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Effects of Extended Aryl-Substituted Bisoxazoline Ligands in Asymmetric Synthesis – Efficient Synthesis and Application of 4,4′-Bis(1-Naphthyl)-, 4,4′-Bis(2-Naphthyl)- and 4,4′-Bis(9-Anthryl)-2,2′-isopropylidenebis(1,3-oxazolines)

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The steric influence of extended aryl substituents on 2,2′-bis(1,3-oxazoline) ligands was investigated in a series of asymmetric catalytic reactions such as Mukaiyama aldol and Michael reactions, hetero-Diels–Alder processes, and allylic alkylation reactions. 4,4′-(2-Naphthyl)- and 4,4′-(9-anthryl)-substituted isopropylidene-bridged 2,2′-bis(1,3-oxazolines) were synthesized and their enantioselective and catalytic properties in combination with different metals evaluated.

Introduction

Bisoxazoline (box) ligands[1] in combination with transition metals have been shown to be excellent catalysts in a wide range of asymmetric transformations such as Diels–Alder[2] and hetero-Diels–Alder reactions[3] and aldol condensations.[4] So far, many variations at the core of the box ligand have been carried out. Although a wide range of differently substituted bisoxazoline ligands have been synthesised over the years, only a few ligands are currently commonly used, which are commercially available or easily prepared from the corresponding amino acids (**A**, Figure 1).

In case of alkyl substituents on C4, a common trend shows that increase of steric bulk of the substituent enhances the enantioselectivity. Thus, generally higher enantioselectivities are obtained with *t*Bu-box than with *i*Pr- or Me-box. Very recently, the group of Moreno-Manas accomplished the synthesis of a new and even bulkier 4-alkyl-substituted bisoxazoline ligand, adamantyl-box (Adam-box).[5] It was found that the use of this ligand resulted in three different reactions in similar enantioselectivity as previously observed for *t*Bu-box (in all instances >95% *ee*). In addition, Evans and co-workers have investigated the contribution of electronic effects of the R-substituent, using a small series of *para*-substituted Ph-box ligands (**B**).[3d] Although no clear electronic effect was observed, possible dipole–dipole and Van der Waals attractions may still be partially responsible for the observed stereoselectivity, since these interactions do not vary with the π-donor capacity of the phenyl group.

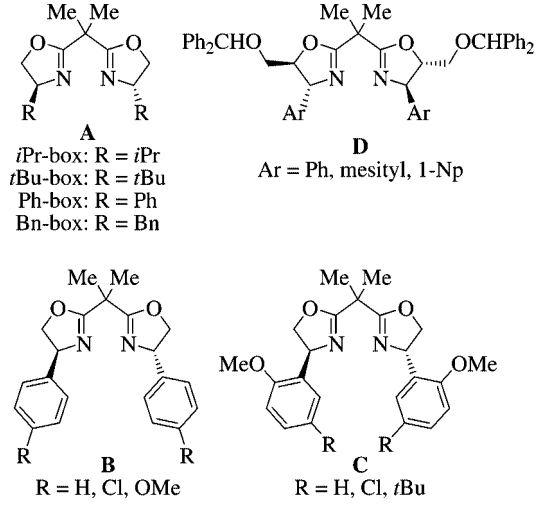

Figure 1. Different types of bisoxazoline ligands.

Recently, Pagenkopf and co-workers investigated the electronic and steric tuning of the aryl substituent by synthesising a small series of *o*-alkyloxyaryl-substituted bisoxazolines.[6] They employed these ligands in the addition of a rather bulky silyl enol ether to methyl pyruvate and other glyoxylate esters (vide infra). They reported a remarkable increase in both yield and selectivity compared to the Ph-box ligand, especially when the triflate counterion was replaced by chloride. However, their attempts to increase the

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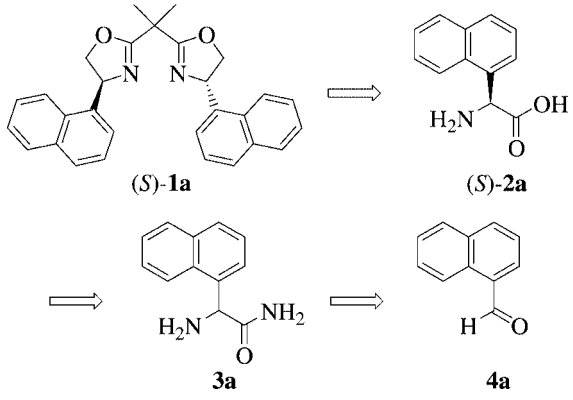
enantioselectivity by increasing steric effects were unsuccessful.

Despite the versatility of box ligands that have been synthesised over the past decades, there is not a single ligand that gives optimal results in every type of conversion. For example, in some reactions alkyl-substituted box ligands provide better results, whereas in other reactions the aryl-substituted analogues are the most suitable ligands. Surprisingly, the steric influence of extended aryl substituents has only once been studied by Desimoni and Faita and they observed that replacement of a phenyl by a 2-naphthyl substituent at the 4-position of the box ligand resulted in a slight increase of enantioselectivity.[7]

A new class of more complex bisoxazoline ligands **D**, bearing an additional ether substituent at the position 5 of both oxazoline rings, was investigated by Pericas and Muller.[8] In palladium-catalysed allylic alkylations, the phenyl-substituted ligand gave similar results as obtained with Ph-box. Extension of the phenyl substituent to a 1-naphthyl group resulted in a similar excellent enantioselectivity and enhanced yield.

Recently, we developed a straightforward and efficient route towards 4-substituted bisoxazoline ligands as depicted in Scheme 1.[9] We have demonstrated the viability of this route for the new (*S*)-1-naphthyl-substituted ligand (**1a**) and observed some increase in enantioselectivity when we applied this ligand in a small range of Lewis acid-catalysed reations. The synthesis of (*S*)-1-Np-box (**1a**) was accomplished in 60% overall yield starting from (*S*)-(1-naphthyl)glycine (**2a**) and in 37% overall yield from 1-naphthaldehyde (**4a**). The crystal structure of (*S*)-**1a** was recently determined, thus confirming its structure unambiguously (Figure 2).[10]



Scheme 1. Retrosynthesis of (*S*)-1-Np-box.

In this contribution, we show the expansion of our set of ligands with the (2-naphthyl)- and the even more extended (9-anthryl)bisoxazoline (Figure 3) and applied these ligands in a range of Lewis acid-catalysed reactions. We also aimed to make a more extensive evaluation of the steric influence of the aryl substituents and to investigate the scope and limitations of these ligands.

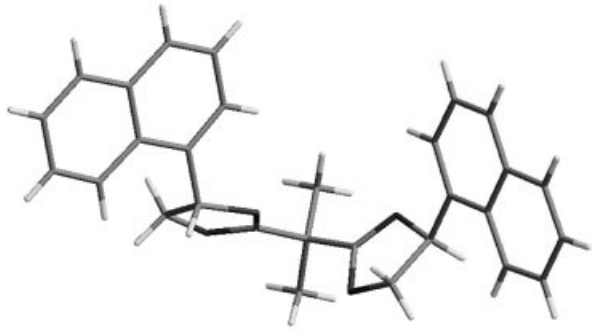


Figure 2. Crystal structure of (*S*)-1-Np-box (**1a**).

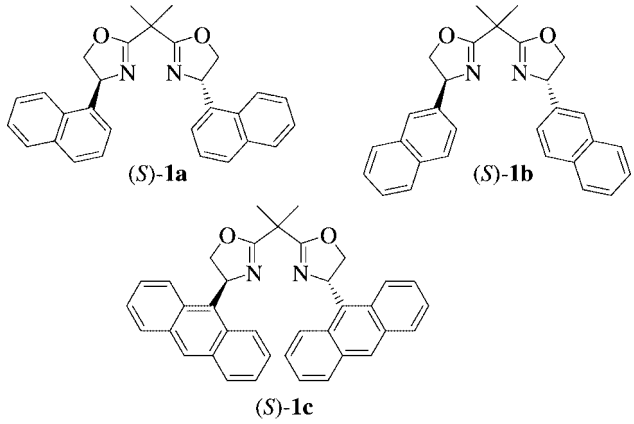


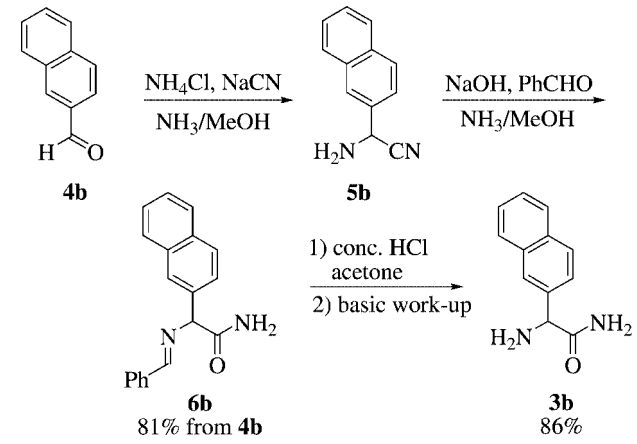
Figure 3. (1-Naphthyl)-, (2-naphthyl)-, (9-anthryl)bisoxazoline ligands, respectively.

