (20 mL), with water (20 mL), with brine (20 mL), and dried over sodium sulfate. After filtration, the organic layer was concentrated under reduced pressure to afford the dichloride bisamide **14b** (10.3 g, 18.6 mmol) as a white solid. Yield = 97 %. M.p. 115–116 °C; $[\alpha]_D^{20} = +24.2$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (d, $J = 6.4$ Hz, 6H; CH–CH_3), 1.40 (s, 6H; C–CH_3), 3.60 (m, 4H; CH_2–Cl), 4.40 (m, 2H; CH–NH), 5.50 (dq, $J = 6.4$ Hz and 4.8 Hz, 2H; CH–OCOPh), 7.20 (d, $J = 8.7$ Hz, 2H; NH), 7.40 (m, 4H; Ar-H), 7.60 (m, 2H; Ar–H) , 8.00 ppm (m, 4H; Ar–H); ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 23.8, 43.9, 49.4, 54.0, 69.6, 128.4, 129.4, 129.5, 133.3, 165.7, 174.0 ppm; elemental analysis calcd (%) for $C_{27}H_{32}N_2O_6Cl_2$ (551.47): C 58.81, H 5.85, N 5.08; found: C 58.40, H 5.52, N 5.05.

(2*R*,3*S*)-*N*,*N*′-Bis-[(3-phenylcarboxy-3-methyl-1-chloropropyl)]-2,2-1,3-propanamide (15b): Following the procedure used for the synthesis of bisamide **14b**, reaction of bisamide **15a** (9.65 g, 19.2 mmol) and thionyl chloride (13.9 mL, 192 mmol) afforded the bis-amide **15b** (9.8 g, 18.2 mmol) as a white solid. Yield = 95 %. This compound was used in the next step without any further purification. ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (d, $J = 6.5$ Hz, 6H; CH–CH_3), 1.50 (s, 6H; C–CH_3), 3.75 (m, 4H; CH_2–Cl), 4.50 (ddd, $J = 4.3$ Hz, 4.5 Hz and 7.0 Hz, 2H; CH–NH), 5.25 (dq, $J = 6.5$ Hz and 7 Hz, 2H; CH–OCOPh), 7.10 (d, $J = 9$ Hz, 2H; NH), 7.25–7.60 (m, 6H; Ar–H), 8.00 ppm (m, 4H; Ar-H); ^{13}C NMR ($CDCl_3$): $\delta = 17.0$, 23.8, 44.0, 49.6, 53.1, 70.0, 128.4, 129.5, 133.2, 165.5, 173.2 ppm.

(*R*,*R*)-2,2-Bis-[2(-1-phenylcarboxy-1-ethyl)-1,3-oxazolinyl)]propane (2a): A solution of bisamide **14b** (7.76 g, 14.40 mmol) and dry triethylamine (10.6 mL, 140.0 mmol) in dry toluene (120 mL) was heated to reflux for 4 h. The solution mixture was allowed to cool to room temperature and was diluted with ethyl acetate (100 mL). The resulting mixture was washed with saturated $NaHCO_3$ (2 × 50 mL) and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography on deactivated alumina (ethyl acetate/pentane; 3:7) afforded the bis(oxazoline) **2a** (5.80 g, 12.1 mmol) as a colorless viscous oil. Yield = 85 %. $[\alpha]_D^{20} = -64.1$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta =$ 1.40 (d, $J = 6.0$ Hz, 6H; CH–CH_3), 1.60 (s, 6H; C–CH_3), 4.30 (m, 4H; O–CH_2), 4.45 (m, 2H; CH–N), 5.30 (m, 2H; CH–OCOPh), 7.50 (m, 6H; Ar–H), 8.05 ppm (m, 4H; Ar–H); ^{13}C NMR ($CDCl_3$): $\delta = 15.2$, 24.4, 38.8, 68.7, 68.9, 71.3, 165.8, 170.5 ppm; elemental analysis calcd (%) for $C_{27}H_{30}N_2O_6$ (478.55): C 67.77, H 6.32, N 5.85; found: C 67.60, H 6.20, N 6.05.

