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Asymmetric Allylic Substitution Catalyzed by C_1-Symmetrical Complexes of Molybdenum: Structural Requirements of the Ligand and the Stereochemical Course of the Reaction

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Dedicated to Professor Richard Heck on the occasion of his 75th birthday

Abstract: Application of new chiral ligands (*R*)-(−)-**12a** and (*S*)-(+)-**12c** (VALDY), derived from amino acids, to the title reaction, involving cinnamyl (linear) and isocinnamyl (branched) type substrates (**4** and **5** → **6**), led to excellent regio- and enantioselectivities (>30:1, ≤98% *ee*), showing that ligands with a single chiral center are capable of high asymmetric induction. The structural requirements of the ligand and the mechanism are discussed. The application of single enantiomers of deuterium-labeled substrates (both linear **38c** and branched **37c**) and analysis of the products (**41**–**43**) by $^2H\{^1H\}$ NMR spectroscopy in a chiral liquid crystal matrix allowed the stereochemical pathways of the reaction to be distinguished. With ligand (*S*)-(+)-**12c**, the matched enantiomer of branched substrate was found to be (*S*)-**5**, which was converted into (*R*)-**6** with very high regio- and stereoselectivity via a process that involves net retention of stereochemistry. The mismatched enantiomer of the branched substrate was found to be (*R*)-**5**, which was also converted into (*R*)-**6**, that is, with apparent net inversion, but at a lower rate and with lower overall enantioselectivity. This latter feature, which may be termed a "memory effect", reduced the global enantioselectivity in the reaction of the racemic substrate (±)-**5**. The stereochemical pathway of the mismatched manifold has been shown also to be one of net retention, the apparent inversion occurring through equilibration via an Mo–allyl intermediate prior to nucleophilic attack. Incomplete equilibration leads to the memory effect and thus to lower enantioselectivity. Analysis of the mismatched manifold over the course of the reaction revealed that the memory effect is progressively attenuated with the nascent global selectivity increasing substantially as the reaction proceeds. The origin of this effect is suggested to be the depletion of CO sources in the reaction mixture, which attenuates turnover rate and thus facilitates greater equilibrium. The linear substrate was also converted into the branched product with net *syn* stereochemistry, as shown by isotopic labeling. An analogous process operates in the generation of small quantities of linear product from branched substrate.

Keywords: allylic substitution · asymmetric catalysis · chiral ligands · deuterium labeling · memory effect · molybdenum

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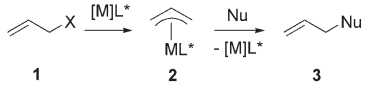
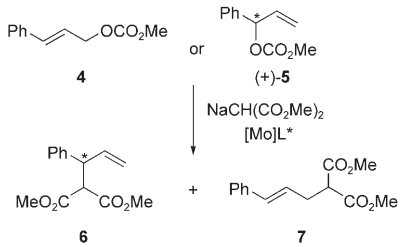
Introduction

The transition-metal-catalyzed allylic substitution reaction, starting with an allylic ester **1** (X = OCOR), involves an initial formation of the intermediate η^3-complex **2** (Scheme 1). The subsequent nucleophilic attack at the latter intermediate affords substitution product **3** with a concomitant release of the metal in its active form.[1] While Pd^0-catalyzed substitution with stabilized C nucleophiles proceeds via double inversion (*inv–inv*),[1,2] rather little is known about its Mo^0-catalyzed counterpart.[3] In the case of bicyclic allylic systems, we have shown that a double retention pathway (*ret–ret*) is operative.[4] However, the stereochemical outcome in this particular case may be dependent on the ligand(s), solvent, and the combination of the reacting partners. Therefore, the classical *inv–inv* pathway could not be excluded in less constrained systems such as the cinnamyl-type carbonates **4** and **5**. Interestingly, the stoichiometric reaction of the allylic systems, involving the isolation of the η^3 complex, is known to proceed via *ret–inv*.[5]



Scheme 1.