Results and Discussion

Ligand Synthesis

We applied our previously established chemoenzymatic pathway[9] to prepare (2-naphthyl)bisoxazoline (2-Np-box, **1b**), despite the fact that a synthesis of this ligand was already accomplished by the group of Desimoni and Faita.[7] The corresponding (2-naphthyl)glycine amide (**3b**) was formed upon treatment of 2-naphthaldehyde (**4b**) with modified Strecker conditions, followed by partial hydrolysis of the resulting aminonitrile **5b** to give Schiff base **6b** (Scheme 2). Acidic hydrolysis of the Schiff base resulted in formation of the crystalline HCl salt of the desired amino acid amide, which was then, after treatment with base, extracted from the basic water layer with dichloromethane to give the free amino acid amide **3b** in 70% overall yield from 2-naphthaldehyde.[11]

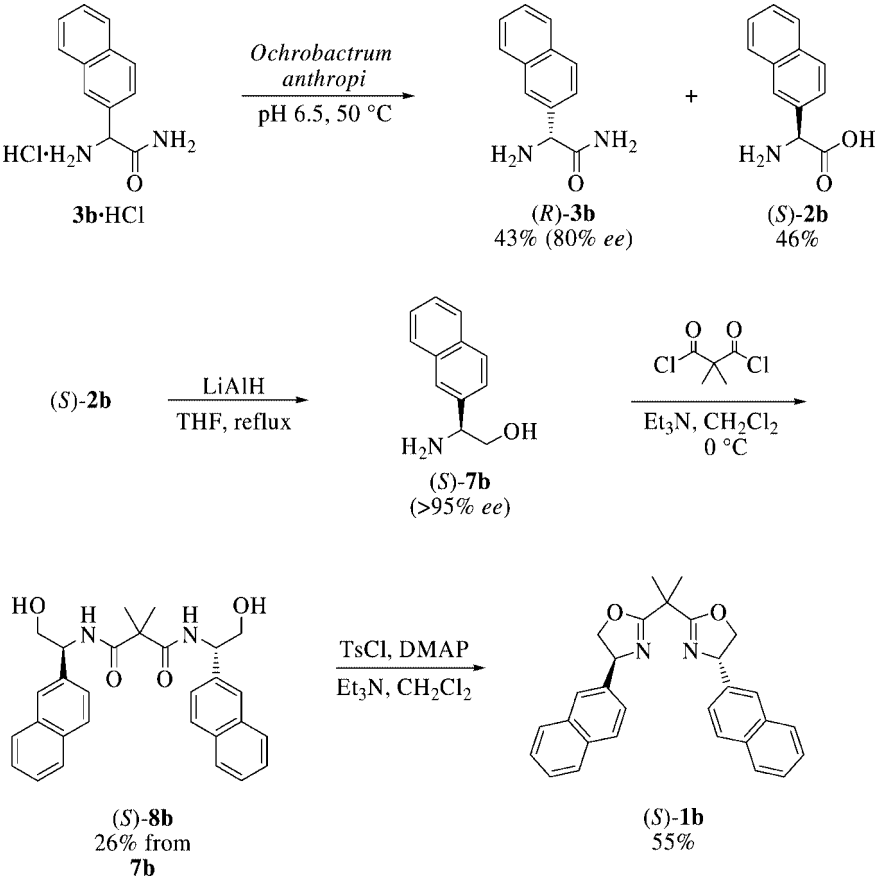
Subjection of racemic **3b**·HCl to an L-specific aminopeptidase from the microorganism *Ochrobactrum anthropi* NCIMB 40321[12] (pH = 6.5, T = 50 °C) led to a mixture of the corresponding (*R*)-amide **3b** and (*S*)-acid **2b** (Scheme 3). The work-up consisted of removal of the whole cell rests by filtration, followed by lowering of the pH to 2 in order to precipitate (*S*)-acid **2b** (46% yield). Unfortunately, we were unable to determine the enantiopurity at this point due to the insolubility of the acid. Raising the pH to 9, filtration and subsequent extraction of the aque-



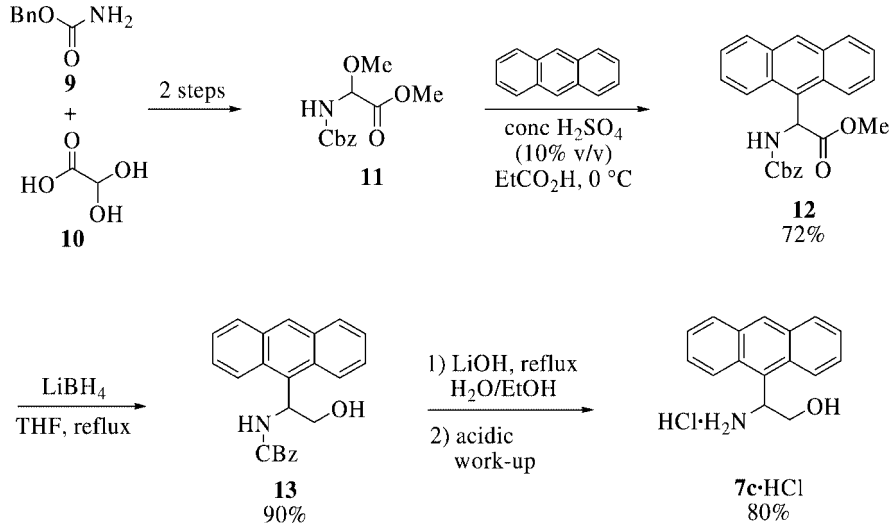
Scheme 2. Synthesis of (2-naphthyl)glycine amide.

ous layer afforded (*R*)-amide **3b** in 43% yield with 80% *ee*. Optically active (2-naphthyl)glycine (**2b**) gave access to (*S*)-2-Np-box (**1b**) in the same fashion as described previously (Scheme 3). Since (*S*)-(2-naphthyl)glycinol is a known compound,[7] comparison of the optical rotation of the $LiAlH_4$ reduction product **7b** indicated that the enantiopurity of the (*S*)-(2-naphthyl)glycine obtained by enzymatic resolution was excellent (>95% *ee*). Base-catalysed cyclisation of diamide **8b** resulted in the desired enantiopure 2-Np-box ligand, which could be readily purified via recrystallisation.

Initially, we aimed to synthesise the 9-anthryl-substituted bisoxazoline, which has hitherto not been described in literature, via an identical approach to that shown above for the two naphthyl-substituted bisoxazolines (Scheme 1). However, from the start we encountered severe problems when applying the same sequence to the exceptionally bulky and lipophilic 9-anthraldehyde. Especially the insolubility of the precursors and resulting products in the modified Strecker reaction led to slow conversions and low yields. Moreover, we envisaged that (9-anthryl)glycine amide might lead to additional problems during the subsequent enzymatic resolution, since it was expected to be even less soluble in the aqueous buffers than its naphthyl counterpart. Therefore, we changed our strategy into a classical resolution approach to obtain optically pure 2-(9-anthryl)glycinol. Starting from benzyl carbamate (**9**) and glyoxylic acid monohydrate (**10**), the spontaneously formed *N*,*O*-acetal was methylated in acidic methanol to give **11** in two smooth steps according to the literature.[13] Next, this carbamate was allowed to react with anthracene via the corresponding *N*-acyliminium ion (Scheme 4).[14] Optimisation studies revealed that propionic acid as a co-solvent was superior to formic and acetic acid in this particular case. In addition, the reaction time had to be restricted to one hour in order to avoid decomposition of both anthracene and the electrophilic aromatic substitution product **12** by sulfuric acid.



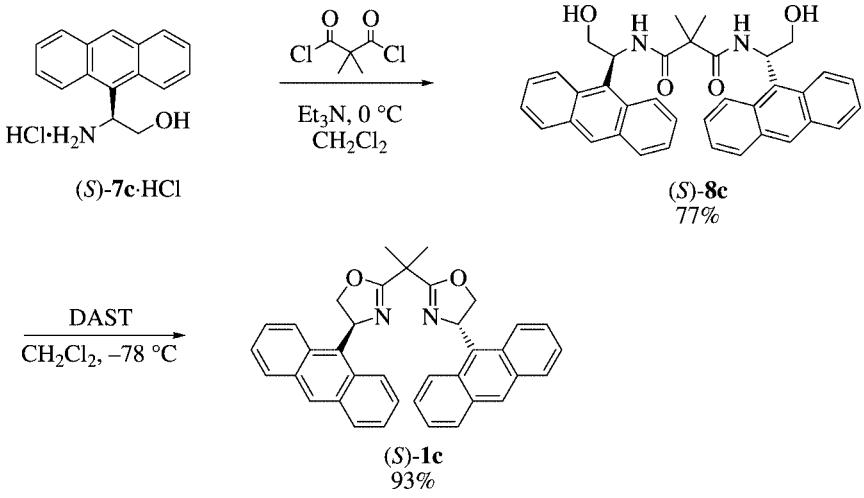
Scheme 3. Synthesis of (*S*)-(2-naphthyl)bisoxazoline (**1b**).



Scheme 4. Synthesis of 2-(9-anthryl)glycinol.

Synthesis of the racemic HCl salt of amino alcohol **7c** was accomplished via $LiBH_4$ reduction[15] of methyl ester **12**, subsequent deprotection of the amine in the presence of LiOH and an acidic work-up (Scheme 4). Surprisingly, the free amino alcohol was relatively unstable, but the decomposition could be significantly slowed down by conversion into the corresponding HCl salt. This suggests that the instability of HCl-free **7c** is caused by the presence of a basic nitrogen atom near the anthracene moiety. This is in agreement with findings of Stack and co-workers, who observed that in the synthesis of 9-aminomethylanthracene there are large variations in the yield,[16] a result that in our view could well be explained by a similar decomposition event.