(2*R*,3*R*)-2,2-Bis-[2(1-hydroxy-1-ethyl)-1,3-oxazolinyl)]propane (2b): A solution of NaOH (200 mg, 3.09 mmol) in methanol (1 mL) and THF (7 mL) was added to a solution of bis(oxazoline) **2a** (500 mg, 1.05 mmol) in THF (5 mL). After the mixture had been stirred for 2 h at room temperature, the solvents were removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (2 × 5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in ether (10 mL) and pentane was added slowly to induce precipitation of the desired product. The white precipitate was recovered by filtration to yield bis(oxazoline) **2b** (248 mg, 0.92 mmol). Yield = 88 %. M.p. 115–116 °C; $[\alpha]_D^{20} = -18.3$ ($c =$ 1.5 in CH_3OH); ^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (d, $J = 6$ Hz, 6H; CH–CH_3), 1.50 (s, 6H; C–CH_3), 3.60 (m, 2H; CH–N), 4.10 (m, 2H; CH–O), 4.30 ppm (m, 4H; CH_2–O); ^{13}C NMR ($CDCl_3$): $\delta = 19.1$, 23.3, 39.1, 69.5, 70.1, 70.6, 171.1 ppm; elemental analysis calcd (%) for $C_{13}H_{22}N_2O_4$ (270.33): C 57.76, H 8.20, N 10.36; found: C 57.50, H 8.30, N 10.70.

(2*R*,3*S*)-2,2-Bis-[2(-1-phenylcarboxy-1-ethyl)-1,3-oxazolinyl)]propane (3a): Following the procedure used for the synthesis of **2a**, reaction bisamide **15b** (7.76 g, 14.4 mmol) with dry triethylamine (10.6 mL, 140.0 mmol) in toluene at reflux gave after purification by chromatography on alumina (ethyl acetate/pentane; 3:7) the bis(oxazoline) **3a** (6.14 g, 12.8 mmol) as a white powder. Yield = 90 %. M.p. 144–145 °C; $[\alpha]_D^{20} = -43.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 12H; C-CH_3; CH–CH_3), 4.20 (m, 6H; CH_2–O; CH–N), 5.20 (m, 2H; CH–OCOPh), 7.25–7.60 (m, 6H; Ar–H), 8.00 ppm (m, 4H; Ar–H); ^{13}C NMR ($CDCl_3$): $\delta = 17.2$, 24.2, 38.5, 69.0, 69.9, 72.0, 128.2, 129.5, 130.2, 132.9, 165.5, 170.5 ppm; elemental analysis calcd (%) for $C_{27}H_{30}N_2O_6$ (478.55): C 67.77, H 6.32, N 5.85; found: C 68.00, H 6.30, N 5.80.

(2*R*,3*S*)-2,2-Bis-[2(1-hydroxy-1-ethyl)-1,3-oxazolinyl)]propane (3b): The bis(oxazoline) **3a** (500 mg, 1.05 mmol) was added in one portion to a solution of NaOH (10 mg, 0.16 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 2 h and the methanol was removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (2 × 5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in ether (10 mL) and pentane was added slowly to induce precipitation of the desired product. The white precipitate was recovered by filtration to yield bis(oxazoline) **3b** (270 mg, 0.99 mmol) as white solid. Yield = 95 %. M.p. 141–143 °C; $[\alpha]_D^{20} = -75.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.05$ (d, $J = 6$ Hz, 6H; CH–CH_3), 1.60 (s, 6H; CH_3–C), 4.10 (m, 4H; CH_2–O), 4.35 (m, 2H; CH–N), 4.60 ppm (m, 2H; CH–OCOPh); ^{13}C NMR ($CDCl_3$): $\delta = 18.6$, 23.4, 39.2, 67.8, 68.2, 71.3, 171.4 ppm; elemental analysis calcd (%) for $C_{13}H_{22}N_2O_4$ (270.33): C 57.76, H 8.20, N 10.36; found: C 57.29, H 7.90, N 10.10.

(S)-4-carbomethoxy-2-phenyloxazoline (16): Triethylamine (10.9 mL, 62.8 mmol) was added slowly (15 minutes) to a solution of ethyl benzimidate hydrochloride (11.6 g, 62.8 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred at room temperature for 30 min and L-serine methyl ester hydrochloride (13.5 g, 79.6 mmol) was added by portion. The resulting mixture was stirred for 48 h at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in acetone (250 mL), the insoluble salts were filtered off, and the filtrate was concentrated. Recrystallization of the crude material from diethyl ether

gave the oxazoline **16** (11.0 g, 53.6 mmol). Yield = 86 %. ^{1}H NMR ($CDCl_3$): δ = 4.60 (dd, J = 10.7 Hz and 8.7 Hz, 1H; OC*H*), 4,70 (dd, J = 8.7 Hz and 8.0 Hz, 1H; OC*H*), 4.93 (dd, J = 10.5 Hz and 8.0 Hz, 1H; OC*H*), 7.56–7.38 (m, 3H; Ar–*H*), 8.00 ppm (d, 2H; J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 53.0, 68.3, 69.8, 127.3, 129.3, 129.6, 131.5, 167.0, 171.5 ppm.