While this work was in progress,[6–9] Trost reported on the first examples of high asymmetric induction in Mo^0-catalyzed allylic substitution employing cinnamyl carbonates **4** and **5** and their aromatic and heteroaromatic counterparts (Scheme 2): with malonate-type nucleophiles and bis-α-picolinic amide **8** as the chiral ligand (see below), he attained excellent regio- and enantioselectivities (Table 1, entries 1 and 2).[10,11]



Scheme 2.

Shortly afterwards, Pfaltz designed analogous ligands with oxazoline units (e.g., **11**) in place of Trost's α-picolinic amide moieties.[12] As a follow-up, Moberg has demonstrated a further improvement of the reactivity of the Mo complexes of **8** by microwave heating.[13] Most recently, Hughes has illustrated the capability of Mo·**8** complex in the kinetic resolution of (±)-**5**.[14]

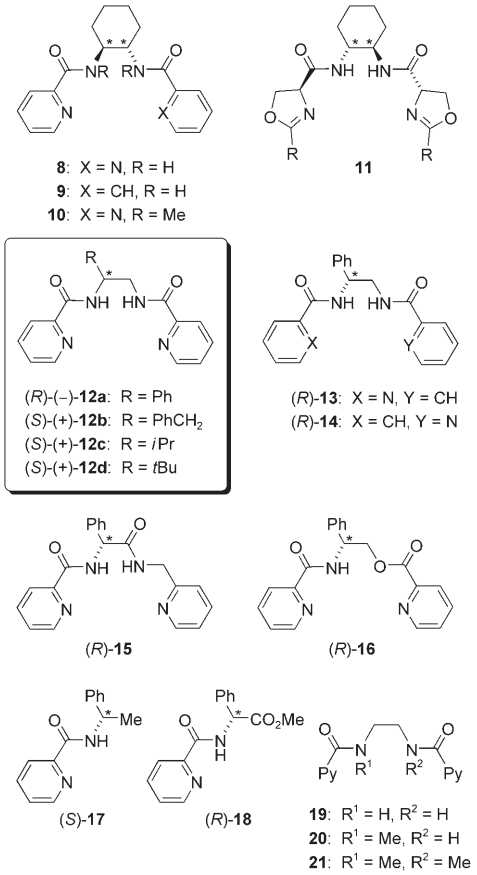
The Trost/Moberg and Pfaltz ligands **8** and **11** and their analogues, which facilitate the asymmetric Mo^0-catalyzed allylic substitution, are limited to one C_2-symmetrical scaffold, namely *trans*-1,2-diaminocyclohexane.[10,12,13] It can be hypothesized that the requisite chiral environment about the metal center might be secured just by one chiral center (rather than two) in the ligand, as in **12a–d** (see below), which may then be as effective as ligands **8** and **11**. This approach would take advantage of the chiral pool of amino acids as starting materials, most of which are now available in both enantiomeric forms at a comparable cost. The proof of this concept has been demonstrated in our preliminary communications[8] and further confirmed by the most recent work of Trost, Hughes, and Krska.[15] Herein, we present an orchestration of our original work and discuss mechanistic