Despite several attempts using the so-called "Dutch Resolution" protocol,[17] involving treatment with families of chiral resolving agents, no successful resolution of racemic 2-(9-anthryl)glycinol into both enantiomers was achieved. Therefore, the amino alcohol was resolved using preparative chiral HPLC (Chiralpak AD column) to afford both enantiomers with excellent enantiopurity: t_R = 39.3 min (90% *ee*) and t_R = 44.1 min (98% *ee*).[18] Assignment of the absolute configuration of both enantiomers was achieved by circular dichroism (CD) measurements. In contrast with known derivatisation methods to elucidate the absolute stereochemistry of the 9-anthryl amino alcohol, we chose to use a newly developed spectroscopic technique. Recently, it was found that circular dichroism may provide a convenient alternative for the direct determination of the absolute configuration of optically active amino alcohols.[19] In this approach, the amino alcohols are converted into cottonogenic derivatives via in situ complexation with dirhodium tetraacetate, which then also acts as the auxiliary chromophore. The absolute stereochemistry was assigned based on the Cotton effect arising in the CD spectra at around 620 nm; this band probably originates from the π^*(Rh–Rh) → σ^*(Rh–O) transition. A negative Cotton effect would indicate that the amino alcohol belongs to the L-series, which corresponds to the (*S*)-configuration and vice versa.[19] The absolute configuration of both enantiomers of 2-(9-anthryl)-glycinol was determined according to this method: the en-



Scheme 5. Synthesis of (*S*)-(9-anthryl)bisoxazoline (**1c**).

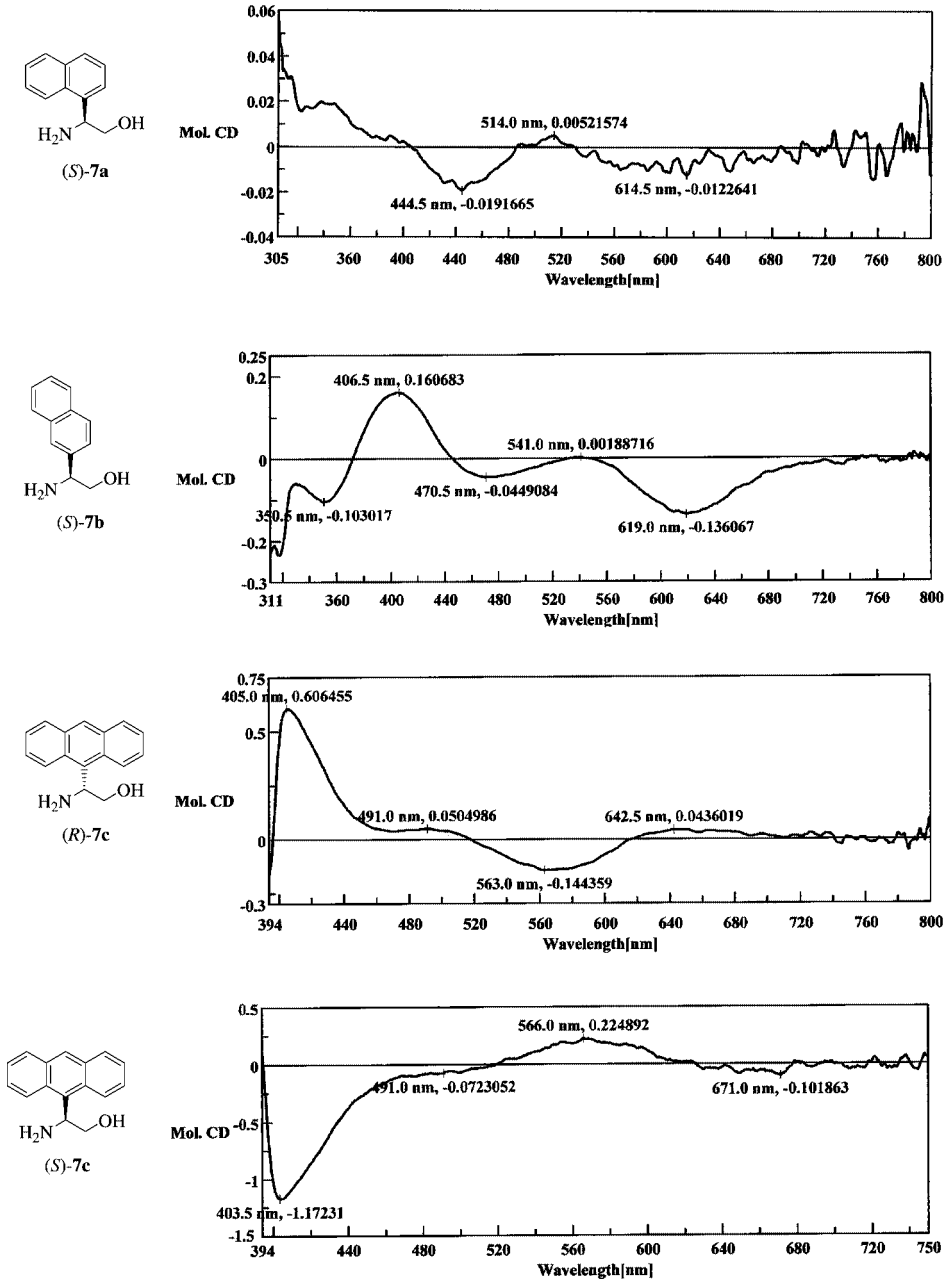


Figure 4. CD spectra of (*S*)-2-(1-naphthyl)glycinol, (*S*)-2-(2-naphthyl)glycinol, (*R*)- and (*S*)-2-(9-anthryl)glycinol complexed to $[Rh(OAc)_4]_2$.

antiomer with t_R = 39.3 min (90% *ee*) was found to be (*R*)-2-(9-anthryl)glycinol and than with t_R = 44.1 min (98% *ee*) was found to be (*S*)-2-(9-anthryl)glycinol. To compare the Cotton effect of (*S*)- and (*R*)-2-(9-anthryl)glycinol with other aryl-substituted amino alcohols, the spectra of (*S*)-1-naphthyl and (*S*)-2-naphthyl were also recorded in the presence of dirhodium tetraacetate (Figure 4).

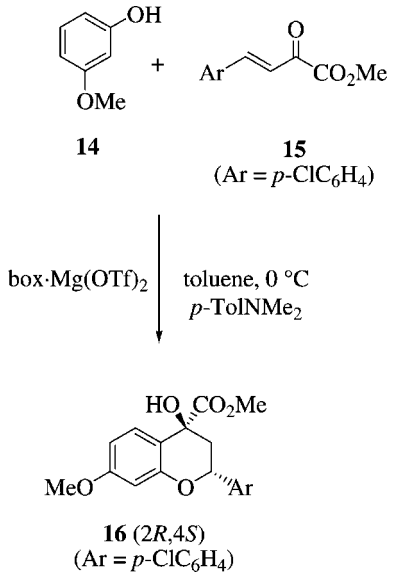
The enantiomerically pure (*S*)-2-(9-anthryl)glycinol (**7c**) was converted into the corresponding (*S*)-9-Ant-box (**1c**) in two steps (Scheme 5). First, acylation of (*S*)-2-(9-anthryl)-glycinol resulted in diamide (*S*)-**8c** in good yield. Under the conditions reported by Evans,[20] i.e. in the presence of two equivalents of tosyl chloride, only one of the oxazoline-rings was formed while the other alcohol remained unreacted. Alternatively, treatment with (diethylamino)sulfur trifluoride (DAST) led to smooth double cyclisation to give the desired (*S*)-9-Ant-box (**1c**) in 93% yield.[21] During subsequent catalysis experiments, we noticed that this ligand is relatively unstable, similar to what was found for 2-(9-anthryl)glycinol.

Catalysis Results

As a starting point, our aryl-substituted ligands were tested in the tandem oxa-Michael addition-Friedel–Craft

alkylation reaction, in combination with $Mg(OTf)_2$ in toluene at 0 °C and in the presence of 10 mol-% of *N*,*N*-dimethyl-*p*-toluidine (Table 1).[22] The 1-Np-box ligand clearly resulted in the best enantioselectivity (74% *ee*), whereas in the presence of both Ph- and 2-Np-box, the product was formed with remarkably better yield, but a slight decrease in enantioselectivity (65% *ee* and 62% *ee*, respectively). Despite the more bulkiness of the 9-Ant-box, the use of this ligand in combination with $Mg(OTf)_2$ resulted in a drastic decrease in enantioselectivity (20% *ee*). This was due to the limited stability of the 9-Ant-box ligand at 0 °C, i.e. the ligand decomposed during reaction (ca. 20 h). Our results show that *t*Bu-box is not an appropriate ligand for this reaction, since tandem product **16** was obtained with only 18% *ee* (entry 5). Surprisingly, the use of Ph-box resulted in the same enantiomer of **16** as when *t*Bu-box was used, whereas all other aryl-substituted box ligands yielded the product as the opposite enantiomer.

Table 1. Results of the tandem oxa-Michael addition-Friedel–Craft alkylation reaction.