(*R*)-4-hydroxymethyl-2-phenyloxazoline (17a): A solution of diisobutylaluminum hydride (142 mL, 1 M in THF) was added over a period of 2 h to a cold (0 °C) solution of the oxazoline **16** (9.70 g, 47.3 mmol) in THF (200 mL). The resulting mixture was stirred continuously for an additional 2 h. The mixture was quenched with a saturated sodium tartrate aqueous solution (300 mL) and stirred vigorously for 4 h at room temperature. The reaction mixture was extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to afford the hydroxy oxazoline **17a** (7.65 g, 43.70 mmol). Yield = 91 %. ^{1}H NMR ($CDCl_3$): δ = 3.60–3.80 (m, 1H), 3.80–3.93 (m, 2H), 4.47–4.60 (m, 2H), 7.50 (m, 2H), 7.65 (m, 1H), 8.10 ppm (dd, J = 8.3 Hz and 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 55.9, 62.7, 65.9, 132.2, 133.5, 137.2, 170.0 ppm.

(*R*)-2-amino-3-benzoyloxy-propan-1-ol (18a): Following the procedure described for the synthesis of **9**, the reaction of the oxazoline **17** (12.0 g, 47.2 mmol) in THF (400 mL) and aqueous HCl (45 mL, 2 M) gave the monoprotected aminodiol **18a** (9.22 g, 47.20 mmol) as a white solid. yield > 99 %. This material was used in the next step without any farther purification. ^{1}H NMR ($CDCl_3$): δ = 3.80–3.60 (m, 1H), 3.93–3.80 (m, 2H), 4.60–4.47 (m, 2H), 7.65 (m, 1H), 7.50 (m, 2H), 8.30 ppm (dd, J = 8.3 Hz and 1.2 Hz, 2H); MS (CI, NH_3): m/z (%): 195 (100) [M + H].

(2*R*)-*N*,*N*′-Bis-[3-phenylcarboxy-1-hydroxypropyl]-2,2-dimethyl-1,3-propanediamide (19a(OH)): Following the procedure described for the synthesis of the bisamide **14a**, triethylamine (7.0 mL, 50.0 mmol), dimethyl malonic chloride (4.85 g, 29.0 mmol) and amino ester **18a** (4.8 g, 25.0 mmol) were reacted to give, after purification by column chromatography on silica gel (ethyl acetate/methanol; 95:5), the bisamide **19a(OH)** (5.4 g, 11.3 mmol) as a white solid. Yield = 90 %. M.p. 85–87 °C; $[\alpha]_D^{20}$ = +16,6 (c = 1.1 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 6H; C*H*$_3$), 3.34 (s, 2H; O*H*), 3.66 (dd, J = 12.1 Hz and 4.8 Hz, 2H), 3.75 (dd, J = 12.1 Hz and 3.9 Hz, 2H), 4.34 (m, 2H; C*H*N), 4.40 (m, 4H; C*H*OH), 7.00 (d, J = 7.7 Hz, N*H*), 7.20–7.40 ppm (m, 10H; Ar–*H*); ^{13}C NMR ($CDCl_3$): δ = 23.5, 49.8, 51.0, 61.5, 63.3, 128.4, 129.5, 130.0, 133.7, 166.8 , 174.2 ppm; MS (CI, NH_3): m/z (%): 540 (25) [M + NH_4^+], 487 (100) [M + H]; elemental analysis calcd (%) for $C_{25}H_{30}N_2O_8$ (486.52): C 61.72, H 6.22, N 5.76; found: C 61.85, H 6.02, N 5.74.