Abstract in Czech: *Nové chirální ligandy (*R*)-(−)-**12a** a (*S*)-(+)-**12c** (VALDY), které jsou odvozené od aminokyselin, byly použity při allylové substituci katalyzované molybdenem v případě cinnamylových (lineárních) a isocinnamylových (rozvětvených) substrátů (**4** a **5** → **6**). Byla pozorována vysoká regioselektivita a enantioselektivita (>30:1, ≤98 %* ee*), což ukazuje, že jediné centrum chirality je schopno zajistit vysokou míru asymetrické indukce. Jsou diskutovány mechanismus reakce a strukturní požadavky na ligandy. Použití jednotlivých enantiomerů substrátů značených deuteriem (jak lineárních **38c** tak rozvětvených **37c**) a analýza produktů (**41**–**43**) pomocí $^2H\{^1H\}$ NMR spektroskopie v chirální kapalně krystalické fázi umožnily rozlišit reakční kanály lišící se z hlediska stereochemie. V případě ligandu (*S*)-(+)-**12c** je při reakci s rozvětveným substrátem souhlasným partnerem enantiomer (*S*)-**5**, který byl převeden na (*R*)-**6** s vysokou regioselektivitou a stereoselektivitou. V uvedeném případě dochází k celkové retenci konfigurace. Při reakci rozvětveného substrátu je nesouhlasným partnerem enantiomer (*R*)-**5**, který byl rovněž převeden na (*R*)-**6**. Reakce probíhá s celkovou inverzí konfigurace, pomaleji a s nižší enantioselektivitou. Pozorovaný jev může být nazván "pamět'ovým efektem" a projevuje se snížením celkové enantioselektivity při konverzi racemického substrátu (±)-**5**. Reakce mezi nesouhlasnými partnery probíhá s celkovou retencí konfigurace, kdy v dílčím kroku dochází k inverzi prostřednictvím ekvilibrace η^1–(allyl)Mo intermediátu ještě před nukleofilním atakem. Pokud tato ekvilibrace není úplná, uplatní se pamět'ový efekt, který pak vede k nižší enantioselektivitě. Z analýzy průběhu reakce nesouhlasných partnerů vyplývá, že je pamět'ový efekt postupně utlumován a nascentní enantioselektivita se zvyšuje tak, jak reakce postupuje. Původ tohoto efektu spočívá pravděpodobně v postupném zániku zdroje CO v reakční směsi, což se projeví snížením reakční rychlosti a tudíž usnadněním ekvilibrace. Lineární substrát rovněž podléhá přeměně na rozvětvený produkt s celkovou* syn *stereochemií, jak bylo ukázáno pomocí izotopového značení. Analogický proces se uplatňuje při vzniku malého množství lineárního produktu z rozvětveného substrátu.*

Table 1. Mo^0-Catalyzed allylic substitution (Scheme 2).[a]

Entry	Substrate	Ligand	R (ligand)	*t* [h]	Ratio[b] **6**:**7**	Yield [%]	*ee* **6** [%][c] (configuration)
1	**4**	(*R*,*R*)-**8**[d]	1,2-*c*Hex	3	32:1	88	99 (*S*)[f]
2	**5**	(*R*,*R*)-**8**[d]	1,2-*c*Hex	3	13:1	70	92 (*S*)[f]
3	**4**	(*R*)-**12a**[d]	Ph	4	8:1	63	92 (*S*)
4	**4**	(*R*)-**12a**[e]	Ph	4	8:1	65	92 (*S*)
5	**5**	(*R*)-**12a**[d]	Ph	4	12:1	72	88 (*S*)
6	**4**	(*S*)-**12b**[d]	$PhCH_2$	4	13:1	69	89 (*R*)[g]
7	**5**	(*S*)-**12b**[d]	$PhCH_2$	4	13:1	68	74 (*R*)[g]
8	**4**	(*S*)-**12c**[d]	*i*Pr	12	32:1	68	98 (*R*)[g]
9	**5**	(*S*)-**12c**[d]	*i*Pr	12	38:1	59	97 (*R*)[g]
10	**4**	(*S*)-**12d**[e]	*t*Bu	72	13:1	64	59 (*R*)[g,h]
11	**4**	(*R*)-**13**[d]	Ph	24	12:1	31	78 (*S*)
12	**4**	(*R*)-**14**[e]	Ph	24	9:1	51	89 (*S*)
13	**4**	(*R*)-**15**[d]		48	–	0	–
14	**4**	(*R*)-**16**[e]		24	1:1	29	10 (*S*)
15	**4**	(*S*)-**17**[d]	Ph	48	2:1	47	27 (*R*)
16	**4**	(*S*)-**18**[d]		3	1:1	57	5 (*R*)

[a] Conditions: THF, 60 °C, cat. 7–10 mol %. [b] Determined from the ^1H NMR spectra of the product mixtures. [c] Determined by chiral HPLC. [d] The catalyst was generated from $[(EtCN)_3Mo(CO)_3]$. [e] The catalyst was generated from $[(C_7H_8)Mo(CO)_3]$. [f] Refs. [10a, 15]. [g] Note that the ligand has the opposite absolute configuration to **12a**. [h] Determined by ^1H NMR with [D]-Eu(hfc)$_3$.