14 **15** (Ar = *p*-ClC_6H_4)

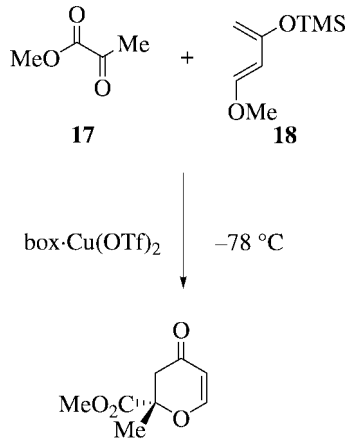
16 (2*R*,4*S*) (Ar = *p*-ClC_6H_4)

Entry	Ligand	Toluene yield [%][a]	*ee* [%]
1	Ph-box	75	65 (2*R*,4*S*)
2	1-Np-box	39	74 (2*S*,4*R*)
3	2-Np-box	67	62 (2*S*,4*R*)
4	9-Ant-box	nd	20 (2*S*,4*R*)
5	*t*Bu-box	77	18 (2*R*,4*S*)

[a] Isolated yields.

Furthermore, we applied the aryl-substituted ligands in the hetero-Diels–Alder reaction of methyl pyruvate with Danishefsky's diene (**18**).[9] In both THF and CH_2Cl_2, we observed no significant differences between Ph-, 1-Np- and 2-Np-box (Table 2, entries 2–4). Replacement of Ph-box by 1-Np-box resulted in an increase in asymmetric induction in CH_2Cl_2 (13% to 19% *ee*, respectively) and a decrease in THF (35% to 22% *ee*, respectively). Comparing 2-Np-box to Ph-box in THF, a similar excellent yield and a comparable enantiopurity (35% *ee*) was observed. A significant increase to 45% *ee* was seen in the presence of 9-Ant-box in CH_2Cl_2 (entry 5), despite partial decomposition of the ligand during catalysis. Nevertheless, the *t*Bu-box ligand gives the best enantioselectivity in both solvents. Additionally, we observed that the stereochemical outcome of this reaction depends on the nature of the ligand used. The use of Ph- and 1-Np-box in THF led to a reversal of facial selectivity compared to *t*Bu-box. Remarkably, 2-Np-box afforded the hetero-Diels–Alder adduct with the same configuration as that obtained in the presence of *t*Bu-box.

Table 2. Results of the hetero-Diels–Alder reaction.



17 **18**

(*S*)-**19**

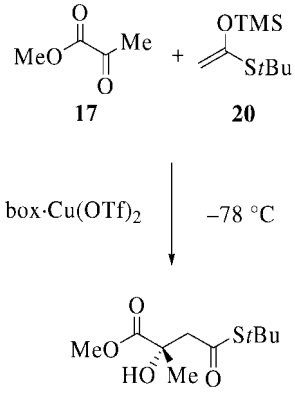
Entry	Ligand	THF yield [%][a]	*ee* [%][b]	CH_2Cl_2 yield [%][a]	*ee* [%][b]
1	*t*Bu-box[c]	99	>95 (*S*)	nd	>98 (*S*)
2	Ph-box[c]	99	35 (*R*)	nd	13 (*S*)
3	1-Np-box	90	22 (*R*)	nd	19 (*S*)
4	2-Np-box	>95	36 (*S*)	–	–
5	9-Ant-box	–	–	82	45 (*S*)

[a] Isolated yields after chromatography. [b] Enantiomeric excesses were determined by GC on a chiral γ-CD column (110 °C). [c] Our results correspond well to literature data.[23]

Another type of reaction in which methyl pyruvate was applied as the substrate in combination with [$Cu(OTf)_2$box] complexes is the Mukaiyama aldol reaction of methyl pyruvate (**17**) with silyl ketene acetal **20**.[9] Going from Ph-box to 2-Np-box, the effect of the steric influence is clearly shown by an increase of the *ee*, both in THF and in CH_2Cl_2 (Table 3, entries 2 and 4). In contrast, the use of 1-Np-box in combination with $Cu(OTf)_2$ only resulted in a decrease of enantioselectivity compared to Ph-box (entries 2 and 3). The results show that 1-Np-box is not an appropriate ligand for this Mukaiyama aldol reaction. However, the use of 2-Np-box results an increase of enantioselectivity in THF compared to Ph-box (31% vs. 24% *ee*) and a significant increase in enantioselectivity in CH_2Cl_2 (60% vs. 46% *ee*). The highest *ee* (>94%) was observed in both solvents when *t*Bu-box was used as ligand (entry 1). These results suggest that in both reactions discussed above, i.e. the Diels–Alder and the aldol reaction, the use of aryl-substituted box li-

gands does not have a crucial influence on the stereochemical outcome of the reaction.

Table 3. Results of the Mukaiyama aldol reaction.



(*S*)-**21**

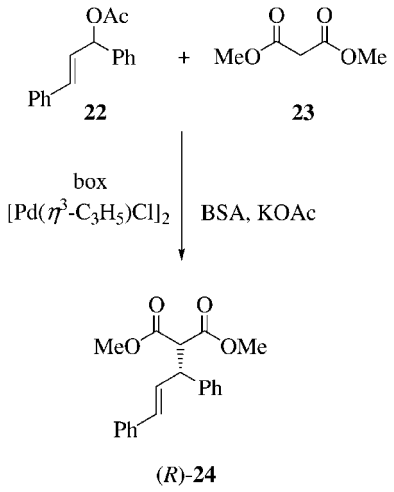
Entry	Ligand	THF yield [%][a]	*ee* [%][b]	CH_2Cl_2 yield [%][a]	*ee* [%][b]
1	*t*Bu-box[c]	89	97 (*S*)	>80	94 (*S*)
2	Ph-box[c]	73	24 (*S*)	>80	46 (*S*)
3	1-Np-box	nd	19 (*S*)	75	3 (*R*)
4	2-Np-box	>95	31 (*S*)	>95	60 (*S*)

[a] Isolated yields after chromatography. [b] Enantiomeric excesses were determined by chiral HPLC analysis on a Chiralcel OD column (hexane/IPA, 99:1, 0.5 mL/min) or by GC analysis using a chiral β-CD column (150 °C). [c] Our results correspond well to literature data.[28a]

Subsequently, we applied our series of aryl-substituted box ligands in the allylic substitution of (*E*)-1,3-diphenyl-2-propenyl acetate, since Ph-box in combination with Pd is known to be an excellent catalyst for this reaction.[8] Using an in situ generated malonate nucleophile from dimethyl malonate (**23**), bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate, the allylic substitution adduct **24** was formed with excellent enantioselectivity (Table 4). Surprisingly, in the presence of *t*Bu-box the reaction did not proceed at all, whereas the use of Ph-, 1-Np- and 2-Np-box afforded indeed the desired product in high yield (>95%) and with excellent enantioselectivity (>95% *ee*).

Previously, we observed a significant enhancement in enantioselectivity in the Mukaiyama Michael reaction of silyl ketene acetal **20** with Knoevenagel adduct **25** catalysed by [$Cu(SbF_6)_2$box] complexes in the presence of 1,1,1,3,3,3-hexafluoro-propan-2-ol (HFIP), depicted in Table 5.[9] Indeed, we were pleased to find that catalysis by both 1-Np- and 2-Np-box afforded the addition product with good enantioselectivity (70% *ee* and 79% *ee*, respectively) being a significant improvement compared to Ph-box (52% *ee*). In this reaction, we also observed a reversal of enantiofacial selectivity: in this case, all aryl-substituted box ligands afforded the opposite enantiomer than *t*Bu-box. Again, the highest enantioselectivity was achieved using *t*Bu-box as the ligand (>90% *ee*). From these results, it may be postulated

Table 4. Results of the allylation of dimethyl malonate.

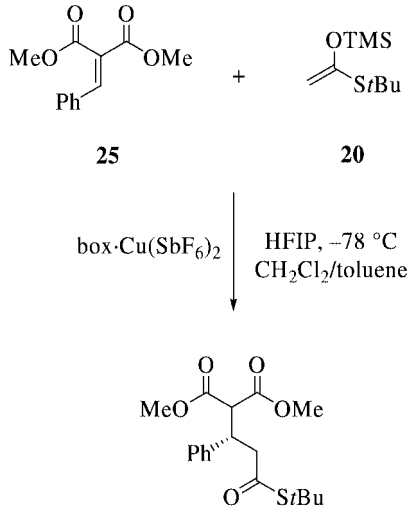


(*R*)-**24**

Entry	Ligand	Yield [%][a]	*ee* [%][b]
1	*t*Bu-box	0	–
2	Ph-box[c]	>95	96 (*R*)
3	1-Np-box	>95	97 (*R*)
4	2-Np-box	>95	97 (*R*)

[a] Isolated yields after chromatography. [b] Enantiomeric excesses were determined by chiral HPLC analysis on a Chiralpak AD column (hexane/*i*PrOH, 90:10, 0.8 mL/min). [c] Our results correspond well to literature data.[8]

Table 5. Results of the Mukaiyama–Michael reaction.



(*S*)-**26**

Entry	Ligand	Yield [%][a]	*ee* [%][b]
1	*t*Bu-box[c]	99	>90 (*R*)
2	Ph-box[c]	67	56 (*S*)
3	1-Np-box	55	70 (*S*)
4	2-Np-box	nd	79 (*S*)

[a] Isolated yields after chromatography. [b] Enantiomeric excesses were determined by chiral HPLC analysis on a Chiralpak AD column (heptane/*i*PrOH, 98:2, 1.0 mL/min). [c] Our results correspond well to literature data.[24]

that the use of extended aryl-substituted bisoxazolines is more promising in reactions, where the reaction centre is relatively remote from the coordination site.