(2R)-*N*,*N*′-Bis-[3-phenylcarboxy-1-chloropropyl]-2,2-dimethyl-1,3-propanediamide (19a(Cl)): Following the procedure used for the synthesis of the bisamide **14b**, the bisamide **19a(OH)** (5.0 g, 10.3 mmol) was allowed to react with thionyl chloride (13.9 mL, 192.0 mmol) to yield the bisamide **19a(Cl)** (5.0 g, 9.6 mmol) as a white solid. The residue was purified by flash chromatography on silica gel (ethyl acetate). Yield = 94 %. $[\alpha]_D^{20}$ = +6,1 (c = 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 6H; C*H*$_3$, 3.66 (dd, J = 11.2 Hz and 6.0 Hz, 2H; C*H*Cl), 3,72 (dd, J = 11.2 Hz and 6.0 Hz, 2H; C*H*Cl), 4.39 (m, 2H; C*H*N), 4.53 (m, 4H; C*H*$_2$O), 7.18 (d, J = 6.3 Hz, 2H; N*H*), 7.48 (m, 4H; Ar–*H*), 7.57 (m, 2H; Ar-*H*), 7.99 ppm (m, 4H; Ar–*H*); ^{13}C NMR ($CDCl_3$): δ = 23.8, 43.6, 49.5, 49.5, 63.1, 128.5, 129.3, 129.7, 133.4, 166.4, 173.4 ppm; elemental analysis calcd (%) for $C_{25}H_{28}Cl_2N_2O_6$ (523.41): C 57.37, H 5.39, N 5.35; found: C 57.43, H 5.68, N 5.92.

(4*R*)-2,2-Bis-[2-(phenylcarboxymethyl-1,3-oxazolinyl)]propane (4a): A solution of bisamide **19a(Cl)** (0.48 g, 0.90 mmol) and dry triethylamine (3.0 mL, 21.6 mmol) in toluene (30 mL) was refluxed for 4 h. The mixture was diluted with saturated $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on deactivated alumina (ethyl acetate) to afford the bis(oxazoline) **4a** (0.30 g, 0.66 mmol) as colorless viscous oil. Yield = 73 %. $[\alpha]_D^{20}$ = −91.2 (c = 1.8 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 6H; C*H*$_3$), 4.20–4.60 (m, 10H), 7.30–7.60 (m, 6H; Ar–*H*), 7.95 ppm (m, 4H; Ar-*H*); ^{13}C NMR ($CDCl_3$): δ = 24.4, 38.6, 64.8 , 65.5, 70.0, 128.3, 129.6, 129.7, 133.0, 166.1, 170.7 ppm; MS (CI, NH_3); m/z (%): 451 (100) [M + H]; elemental analysis calcd (%) for $C_{25}H_{26}N_2O_6$ (450.49): C 66.66, H 5.82, N 6.22, found: C 66.86, H 5.62, N 6.02.

(4*R*)-2,2-Bis-[2-(hydroxymethyl-1,3-oxazolinyl)]propane (4b): Bis(oxazoline) **4a** (0.36 g, 0.83 mmol) was added in one portion to a solution of NaOH (1 % wt) in methanol (10 mL). The reaction mixture was stirred for 30 min at room temperature, then quenched with water (2 mL) and concentrated. The residue was then purified by column chromatography on silica gel (ethyl acetate) to afford the dihydroxy bis(oxazoline) **4b** (0.19 g, 0.81 mmol) as colorless oil. Yield = 97 %. $[\alpha]_D^{20}$ = −70.5 (c = 1.2 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 6H; C*H*$_3$), 3.43 (dd, J = 2.8 Hz and 11.7 Hz, 2H), 3.69 (dd, J = 2.8 Hz and 2.8 Hz, 2H), 4.15 ppm (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 23.5, 39.4, 63.8, 70.0, 70.1, 170.7 ppm; MS (CI, NH_3): m/z (%): 243 (100) [M + H]; elemental analysis calcd (%) for $C_{11}H_{18}N_2O_4$ (242.27): C 54.53, H 7.49, N 11.56; found: C 54.05, H 7.54, N 8.24.