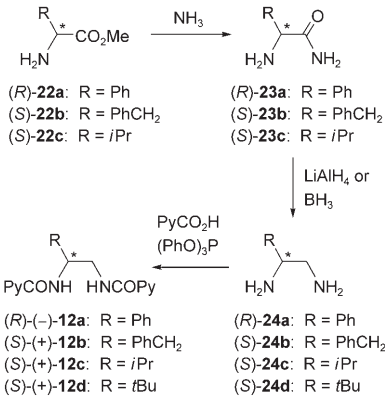


issues in light of our earlier and current results and of the mechanistic pictures proposed by others. A key outcome of this study is a) the full account of the structure–enantioselectivity relationship for the ligands coordinated to Mo; b) the demonstration that Mo-catalyzed allylation of cinnamyl-type substrates is a stereospecific process (net retention), with the linear and both enantiomers of the branched isomers of substrate all following the same stereochemical pathway; and c) that π–σ–π equilibration, and not Mo–Mo transfer, is the mechanism by which stereochemical convergence is achieved, thereby facilitating asymmetric induction through chiral ligand control.

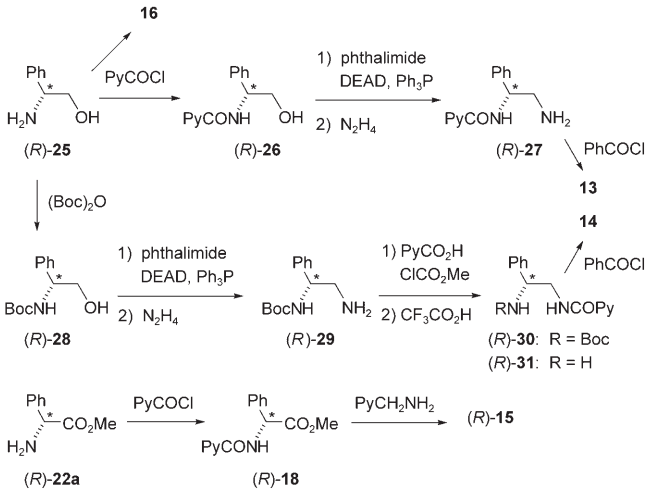
Results and Discussion

Although the mode of coordination of **8** and **11** to Mo in the active catalyst has not been firmly established,[10,15,16] there is a growing body of evidence that a tridentate, anionic, *fac*-binding mode is involved. By analogy, it can be argued that the R group in ligands **12** could act as an anchor, presumably occupying an "equatorial" position in the cyclic complex, thereby mimicking the rigid scaffold of **8**. We reasoned that the ligand performance may be tuned by varying the bulk of the anchor R with the goal of finding an optimal architecture of the whole framework. Therefore, we synthesized a set of ligands **12a–d**, derived from vicinal diamines, originating from amino acids with the varied side-chain R (phenylglycine, Phe, Val, and *t*Leu) and the analogues **13–21**.

Synthesis of ligands 12a–d: Ligand (*R*)-**12a** (Scheme 3) was readily prepared by conversion of methyl phenylglycinate (*R*)-**22a** into amide (*R*)-**23a** (aq. NH_3, toluene; 70 %),[17] followed by reduction ($LiAlH_4$, THF; 45 %),[18] and transformation of the resulting diamine (*R*)-**24a** into the desired bisamide (*R*)-(−)-**12a** [α-picolinic acid, $(PhO)_3P$, pyridine, 100 °C, overnight; 62 %].[19,20] The remaining members of the series, that is, (*S*)-**12b–d**, were synthesized in a similar fashion. Thus, the methyl ester of (*S*)-phenylalanine (*S*)-**22b** was converted into amide (*S*)-**23b** (aq. NH_3, toluene; 74 %);[17] its reduction (BH_3·THF, THF, 70 °C, 5 h) furnished diamine (*S*)-**24b** (76 %). The final acylation [α-picolinic acid, $(PhO)_3P$, pyridine, 100 °C, overnight][19] produced the desired bisamide (*S*)-(+)-**12b** (55 %). An analogous sequence, starting with the commercially available valine amide (*S*)-**23c** and proceeding through diamine (*S*)-**24c** ($LiAlH_4$, THF; 63 %) afforded on final acylation [α-picolinic acid, $(PhO)_3P$, pyridine, 100 °C, overnight] the isopropyl analogue (*S*)-(+)-**12c** (84 %). The *tert*-butyl ligand (*S*)-(+)-**12d** was prepared from the dihydrochloride of diamine (*S*)-**24d**[21] [2.0 equiv α-picolinic acid, 1-hydroxybenzotriazole (2.0 equiv), *N*-methylmorpholine (4.1 equiv), CH_2Cl_2, 0 °C, 5 min, then *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (2.2 equiv), 0 °C to RT, overnight, 44 %].[22]