While exploring the scope of aryl-substituted bisoxazoline ligands, we observed a reversal of enantiofacial selectivity between differently substituted box ligands. Other groups have also addressed this phenomenon, which was first reported by the group of Jørgensen[25] and is usually encountered in combination with copper(II). Although these groups have suggested a rationale over the years, so far there is no agreement on a suitable explanation. Evans suggested a mechanism in which π-stabilisation of the product-like transition state is responsible for the observed reversal of selectivity.[3d,26] However, Jørgensen and coworkers addressed the observed effect to the more flexible character of the Ph-box compared to *t*Bu-box complexes due to interconversion between square planar and tetrahedral conformations and thereby "flipping" of the oxazoline substituent between pseudo-axial and pseudo-equatorial positions.[27] These preliminary conclusions were derived from X-ray analyses and PM3-modelling experiments. Additional EPR measurements unambiguously confirm the dissimilarity in conformation of the Cu^{II} complexes of *t*Bu- and Ph-box.[28]

We also observed that the stereochemical outcome of the reaction is strongly dependent on the ligand and that the facial selectivity even changed by going from one aryl ligand to another. In order to acquire more insight into this phenomenon, we performed several experimental and theoretical investigations on the geometry of our [Cu^{II}box] complexes. In Figure 5, the crystal structures of the [$CuCl_2$(1-Np-box)] and the [$CuCl_2$(2-Np-box)] are depicted, which are also quite different from each other. Comparing their geometry with those of the corresponding *t*Bu- and Ph-box complexes,[29] we observed that the [$CuCl_2$(1-Np-box)] complex strongly resembles the [$CuCl_2$(*t*Bu-box)] complex, whereas the [$CuCl_2$(2-Np-box)] complex is more similar to the [$CuCl_2$(Ph-box)] complex. These different conformations could to some extent explain the occasional reversal in facial selectivity in our experiments, but in order to be able to give a conclusive explanation more detailed studies will have to be carried out.

Conclusions

The (*S*)- and (*R*)-enantiomers of (2-naphthyl)glycine were accessible through enzymatic resolution using an L-specific aminopeptidase in good yield and excellent *ee*. These synthetically versatile amino acids could also be effectively transformed into the corresponding enantiopure bisoxazoline ligands. The (*S*)-9-Ant-box ligand could not be prepared in an analogous fashion, but instead was obtained from the corresponding racemic amino alcohol, which was resolved into both enantiomers by chiral preparative HPLC. Subsequently, assignment of the absolute configuration of the anthryl-substituted amino alcohols was achieved by circular dichroism measurements in the presence of dirhodium tetraacetate.

Our studies towards the application of aryl-substituted box ligands afforded several interesting results. Both in the Mukaiyama aldol and in the hetero-Diels–Alder reaction, extension of the aryl-substituent did not lead to any dramatic improvement, although in the latter reaction, the use of 9-Ant-box resulted in an enhancement of the enantioselectivity (45% *ee* compared to 13% *ee* for Ph-box). In the tandem reaction, 1-Np-box gave the best results (74% *ee*), while the Ph- and 2-Np-box also afford the tandem product with good enantioselectivity (65% and 62% *ee*, respectively). A second example in which the aryl-substituted ligands were superior, was the allylic substitution reaction. While no reaction occurred using *t*Bu-box, excellent yields (>95%) and enantioselectivities (>95%) were observed using Ph-, 1-Np- and 2-Np-box. A significant effect of enlargement of the aryl substituent on the enantioselectivity was observed in the Mukaiyama Michael reaction, in which both 1-Np and 2-Np-box resulted in a clear improvement of the enantiopurity. This result once more demonstrates the beneficial influence of extension of the aryl substituent in reactions where the distance between reaction centre and coordination site is relatively large.

Despite the use of X-ray crystallography to acquire more details about the exact geometry of our [Cu^{II}box] complexes, we could not find a conclusive explanation for the strong dependency of the stereochemical outcome of the reaction on a particular ligand.

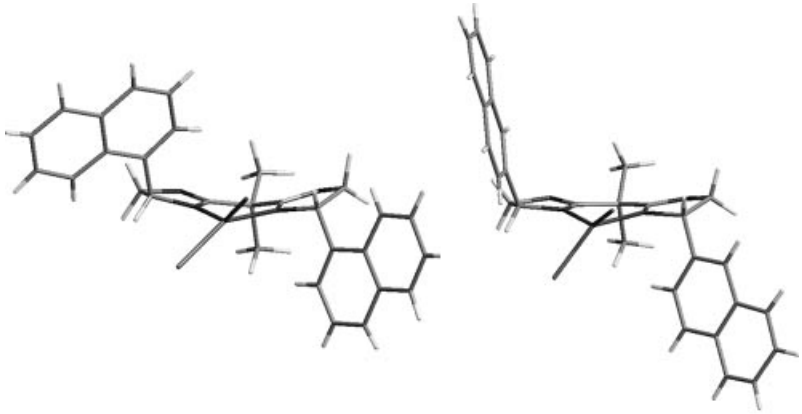


Figure 5. X-ray structures of [$CuCl_2$(1-Np-box)] (left) and [$CuCl_2$(2-Np-box)] (right).

Experimental Section

General Remarks: All reactions were carried out under an atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. Flash chromatography was performed with Acros Organic silica gel (0.035–0.070 mm). R_f values are obtained using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F_{254}) with the indicated solvents. Melting points were determined using a Büchi melting point B-545 apparatus and are uncorrected. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. NMR spectra were recorded with Bruker DMX 200 and DMX300 spectrometers and with a Varian Inova 400 MHz spectrometer with TMS as internal standard. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. Mass spectra were measured with a Fisons (VG) Micromass 7070E apparatus. Elemental analyses were carried out by using the CHNS-O EA 1108 element analyser from Carlo–Erba Instruments. CD spectra were recorded in the 250–800 nm range, at room temperature, with a Jasco 715 spectropolarimeter using chloroform solutions in cells of 2, 10 or 20 mm path length (spectral band with 2 nm, sensitivity 10×10^{-6} or 20×10^{-6} ΔA-unit/nm). Depending on the S/N ratio the λ-scan speed was 0.2 or 0.5 nm/s. For CD standard measurements the solid chiral amino alcohol (1–5 mg, ca. 0.003 M) was dissolved in a stock solution of the dirhodium tetraacetate (6–7 mg, ca. 0.002 M) in chloroform so that the molar ratio of the stock complex to ligand was about 1:1.5. HPLC′s were run using a Shimadzu CLASS-VP instrument, equipped with a Chiralpak AD column and a Chiralcel OD column. For chiral GC, a Hewlett–Packard 6890 instrument was used, equipped with a GammaDEX 120™ fused silica capillary column of Supelco (30 m, 0.25 mm ID, 0.25 μm film thickness) with H_2 as carrier gas.

Materials: Solvents were distilled from appropriate drying agents immediately prior to use. Unless stated otherwise, all chemicals were purchased and used as such. 2-Naphthaldehyde was distilled before use. (*S*,*S*)-DBTAAN, and a cell-free extract containing the *Ochrobactrum anthropi* NCIMB 40321 L-amidase were kindly provided by DSM. Dowex 50W×4 (Fluka) was used for ion exchange chromatography with 2 N NH_4OH as the eluent and 2 N HCl as regeneration agent. Aryl-substituted β,γ-unsaturated α-keto esters **14** was kindly provided by prof. Jørgensen.

Crystal Structure Determination of (*S*)-1-Np-box [(*S*)-1a]:[10] $C_{29}H_{26}N_2O_2$, M = 434.52, crystallises in the monoclinic space group $P2_1$, with a = 11.2514(17) Å, b = 7.7746(13) Å, c = 14.283(3) Å, V = 1148.8(3) Å^3, T = 293(2) K, Z = 2, μ = 0.079 mm^{-1}; 22993 reflections were measured, giving 24020 independent, of which 2986 with $I > 2\sigma(I)$ were used in the refinements. The internal agreement had R = 0.0731, the final R = 0.0450, Rw = 0.0782, GOF = 1.035, for the significant reflections.

***N*-Benzylidene-(2-naphthyl)glycine Amide (6b):** To a solution of NaCN (15.5 g, 0.32 mol) in methanol (250 mL) was added concentrated ammonia (25% in H_2O, 225 mL), NH_4Cl (16.9 g, 0.32 mol) and 2-naphthaldehyde (49.2 g, 0.32 mol). After stirring overnight at room temp., the reaction was complete according to TLC (Et_2O/heptane, 1:1). To the reaction mixture was added toluene (300 mL), aqueous NaOH (1 N, 315 mL, 0.32 mol) and benzaldehyde (32.0 mL, 0.31 mol). After stirring for 1 h, a precipitate was formed, which was collected by filtration, washed with heptane and dried in vacuo. Benzaldimine **6b** was isolated as an off-white solid (72.9 g, 81% from 2-naphthaldehyde) and used directly for the next step: m.p. 148 °C. IR: $\tilde{\nu}$ = 3443, 3286–3058, 1684, 1640, 1580, 1359 cm^{-1}. ^{1}HNMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.37 (s, 1 H), 7.82–7.48 (m, 12 H), 7.13 (s, 1 H), 5.63 (s, 1 H), 5.17 (s, 1 H) ppm. ^{13}CNMR (50 MHz, $CDCl_3$, 25 °C): δ = 173.7, 163.2, 136.4, 135.2, 133.1, 132.8, 131.3, 128.5, 128.3, 128.3, 127.8, 127.4, 126.2, 126.0, 125.9, 124.7, 76.9 ppm. HRMS(EI) calcd. for $C_{19}H_{16}N_2O$ 288.1263, found 288.1256. R_f (Et_2O/heptane, 1:1) = 0.12.