(4*S*)-[(2-hydroxyethyl-2-methyl]-2 phenyloxazoline (17b): A solution of methyl magnesium iodide (32.5 mL, 3 M in diethyl ether) was added dropwise by canula to a refluxed and vigorously stirred solution of **16** (8.0 g, 38.0 mmol) in diethyl ether (250 mL). The reaction mixture was stirred at reflux for further 3 h and then quenched carefully with saturated NH_4Cl aqueous solution (200 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford **17b** (6.22 g, 29.6 mmol). Yield = 78 %. $[\alpha]_D^{20}$ = +64.4 (c = 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.17 (s, 3H; C*H*$_3$), 1.34 (s, 3H; C*H*$_3$), 2.02 (s, 1H; O*H*), 4.20 (dd, J = 10.2 Hz and 8 Hz, 1H), 4.34 (dd, J = 8.0 Hz and 8.3 Hz, 1H), 4.43 (dd, J = 8,3 Hz and 10.2 Hz, 1H), 7.24–7.48 (m, 3H; Ar–*H*), 7.94 ppm (m, 2H; Ar–*H*); ^{13}C NMR ($CDCl_3$): δ = 26.0, 68.7, 71.5, 75.6, 122.8, 128.2, 128.3, 131.4, 164.5 ppm; MS (CI, NH_3): m/z (%): 206 (100) [M + H]; elemental analysis calcd (%) for $C_{12}H_{15}NO_2$ (205.25): C 70.22, H 7.37, N 6.82; found: C 70.64, H 7.02, N 6.25.

(*S*)-4-phenylcarboxy-3-amino-2-methylbutan-1-ol (18b): Following the procedure described for the synthesis of **13**, the oxazoline **17b** (4.8 g, 23.4 mmol) was stirred in a mixture of THF (400 mL) and aqueous HCl (45 mL, 2 M) to yield **18b** (6.0 g, 23.0 mmol). This product was used in the next step without further purification. Yield = 97 %. ^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 3H; C*H*$_3$), 1.36 (s, 3H; C*H*$_3$), 3.71 (s, 1H; O*H*), 4.43 (m, 2H; C*H*$_2$), 4.54 (m, 1H; C*H*), 7.34 (dd, J = 7.3 Hz and 7.5 Hz, 2H; Ar–H_{meta}), 7.48 (dd, J = 7.5 Hz and 7.3 Hz, 1H; Ar–H_{para}), 8.12 ppm (d, J = 7.5 Hz, 2H; Ar–H_{ortho}); ^{13}C NMR ($CDCl_3$): δ = 23.8, 28.1, 59.7, 62.0, 70.2, 128.4, 130.2, 133.5, 166.1 ppm; MS (CI, NH_3): m/z (%): 224 (100) [M + H].

(3*S*)-2,2-Bis-[4-phenylcarboxy-2-methyl-2-hydroxybutyl]-2,2-dimethyl-1,3-propanediamide (19b): Following the procedure described for the synthesis of bisamide **14a**, the addition of a solution of triethylamine (7.0 mL, 50.0 mmol) and dimethyl malonic chloride (4.85 g, 29.0 mmol) in CH_2Cl_2 to the amino ester **18b** (6.5 g, 25.0 mmol) led, after purification by column chromatography on silica gel (ethyl acetate/methanol; 95:5), to **19b** (6.0 g, 11.0 mmol) as a white solid. Yield = 89 %. M.p. 75–77 °C; $[\alpha]_D^{20}$ = +24,6 (c = 1.1 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.22 (s, 6H; C*H*$_3$), 1.28 (s, 6H; C*H*$_3$), 1.34 (s, 6H; C*H*$_3$), 2.95 (s, 2H; O*H*), 4.10 (ddd, J = 9.0 Hz, 5.4 Hz and 6.3 Hz, 2H; C*H*N), 4.46 (d, J = 5.4 Hz, 1H; C*H*$_2$O), 4.47 (d, J = 6.3 Hz, 1H; C*H*$_2$O), 7.08 (d, J = 9 Hz, 2H; N*H*), 7.38 (m, 4H; Ar–*H*), 7.41 (m, 2H; Ar–*H*), 7.94 ppm (m, 4H; Ar–*H*); ^{13}C NMR ($CDCl_3$): δ = 23.6, 26.5, 27.5, 49.6, 56.6, 63.5, 71.7, 128.3, 129.5, 133.1, 166.5, 173.4 ppm; MS (CI, NH_3): m/z (%): 543 (100) [M + H]; elemental analysis calcd (%) for $C_{29}H_{38}N_2O_8$ (542.62): C 64.19, H 7.06, N 5.16; found: C 64.57, H 6.84, N 5.52.