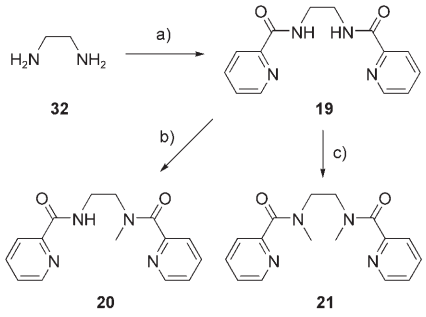
Scheme 3. Py = α-pyridyl.



Scheme 4. Ar = Ph or 4-$C_6H_4NO_2$.

The other required ligands were synthesized as follows (Scheme 4). Phenylglycinol (*R*)-**25** was acylated with α-picolinic acid chloride (Et_3N, CH_2Cl_2, RT, 2 h) and the resulting hydroxyamide **26** (69%) was converted into amino amide **27** by the Mitsunobu reaction (phthalimide, DEAD, Ph_3P, RT, overnight; 51%), followed by hydrazinolysis ($N_2H_4{\cdot}H_2O$, DMF, RT, overnight; 54%). Amine **27** thus obtained was acylated with PhCOCl (Et_3N, CH_2Cl_2, RT, 2 h) to afford the desired amide **13** (80%). In the synthesis of **14**, the straightforward route from **25** via N-benzoylation, followed by the Mitsunobu-type amination, could not be used since the benzamide derived from **25** underwent the $5(O)^{\pi,n}$–*exo-trig* cyclization[23] under the Mitsunobu conditions to produce the corresponding oxazoline. Therefore, the nitrogen in **25** was first protected by Boc group [$(Boc)_2O$, CH_2Cl_2, 0°C, 12 h] and the resulting N-protected amino alcohol **28** (96%) was submitted to the Mitsunobu reaction (phthalimide, DEAD, Ph_3P, 0°C to RT, 18 h), followed by hydrazinolysis (N_2H_4, EtOH, 80°C, 5 h) that afforded the monoprotected diamine **29** (48% overall). Acylation of **29** using the mixed anhydride method ($PyCO_2H$, $ClCO_2Me$, THF; 94%), followed by deprotection (CF_3CO_2H, RT, 2 h), furnished amino amide **31** (86%); benzoylation (PhCOCl, Et_3N, THF, 0°C, 2 h) afforded the required diamide **14** (49%). The "inverted" ligand **15** was prepared in two steps from methyl phenylglycinate **22a** via N-acylation (PyCOCl, Et_3N, CH_2Cl_2, RT, 2 h) to give (*R*)-**18** (89%), followed by aminolysis of the ester group ($PyCH_2NH_2$, NH_4Cl, 85°C, 2 h; 78%). Amide ester **16** was obtained via acylation of (*R*)-phenylglycinol (*R*)-**25** [PyCOCl (2 equiv), Et_3N, CH_2Cl_2, RT, 2 h; 67%). Finally, acylation of (*S*)-(−)-α-methylbenzylamine under the same conditions (PyCOCl, Et_3N, CH_2Cl_2, RT, 2 h) afforded (*S*)-**17** (72%).