(2-Naphthyl)glycine Amide (3b): To a solution of **6b** (72.9 g, 0.25 mol) in acetone (3.00 L) was added concentrated HCl (24.7 mL, 0.24 mol). After stirring for 1 h at room temp., a precipitate was formed, which was collected by filtration, washed with acetone and dried in vacuo. The amide **6b** was isolated as its HCl salt (61.7 g, 88%): ^{1}HNMR ([D$_6$]DMSO, 200 MHz): δ = 7.99–7.60 (m, 7 H), 5.02 (s, 1 H). Extraction of an aqueous solution of the HCl salt (pH, 10, 500 mL) with CH_2Cl_2 (3×200 mL) afforded the HCl-free product as an off-white, crystalline solid (41.2 g, 86% from **3b**): m.p. 163 °C. IR: $\tilde{\nu}$ = 3366, 3297, 3053, 1660, 1641, 1576, 1405, 1294 cm^{-1}. ^{1}HNMR (300 MHz, CD_3CN, 25 °C): δ = 7.94–7.78 (m, 4 H), 7.58–7.42 (m, 3 H), 6.89 (br. s, 1 H), 5.81 (br. s, 1 H), 4.56 (s, 1 H) ppm. ^{13}CNMR (75 MHz, CD_3CN, 25 °C): δ = 129.2, 128.8, 128.6, 127.3, 127.0, 126.8, 126.2, 118.4, 61.0 ppm. HRMS(EI) calcd. for $C_{12}H_{12}N_2O$ 200.0950, found 200.0945. R_f (Et_2O/heptane, 1:1) = 0.06.

Enzymatic Synthesis of (*S*)-(2-Naphthyl)glycine [(*S*)-2b] and (*R*)-(2-Naphthyl)glycine Amide [(*R*)-3b]: A solution of **3b** (78.8 g, 0.39 mol) in H_2O (3.00 L) was brought to pH 6.5 using aqueous KOH. After addition of aqueous $ZnSO_4$ (1.13 g, 3.9 mmol) and a cell-free extract containing the L-amidase from *Ochrobactrum anthropi* NCIMB 40321 in water (20 mL), water was added to attain a 2% suspension of the amide. The mixture was shaken for 18 h 30 at 50 °C. After cooling to room temp., the mixture was brought to pH 2.0 using aqueous H_2SO_4. The mixture was filtered to afford acid (*S*)-**2b** as a white solid (44.8 g including approximately 20% salts, 46%): since the amino acid was not soluble in any common solvent (D_2O, CD_3CN, CD_3OD, [D$_6$]DMSO), at this stage no spectroscopic data could be recorded. HRMS(EI) calcd. for $C_{12}H_{11}N_2O$ 201.0790, found 201.0783. The resulting clear filtrate was brought to pH 9 by addition of aqueous KOH (5 N), so that a precipitate was formed, which was collected by filtration, affording amide (*R*)-**3b** (25.8 g) as a white solid. The aqueous layer was then concentrated in vacuo to a volume of 1.5 L (pH, 9) and extracted in portions of 400 mL with CH_2Cl_2 (3×200 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, affording amide (*R*)-**3b** as a white solid (7.2 g). The combined batches afforded amide (*R*)-**3b** as a white solid (33.0 g, 43%): the *ee* was determined by ^{1}H NMR using (*S*,*S*)-DBTAAN[9] to be 80%: ^{1}HNMR (300 MHz, CD_3CN, 25 °C): δ = 7.94–7.78 (m, 4 H), 7.58–7.42 (m, 3 H), 6.89 (br. s, 1 H), 5.81 (br. s, 1 H), 4.56 (s, 1 H) ppm.

(*S*)-2-(2-Naphthyl)glycinol [(*S*)-7b]: To a suspension of acid (*S*)-**2b** (5.00 g, 25.0 mmol) in THF (350 mL) at 0 °C was added $LiAlH_4$ (10.2 g, 268 mmol) in portions. After refluxing for 18 h, the mixture was cooled to 0 °C and quenched through addition of H_2O (9 mL), aqueous NaOH (4 N, 9 mL) and H_2O (20 mL) over a period of 15 min. After stirring for 30 min at room temp., the mixture was filtered. The residue was washed with EtOAc (3×225 mL) and the combined filtrates were concentrated in vacuo to yield amino alcohol (*S*)-**7b** as a yellow foam (3.72 g, 81%): $[\alpha]_D^{25}$ = +39 (c = 0.59, $CHCl_3$) [ref.[7] for (*S*)-**7b** $[\alpha]_D^{25}$ = +33.9 (c = 1.39, $CHCl_3$)]. IR: $\tilde{\nu}$ = 3360–2863, 2358, 2336, 1597, 1048 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.87–7.72 (m, 4 H), 7.52–7.40 (m, 3 H), 4.20 (dd, ^3J(H,H) = 4.5, 8.1 Hz, 1 H), 3.82 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 10.5 Hz, 1 H), 3.63 (dd, $^3J_{H,H}$ = 8.1, $^2J_{H,H}$ = 10.5 Hz, 1 H) ppm. ^{13}CNMR (75 MHz, CD_3OD, 25 °C): δ = 139.4, 133.0, 132.6, 128.0, 127.5, 127.4, 125.9, 125.6, 124.9, 124.5, 67.7, 57.4 ppm.

***N*,*N*′-Bis[(*S*)-2-hydroxy-1-(2-naphthyl)ethyl]-2,2-dimethylpropanediamide [(*S*)-8b]:** A solution of amino alcohol (*S*)-**7b** (5.75 g,

30.8 mmol) and Et_3N (22 mL, 159 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C. A solution of 2,2-dimethylmalonyl dichloride[20a] (2.69 g, 15.8 mmol) in CH_2Cl_2 (70 mL) was added via a cannula. After stirring for 16 h, CH_2Cl_2 (200 mL) was added and the mixture was washed with aqueous HCl (1 N, 300 mL). The aqueous layer was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (300 mL) and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layers were washed with brine (300 mL) and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting brown solid was recrystallised from EtOAc, yielding diamide (*S*)-**8b** as an off-white solid (3.74 g, 52%): m.p. 160 °C. $[\alpha]_D^{25}$ = +122 (*c* = 0.55, $CHCl_3$). $[\alpha]_D^{25}$ = +99 (*c* = 0.20, 96% EtOH) [ref.[7] for (*S*)-**8b** $[\alpha]_D^{25}$ = +85.0 (*c* = 0.20, 95% EtOH)]. IR: $\tilde{\nu}$ = 3378, 2976, 2868, 2487, 1632, 1411, 1044 cm^{-1}. ^{1}HNMR (300 MHz, CD_3OD, 25 °C): δ = 7.74–7.61 (m, 8 H), 7.44–7.32 (m, 6 H), 5.22 (dd, $^3J_{H,H}$ = 4.8, 7.5 Hz, 2 H), 3.91 (dd, $^3J_{H,H}$ = 5.1, $^2J_{H,H}$ = 11.4 Hz, 2 H), 3.84 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 11.4 Hz, 2 H), 1.55 (s, 6 H) ppm. ^{13}CNMR (75 MHz, CD_3OD, 25 °C): δ = 175.4, 137.9, 134.4, 133.9, 128.9, 128.6, 128.3, 126.8, 126.5, 126.3, 125.6, 65.8, 57.3, 51.6, 24.4 ppm.

2,2-Bis[(*S*)-4-(2-naphthyl)-1,3-oxazolin-2-yl]propane [(*S*)-1b]: To a solution of (*S*)-**8b** (1.02 g, 2.20 mmol), DMAP (29 mg, 0.24 mmol) and triethylamine (1.52 mL, 10.9 mmol) in CH_2Cl_2 (55 mL) was added a solution of tosyl chloride (1.00 g, 5.25 mmol) in CH_2Cl_2 (25 mL) via cannula. After stirring at room temp. for 90 min, the mixture was washed with saturated aqueous NH_4Cl (85 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×85 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (170 mL), the aqueous layer was extracted with CH_2Cl_2 (3×130 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an off-white solid. Purification by column chromatography (EtOAc/heptane, 4:6) resulted in isolation of (*S*)-**1b** as a white solid (0.53 g, 55%). The product was purified by recrystallisation from EtOAc: m.p. 172 °C [ref.[7] for (*S*)-**1b** m.p. 173–174 °C]. $[\alpha]_D^{25}$ = –246 (*c* = 0.55, $CHCl_3$) [ref.[7] for (*S*)-**1b** $[\alpha]_D^{25}$ = –233 (*c* = 0.55, $CHCl_3$)]. IR: $\tilde{\nu}$ = 3049, 2977, 2939, 2897, 1653 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82–7.66 (m, 8 H), 7.47–7.31 (m, 6 H), 5.41 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 9.9 Hz, 2 H), 4.74 (dd, $^3J_{H,H}$ = 8.1, $^2J_{H,H}$ = 9.9 Hz, 2 H), 4.26 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H), 1.75 (s, 6 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.2, 139.4, 133.1, 132.7, 128.5, 127.7, 127.4, 125.9, 125.6, 125.4, 124.4, 75.4, 69.8, 39.2, 24.7 ppm. HRMS(EI) calcd. for $C_{29}H_{26}N_2O_2$ 434.1994, found 434.1988.