(4R)-2,2-Bis-[2-(3,3-dimethyl-4-phenylcarboxymethyl-1,3-oxazolinyl)]-propane (5a): In a 500 mL one-neck round bottom flask bisamide **19a(OH)** (0.86 g, 1.59 mmol) was dissolved in CH_2Cl_2 (150 mL). The flask was then fitted with a Soxhlet apparatus containing a cartridge with 3 g of CaH_2. Methane sulfonic acid (0.52 mL, 7.95 mmol) was added to the solution and the mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was washed with saturated $NaHCO_3$ (2 × 50 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to afford **5a** (0.62 g, 1.22 mmol) as colorless viscous oil. Yield = 78 %. $[\alpha]_D^{20}$ = −61.0 (c = 1.35 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 6H; C*H*$_3$), 1.42 (s, 6H; C*H*$_3$), 1.45 (s, 6H; C*H*$_3$), 4.00 (dd, J = 4.5 Hz and 7.4 Hz, 2H), 4.34 (dd, J = 11.6 Hz and 7.4 Hz, 2H), 4.46 (dd, J = 11.6 Hz and 4.5 Hz, 2H), 7.40 (m, 4H; Ar–*H*), 7.53 (m, 2H; Ar–*H*), 7.98 ppm (m, 4H; Ar–*H*); ^{13}C NMR

($CDCl_3$): δ = 21.3, 23.7, 28.7, 35.6, 63.6, 71.6, 85.9, 128.3, 129.5, 129.8, 133.1, 166.0, 169.3 ppm; MS (CI, NH_3): *m*/*z* (%): 507 (100) [*M* + H]; elemental analysis calcd (%) for $C_{29}H_{34}N_2O_6$ (506.59): C 68.76, H 6.76, N 5.53; found: C 68.35, H 6.90, N 5.65.

(4R)-2,2-Bis-[2-(3,3-dimethyl-4-hydroxymethyl-1,3-oxazolinyl)]propane (5b): Following the procedure described for the synthesis of bis(oxazoline) **4b**, the reaction of bis(oxazoline) **5a** (0.35 g, 0.71 mmol) with NaOH (1% wt) in methanol (10 mL) yielded **5b** (0.20 g, 0.69 mmol). Yield = 96%. $[\alpha]_D^{20} = -79.2$ (c = 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 6H; CH_3), 1.44 (s, 6H; CH_3), 1.47 (s, 6H; CH_3), 3.70 ppm (m, 8H); ^{13}C NMR (CD_3OD): δ = 21.6, 24.3, 29.4, 62.5, 75.5, 88.4, 171.3 ppm; MS (CI, NH_3): *m*/*z* (%): 299 (100) [*M* + H]; elemental analysis calcd (%) for $C_{15}H_{26}N_2O_4$ (298.38): C 60.38, H 8.78, N 9.39; found: C 60.25, H 8.75, N 9.10.

Alkylation of (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate: general procedure: Dimethyl malonate (0.170 mL, 1.5 mmol) and two equivalents of the appropriate base system were mixed in dichloromethane (3 mL) under argon. In a separate flask, the chiral BO ligand (0.02 mmol), [{Pd(η^3-C_3H_5)Cl}$_2$] (1.80 mg, 0.005 mmol) and racemic (E)-1,3-diphenyl-2-propenyl-1-acetate **20** (126 mg, 0.5 mmol) in dichloromethane (2 mL) were stirred for 20 minutes, and then added dropwise to the above mixture. The resulting mixture was refluxed and the reaction was monitored by thin layer chromatography on silica plate (ethyl acetate/pentane; 15:85). After consumption of (*E*)-1,3-diphenyl-2-propenyl-1-acetate 20, the reaction mixture was diluted with a NH_4Cl saturated aqueous solution (10 mL) and washed with dichloromethane (2 × 10 mL). The organic layers were assembled, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (ethyl acetate/pentane; 15:85) to yield **21**. The enantiomeric excess was determined by HPLC analysis with a chiral analytical column. ^{1}H NMR ($CDCl_3$, for **21**): δ = 3.53 (s, 3H), 3.70 (s, 3H), 3.95 (d, J = 11 Hz, 1H), 4.27 (dd, J = 11 Hz, 8Hz, 1H), 6.32 (dd, J = 15 Hz, 8 Hz, 1H), 6.48 (d, J = 15 Hz, 8 Hz, 1H), 7.15–7.44 ppm (m, 10H). $[\alpha]^{20} = +19.2$ (c = 1.30 in $CHCl_3$) (+)-(*R*). HPLC Pharmacir 7C (*n*BuOH/*n*-hexane; 10:90; 0.7 mL min^{-1}): t_R (*S*) 10.66 min. and t_R (*R*) 11.88 min.

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