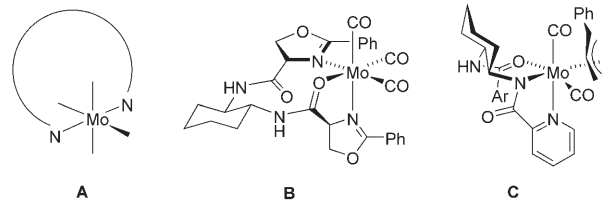
In order to further elucidate the role of the nature of the amide groups in the ligand, we prepared the nonchiral ligand **19** (Scheme 5) and its mono- and bismethylated analogues **20** and **21**. The parent diamide **19** was obtained by acylation of ethylene diamine **32**; selective mono- and bis-N-methylation afforded **20** (37%) and **21** (37%), respectively.



Scheme 5. a) 2.1 equiv $PyCO_2H$, 2.1 equiv $(PhO)_3P$, pyridine, 100°C, 24 h; 76%; b) 1.1 equiv NaH, DMF, 40°C, 45 min, then 1.1 equiv CH_3I, RT, 2 h, 37%; c) 2.2 equiv NaH, DMF, 40°C, 45 min, then 2.2 equiv CH_3I, RT, overnight, 37%.

Allylic substitution catalyzed by complexes of Mo^0 with ligands 12a–d: Cinnamyl and isocinnamyl carbonates **4** and **5** were employed in conjunction with malonate nucleophile $NaCH(CO_2Me)_2$ to probe the efficiency of ligands **12a–d** (Scheme 2, Table 1). The catalyst was generated in situ from $[(EtCN)_3Mo(CO)_3]$[24] or $[(C_7H_8)Mo(CO)_3]$[25] and the ligand in THF.[26] The reactions with $NaCH(CO_2Me)_2$, carried out in THF at 60°C, proved to be regio- and enantioselective in favor of the branched product **6** with good yields (entries 3 and 4).[27] The benzyl ligand (*S*)-(+)-**12b** (entries 6 and 7) turned out to exhibit rather lower enantioselectivity (74–89% *ee*)[28] than the phenyl derivative (*R*)-(−)-**12a** (compare entries 3–5 with 6 and 7). By contrast, the isopropyl ligand (*S*)-(+)-**12c** (VALDY)[29] gave much improved results (entries 8 and 9),[30] whereas the *tert*-butyl ligand (*S*)-(+)-**12d** performed worse than any other member of this series (entry 10). Some small differences were observed between the regioisomeric substrates **4** and **5** (e.g., compare entries 3 vs 5 and 8 vs 9) and identical results were obtained with the catalyst generated from $[(EtCN)_3Mo(CO)_3]$ and $[(C_7H_8)Mo(CO)_3]$ (compare entries 3 and 4).[26]

Structural features of the ligands relevant to catalysis: Ligands **8**, **11**, and **12** can offer a maximum of four ligating atoms, namely the pyridine nitrogens[31] and either the amidic carbonyl groups or nitrogen atoms. Trost originally proposed a bidentate coordination of ligand **8** to molybdenum with *trans*-configuration of the ligating nitrogens about the metal center (**A**, see below).[10] Pfaltz has reported an X-



ray structure of the complex obtained from ligand **11** and $[(EtCN)_3Mo(CO)_3]$, which shows a tridentate coordination **B** (with two sp^2 nitrogens and one carbonyl group involved in the coordination).[16] Most recently, Krska, Hughes and Trost have reported on the X-ray structure of the Mo–η^3-complex **C** (Ar = Ph), in which the binding to the deprotonated amidic nitrogen has been confirmed by solution ^{15}N NMR spectroscopy.[15] However, external nucleophilic attack on **C** would give rise to the "wrong" enantiomer of the product, which illustrates the difficulties associated with the mechanistic issues of this reaction.[32]