Methyl 2-(9-Anthryl)-2-(benzyloxycarbonylamino)acetate (12): To a solution of **11**[13] (0.93 g, 3.7 mmol) and anthracene (0.65 g, 3.6 mmol) in propionic acid (18 mL) at 0 °C was added concentrated sulfuric acid (2.0 mL, 10% v/v) dropwise and stirred for 1 h. The slightly yellow solution was poured into an ice/saturated aqueous $NaHCO_3$ mixture (100 mL) and extracted with CH_2Cl_2 (3×85 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (EtOAc/heptane, 1:5) resulted in isolation of methyl ester **12** as an off-white solid (1.0 g, 72%): m.p. 160 °C. IR: $\tilde{\nu}$ = 3369, 3051, 2958, 1728, 1714, 1518, 1306, 1221 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.50 (s, 1 H), 8.37–8.24 (m, 2 H), 8.05 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H), 7.63–7.52 (m, 2 H), 7.52–7.44 (m, 2 H), 7.35–7.29 (br. s, 5 H), 6.99–6.93 (m, 1 H), 6.04–5.97 (m, 1 H), 5.19–5.03 (m, 2 H), 3.64 (s, 3 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.1, 155.4, 135.4, 131.1, 129.3, 129.0, 128.7, 128.0, 127.7, 127.6, 127.2, 126.7, 124.6, 122.8, 67.0, 52.7, 52.1 ppm. HRMS(EI) calcd. for $C_{25}H_{21}NO_4$ 399.1471, found 399.1471. R_f (EtOAc/heptane, 2:1) = 0.45.

2-(9-Anthryl)-2-[(benzyloxycarbonyl)amino]ethanol (13): To a solution of methyl ester **12** (0.70 g, 1.76 mmol) in THF (20 mL) at 0 °C was added $LiBH_4$ (2.0 M *in* THF, 1.7 mL, 3.4 mmol). After stirring for 18 h at reflux, the reaction was quenched with EtOAc (2 mL) and saturated aqueous $NaHCO_3$ (3 mL). After addition of brine (30 mL), the reaction mixture was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The off-white solid obtained was crystallised from CH_2Cl_2/hexane, yielding CBz-protected amino alcohol **13** as a white, crystalline solid (0.59 g, 90%): m.p. 134 °C. IR: $\tilde{\nu}$ = 3322, 3057, 1695, 1533, 1525, 1251, 1063, 1032 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.46 (s, 1 H), 8.38 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H), 8.07–8.02 (m, 2 H), 7.58–7.52 (m, 2 H), 7.52–7.44 (m, 2 H), 7.38–7.27 (m, 5 H), 6.38 (dt, $^3J_{H,H}$ = 4.7, 8.2 Hz, 1 H), 5.76 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H), 5.21–5.07 (m, 2 H), 4.71–4.59 (m, 1 H), 4.15–4.07 (m, 1 H), 3.49 (br. s, 1 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$, 25 °C): δ = 155.2, 135.7, 131.5, 129.5, 128.7, 128.4, 128.3, 128.1, 127.9, 126.5, 125.1, 124.8, 123.8, 67.5, 67.2, 54.8 ppm. HRMS(EI) calcd. for $C_{24}H_{21}NO_3$ 371.1521, found 371.1521. R_f (EtOAc/MeOH, 9:1) = 0.69.

2-(9-Anthryl)glycinol·HCl (7c·HCl): To a solution of CBz-protected amino alcohol **13** (50 mg, 0.14 mmol) in EtOH (1.5 mL) was added aqueous LiOH (2.0 N, 1.5 mL, 3.0 mmol). After stirring for 2 h at reflux, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, yielding amino alcohol *rac*-**7c** as an off-white salt (33 mg, quant): IR: $\tilde{\nu}$ = 3380–2840, 2244, 1942, 1618, 1447, 1038 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.46 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H), 8.28 (s, 1 H), 7.95–7.86 (m, 2 H), 7.44–7.19 (m, 4 H), 5.51 (dd, $^3J_{H,H}$ = 5.0, 9.5 Hz, 1 H), 4.30 (t, $^2J_{H,H}$ = 10.3 Hz, 1 H), 3.84 (dd, $^3J_{H,H}$ = 5.0, $^2J_{H,H}$ = 10.9 Hz, 1 H) 2.81 (br. s, 3 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$, 25 °C): δ = 131.4, 129.3, 128.2, 127.8, 127.2, 126.7, 125.5, 124.5, 66.0, 53.0 ppm. A solution of *rac*-**7c** in EtOAc was added to aqueous HCl (2 N) to form the corresponding HCl salt *rac*-**7c**·HCl as an off-white solid (38 mg, 80%): m.p. 186 °C. IR: $\tilde{\nu}_{max}$ = = 3399, 3205, 2950, 2894, 1627, 1519, 1057 cm^{-1}. ^{1}HNMR (300 MHz, CD_3OD, 25 °C): δ = 8.63 (s, 1 H), 8.38 (d, *J* = 9.0 Hz, 2 H), 8.12 (d, *J* = 8.4 Hz, 2 H), 7.72–7.63 (m, 2 H), 7.58–7.50 (m, 2 H), 5.95 (dd, *J* = 4.8, 9.6 Hz, 1 H), 4.64 (dd, *J* = 9.9, 11.7 Hz, 1 H), 4.09 (dd, *J* = 4.8, 12.0 Hz, 1 H) ppm. ^{13}CNMR (75 MHz, CD_3OD, 25 °C): δ = 132.7, 131.3, 131.2, 130.8, 128.3, 126.0, 125.4, 123.7, 63.3, 54.2 ppm. HRMS(EI) calcd. for $C_{16}H_{15}NO$ 237.1154, found 237.1155. R_f (EtOAc/heptane, 3:1) = 0.2–0.5. Separation of the enantiomers was accomplished by preparative chiral HPLC analysis (chiralpak AD column; heptane with 0.5% EtOH and 0.2% Et_3N): the enantiomeric excess was determined by HPLC on a Chiralpak AD column (heptane with 5% EtOH and 0.2% $EtNH_2$, 0.5 mL/min): t_R = 39.3 min (*R*)-**7c**·HCl (90% *ee*): $[\alpha]_D^{25}$ = +27 (*c* = 0.28, MeOH); t_R = 44.1 min (*S*)-**7c**·HCl (98% *ee*): $[\alpha]_D^{25}$ = –28 (*c* = 0.25, MeOH).

***N*,*N*′-Bis[(*S*)-2-hydroxy-1-(9-anthryl)ethyl]-2,2-dimethylpropanediamide [(*S*)-8c]:** To a solution of amino alcohol (*S*)-**7c**·HCl (40 mg, 0.17 mmol) and Et_3N (59 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added 2,2-dimethylmalonyl dichloride[20a] (14 mg, 84 μmol). After stirring for 16 h, the reaction mixture was quenched with H_2O (1 mL), CH_2Cl_2 (10 mL) was added and the mixture was washed with aqueous HCl (1 N, 5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with H_2O (10 mL) and the aqueous layer was extracted

with CH_2Cl_2 (5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (acetone/CH_2Cl_2, 1:4 to 1:2) resulted in isolation of (*S*)-**8c** as an off-white solid (74 mg, 77%): $[\alpha]_D^{25} = -55$ (*c* = 1.6, MeOH). IR: $\tilde{\nu}_{max}$ = = 3500–3100, 2924, 2250, 1658, 1502, 1260, 1031 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.39 (s, 2 H), 8.32 (d, *J* = 9.0 Hz, 4 H), 7.97 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H), 7.75 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H), 7.57–7.36 (m, 6 H), 6.56–6.47 (m, 2 H), 4.61 (dd, $^3J_{H,H}$ = 8.7, $^2J_{H,H}$ = 11.7 Hz, 2 H), 4.26 (br. s, 2 H), 4.05 (dd, $^3J_{H,H}$ = 3.9, $^2J_{H,H}$ = 11.7 Hz, 2 H), 1.38 (s, 6 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$, 25 °C): δ = 131.5, 129.5, 129.0, 128.7, 126.5, 124.8, 123.5, 66.8, 54.1, 49.9, 23.8 ppm. R_f (EtOAc/heptane, 2:1) = 0.29.

2,2-Bis[(*S*)-4-(9-anthryl)-1,3-oxazolin-2-yl]propane [(*S*)-1c]: To a solution of diamide (*S*)-**8c** (32 mg, 56 μmol) in CH_2Cl_2 (1 mL) at –78 °C was added (diethylamino)sulfur trifluoride (22 μL, 0.17 mmol). After stirring at room temp. for 10 min, CH_2Cl_2 (10 mL) was added, the mixture was washed with saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with saturated aqueous H_2O (5 mL), the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an off-white solid. Purification by column chromatography (EtOAc/heptane, 1:3 to 1:2) resulted in isolation of (*S*)-**1c** as a white solid (28 mg, 93%), which was directly used for catalysis: IR: $\tilde{\nu}_{max}$ = = 3500–3050, 3047, 2982, 2921, 1649, 1145 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.42 (s, 2 H), 8.37 (d, $^3J_{H,H}$ = 9.9 Hz, 4 H), 8.00–7.94 (m, 4 H), 7.39–7.34 (m, 8 H), 6.81 (t, $^2J_{H,H}$ = 10.8 Hz, 2 H), 5.01 (dd, $^3J_{H,H}$ = 8.4, $^2J_{H,H}$ = 11.4 Hz, 2 H), 4.74 (dd, $^3J_{H,H}$ = 8.4, 10.8 Hz, 2 H), 1.84 (s, 6 H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.4, 131.5, 130.0, 128.6, 128.3, 126.7, 125.7, 124.5, 123.7, 73.8, 39.6, 24.5 ppm. R_f (EtOAc/heptane, 1:3) = 0.23.