Ligand **13**, lacking one pyridine nitrogen atom, exhibited high enantioselectivity in the Mo-catalyzed reaction (Table 1, entry 11) but the conversion was lower.[33] Interestingly, monopyridine ligand **14** (with the pyridine moiety remote from the chiral center) exhibited higher reactivity and selectivity than its positional isomer **13** (entry 12). Similarly, Trost and Hughes[15b] have demonstrated good reactivity of the monopyridine derivative **9**. By contrast, ligands **15** and **16** turned out to be inferior (entries 13 and 14). Thus, **15** (a positional isomer of **12a**) failed to bring about the reaction, while **16** (an ester/amide) was non-selective and gave a practically racemic product in low conversion. Interestingly, the truncated analogue **17**, which can be regarded as "semi-**12a**", was found to catalyze the reaction (entry 15) with better selectivity than **16** and **18**. Finally, ligand **18** proved to be the most reactive in the series (57% yield in 3 h; entry 16), albeit giving a racemic product. These experiments show that 1) the original structural characteristics of the Trost–Moberg and Pfaltz ligands **8** and **11**, namely the two rigid amide groups, are essential for the reaction to occur and that 2) one chiral center in the scaffold is sufficient to induce high levels of enantioselectivity. Noteworthy is the enhanced reactivity of these Mo catalysts, as compared to the previously studied bipyridine and phenanthroline complexes.[31]

The comparison of the bispicolinic ligands **12** with the monopicolinic analogues **13** and **14** shows that the catalysts generated from the latter ligands react more slowly but retain high enantioselectivities. This behavior indicates a tridentate coordination as an essential feature in controlling the level of asymmetric induction. The enhanced reaction rate attained with bispicolinic amides **12** suggests that the additional sp^2 nitrogen increases the reactivity of the resting state of the catalyst, but has a minor effect on the stereoselectivity.

The role of the NH in the amide groups was assessed with the aid of the nonchiral ligand **19** and its mono- and bismethylated analogues **20** and **21**. Molybdenum complexes of ligands **19–21** were generated in situ in the same way as those of **12a–d** and employed as catalysts for the reaction of **4** with $NaCH(CO_2Me)_2$ under the same conditions (Scheme 2). Ligand **19** proved to react with a similar efficiency as its chiral counterparts **12a–d**, giving a 5:1 ratio of **6** and **7** (58% in 8.5 h).[34–37] Reduced catalytic activity was observed with the monomethylated ligand **20** (**6**/**7** 3.5:1; 42% in 41 h); bismethyl analogue **21** failed to promote the reaction. These results clearly demonstrate that at least one but preferentially two secondary amide functions (-CO-NH-) are crucial for the reaction to occur with a reasonable rate.[38] Similar observations were subsequently reported by Trost and Hughes,[15b] who employed the *N*,*N*′-dimethyl ligand analogue **10**.

The deprotonation of a secondary amide unit in **8** was demonstrated by Trost, Hughes and Krska using NMR spectroscopy.[15] The behavior of **19–21** sheds light on the question whether mono- or bisdeprotonation is required: The *N*,*N*-bismethyl ligand **21**, that cannot be deprotonated, is inert, whereas **20**, that can be mono-deprotonated reacts similarly to **19** (though more slowly). Hence, these observations can be regarded as indirect evidence in favor of monodeprotonation as the decisive factor in the reactivity of these bisamidic ligands, which is consistent with the ^{15}N NMR study.[15,39]

Using scalemic and racemic samples of ligand (*R*)-(−)-**12a**, we tested whether there is a linear or nonlinear relationship between the enantiomeric excess of the ligand and that of (*S*)-**6**, the product from the asymmetric Mo-catalyzed alkylation reaction.[40] As is evident in Figure 1, there is a small positive deviation from linearity resulting in a modest amplification of the *ee* of (*S*)-**6** (Figure 1, large data points). The simple shape of this curve, with maximum amplification (ca. 6% *ee*) when the ligand is of 40–50% *ee*, suggests that the nonlinear effect arises from equilibrium of "Mo(L)" with "$(Mo)_n(L)_2$", where $n=1$ (doubly ligated) or $n=2$ (dimeric species). Given the crystallographic evidence from Krska et al. of a $[Mo(CO)_2L(allyl)]$ intermediate[15b] and the above study, which strongly suggests that only ligands that can operate in a tridentate monoanionic coordination mode generate an active and selective species, it seems unlikely that complexes of the type "$(Mo)_n(L)_2$" would be involved in turnover. Nonetheless, such species could act as reservoirs of active "Mo(L)" species and if the homochiral form of "$(Mo)_n(L)_2$" is less stable than the heterochiral, then a positive nonlinear relationship would arise. Using the Kagan "reservoir" model[40e] [employing Equations (1), (2) and (3) in ref. [40a], with the limitation that $(Mo)_n(L)_2$ is catalytical-