Representative Experimental Procedure for the Tandem Reaction to Chromane 16: To a flame-dried Schlenk tube was added $Mg(OTf)_2$ (8.0 mg, 0.025 mmol) and (*S*)-1-Np-box (12 mg, 0.028 mmol). The mixture was dried in vacuo for 0.5 h and distilled anhydrous toluene (0.5 mL) was added. After stirring for 0.5 h, **15** (58 mg, 0.25 mmol) and *N*,*N*-dimethyl-*p*-toluidine (3.6 μL, 0.025 mmol) were added and the mixture was cooled to 0 °C. After addition of **14** (55 μL, 0.50 mmol), the mixture was stirred overnight at 0 °C. Flash chromatography (Et_2O/pentane, 1:4) afforded **16** as a colourless oil (77 mg, 89%): the *ee* was determined by HPLC to be 73%: OD column; hexane/*i*PrOH, 95:5; 1.0 mL/min; t_R(major) = 12.9 min, t_R(minor) = 14.4 min. $[\alpha]_D^{25}$ = +0.28 (*c* = 0.63, $CHCl_3$, 73% *ee*). ^{1}HNMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31 (dt, $^3J_{H,H}$ = 2.0, 8.4 Hz, 2 H), 7.19 (dt, $^3J_{H,H}$ = 2.0, 8.4 Hz, 2 H), 6.60 (dd, $^3J_{H,H}$ = 0.8, 8.8 Hz, 1 H), 6.45–6.41 (m, 2 H), 4.43 (d, $^3J_{H,H}$ = 2.0 Hz, 1 H), 4.27 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 13.2 Hz, 1 H), 3.90 (s, 3 H), 3.74 (s, 3 H), 2.38 (td, $^3J_{H,H}$ = 2.0, $^2J_{H,H}$ = 13.2 Hz, 1 H), 2.24 (dd, $^3J_{H,H}$ = 5.6, $^2J_{H,H}$ = 13.2 Hz, 1 H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.3, 159.8, 152.4, 142.3, 132.9, 130.4, 130.1, 129.1, 117.4, 108.8, 102.1, 101.9, 94.6, 55.6, 55.5, 53.8, 36.9, 36.8 ppm. HRMS [M + Na] calcd. 371.0662; found 371.0665.

Representative Experimental Procedure for the Hetero-Diels–Alder Reaction to Pyran 19: To a flame-dried Schlenk tube was added $Cu(OTf)_2$ (10 mg, 28 μmol) and (*S*)-*t*Bu-box (9.0 mg, 31 μmol). The mixture was dried under vacuum for 0.5 h and distilled anhydrous THF (1.0 mL) was added. After stirring for 1 h, methyl pyruvate (**17**) (25 μL, 0.28 mmol) was added and the mixture was cooled to –78 °C. After addition of Danishefsky's diene **18** (72 μL, 0.34 mmol), the mixture was warmed up to room temp. overnight. Et_2O (10 mL) was added and the mixture was washed using saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, affording **19** as a slightly yellow oil (47 mg, 99%): the *ee* was determined by GC to be >95%: chiral γ-CD column (110 °C), t_R (minor) = 15.7 min (*R*), t_R(major) = 16.4 min (*S*). ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H), 5.58 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H), 3.68 (s, 3 H), 3.00 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H), 2.68 (d, $^2J_{H,H}$ = 16.5 Hz, 1 H), 1.49 (s, 3 H) ppm.

Representative Experimental Procedure for the Mukaiyama Aldol Reaction to Thioacetate 21: To a flame-dried Schlenk tube was added $Cu(OTf)_2$ (10 mg, 28 μmol) and (*S*)-*t*Bu-box (9.0 mg, 31 μmol). The mixture was dried under vacuum for 0.5 h and THF (1.0 mL) was added. After stirring for 1 h, methyl pyruvate (**17**, 25 μL, 0.28 mmol) was added and the mixture was cooled to –78 °C. After addition of silyl ketene acetal **20**[30] (83 μL, 0.34 mmol), the mixture was warmed up to room temp. overnight. Et_2O (10 mL) was added and the mixture was washed using saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/heptane, 1:9 to 1:4) afforded **21** as a colourless oil (58 mg, 89%): the *ee* was determined by HPLC to be 97%: OD column; hexane/*i*PrOH, 99:1; 0.5 mL/min; t_R(minor) = 14.9 min (*R*), t_R(major) = 16.0 min (*S*). ^{1}HNMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.80 (s, 3 H), 3.72 (br. s, 1 H), 3.08 (d, $^2J_{H,H}$ = 15.9 Hz, 1 H), 2.83 (d, $^2J_{H,H}$ = 15.8 Hz, 1 H), 1.45 (s, 9 H), 1.41 (s, 3 H) ppm.

Representative Experimental Procedure for the Allylic Substitution Reaction to Acetate 24: To a flame-dried Schlenk tube was added $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4.8 mg, 13 μmol) and (*S*)-Ph-box (13 mg, 39 μmol). The mixture was dried under vacuum for 0.5 h and distilled anhydrous CH_2Cl_2 (1.0 mL) was added. After stirring for 1 h, acetate **22**[31] (101 mg, 0.48 mmol), malonate **23** (0.14 mL, 1.2 mmol), bis(trimethylsilyl)acetamide (BSA) (0.30 mL, 1.8 mmol) and KOAc (2 mg, 20 μmol) were added and the mixture was stirred overnight. Et_2O (10 mL) was added and the mixture was washed using saturated aqueous NH_4Cl (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/heptane, 1:15) afforded **24** as a colourless oil (ca, 150 mg, >95%): the *ee* was determined by HPLC to be 96%: AD column; hexane/*i*PrOH, 90:10; 0.8 mL/min; t_R(minor) = 17.3 min (*S*), t_R(major) = 20.8 min (*R*). ^{1}HNMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.13 (m, 10 H), 6.45 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 6.30 (dd, $^3J_{H,H}$ = 8.4, 15.6 Hz, 1 H), 4.25 (dd, $^3J_{H,H}$ = 8.4, 10.8 Hz, 1 H), 3.93 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H), 3.69 (s, 3 H), 3.51 (s, 3 H) ppm.

Representative Experimental Procedure for the Mukaiyama Michael Reaction to Diester 26: To a flame-dried Schlenk tube was added $CuCl_2$ (7.3 mg, 54 μmol) and (*S*)-*t*Bu-box (17 mg, 59 μmol). The mixture was dried under vacuum for 0.5 h and distilled anhydrous CH_2Cl_2 (2.0 mL) was added. After stirring overnight, the solvent was removed in vacuo. The resulting fluorescent green solids were dissolved in CH_2Cl_2 (0.54 mL) and the flask was protected from light. After addition of $AgSbF_6$ (37 mg, 0.11 mmol), the mixture was stirred for 4 h at room temp. The white solids (AgCl) were removed by filtering the solution through an oven-dried glass pipette tightly packed with cotton. The resulting turquoise solution contained $Cu(SbF_6)_2$-*t*Bu-box catalyst complex (0.1 M *in* CH_2Cl_2). Alkylidene malonate **25**[32] (60 mg, 0.27 mmol) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (50 μL, 0.46 mmol) were dissolved

in toluene (0.7 mL) and the mixture was cooled to –78 °C. After addition of the $Cu(SbF_6)_2$-*t*Bu-box catalyst solution (0.1 M *in* CH_2Cl_2, 0.54 mL, 54 μmol), the mixture was stirring for 1 h at –78 °C. Silyl ketene acetal **20**[31] (0.10 mL, 0.41 mmol) was added and the mixture was warmed up to room temp. overnight. The mixture was concentrated in vacuo. Flash chromatography (EtOAc/heptane, 1:5) afforded **26** as a white solid (94 mg, 99%): the *ee* was determined by HPLC to be >90%: OD column; hexane/*i*PrOH, 98:2; 1.0 mL/min; t_R(major) = 14.1 min (*R*), t_R(minor) = 15.6 min(*S*). ^{1}HNMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.19 (m, 5 H), 3.95 (dt, $^3J_{H,H}$ = 5.4, 10.0 Hz, 1 H), 3.80 (t, $^3J_{H,H}$ = 10.0 Hz, 1 H), 3.75 (s, 3 H), 3.49 (s, 3 H), 3.01–2.84 (m, 2 H), 1.31 (s, 9 H) ppm.

Crystal Structure Determination of [$CuCl_2$(1-Np-box)]:[10] $C_{29}H_{26}Cl_2CuN_2O_2$, M = 569, crystallises in the orthorhombic space group $P2_12_12_1$, with a = 10.066(1) Å, b = 12.920(2) Å, c = 19.424(2) Å, V = 2526(1) Å^3, T = 120 K, Z = 4, μ = 1.106 mm^{-1}; 30861 reflections were measured, giving 7316 independent, of which 6592 with $I > 3\sigma(I)$ were used in the refinements. The internal agreement had R = 0.087, the final R = 0.028, Rw = 0.035, GOF = 1.21, for the significant reflections.

Crystal Structure Determination of [$CuCl_2$(2-Np-box)]:[10] $C_{29}H_{26}Cl_2CuN_2O_2$, M = 568.96, crystallises in the orthorhombic space group $P2_12_12_1$, with a = 11.7629(12) Å, b = 11.7891(6) Å, c = 19.4027(17) Å, V = 2690.7(4) Å^3, T = 208(2) K, Z = 4, μ = 1.039 mm^{-1}; 78222 reflections were measured, giving 4708 independent, of which 4050 with $I > 2\sigma(I)$ were used in the refinements. The internal agreement had R = 0.0623, the final R = 0.0465, Rw = 0.1155, GOF = 1.110, for the significant reflections.

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