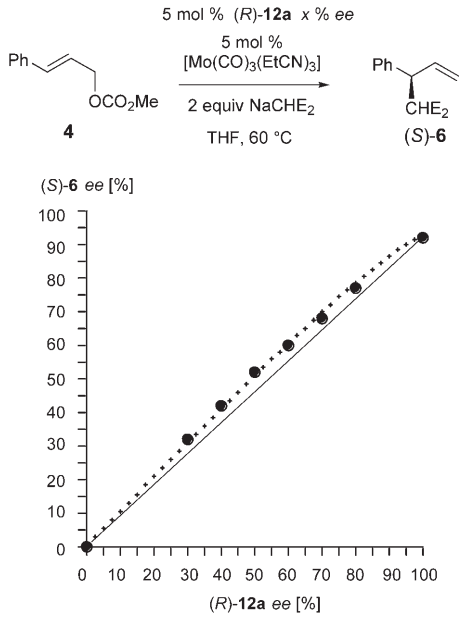
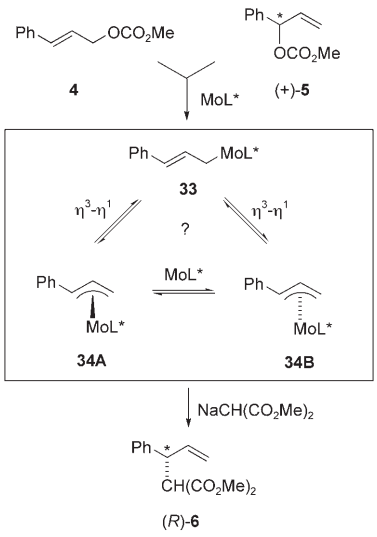


Figure 1. Non-linear relationship between the enantiomeric excess of ligand (*R*)-**12a** and branched product (*S*)-**6** obtained on asymmetric Mo-catalyzed allylic alkylation of **4**. ●: data points from experiments; -----: linear correlation; +: calculated relationship based on the Kagan "reservoir model" for ML_2 with $g=0$ and $K=0.06$.[39a]

ly inactive and thus $g=0$], the data may be fit by nonlinear regression to yield an equilibrium constant $K=0.06$ between Mo(L) and $(Mo)_n(L)_2$ (Figure 1, small data points). In an analogous series of experiments with ligand (*R*)-**14**, which bears just one picolinic amide group, no deviation from linearity was observed.

Determination of the net stereochemical pathways leading to asymmetric induction: Racemic isocinnamyl carbonate (±)-**5** proved to give similar but not identical regio- and enantioselectivities as its nonchiral counterpart **4** (Table 1, entries 1–3, 5–9). This behavior is in sharp contrast to W^0-catalyzed allylation, where asymmetric induction was only achieved with linear substrates, whereas the branched racemic substrates gave racemic product.[6] Indeed, it was later demonstrated that such reactions proceed with essentially perfect stereospecificity to give products of net retention.[3h] The observation that under the asymmetric Mo-catalyzed conditions, both enantiomers of **5** are converted into the same enantiomer of product, demonstrates that one enantiomer reacts with overall retention, while the other with inversion. This analysis indicates that either i) isomerization must occur in the case of the mismatched pair (of **5** and the chiral catalyst), either by prior inversion of **5** or at the stage of an intermediate, or ii) the enantiomers of **5** react with a Mo complex in an enantiodivergent manner, such that one reacts with inversion and the other with retention, to yield the same intermediate (Scheme 6). In the former case, isomerization can be conjectured to occur either via diastereofacial interconversion of the η^3-complexes **34A** and **34B** (which are diastereoisomeric by virtue of planar chirality)



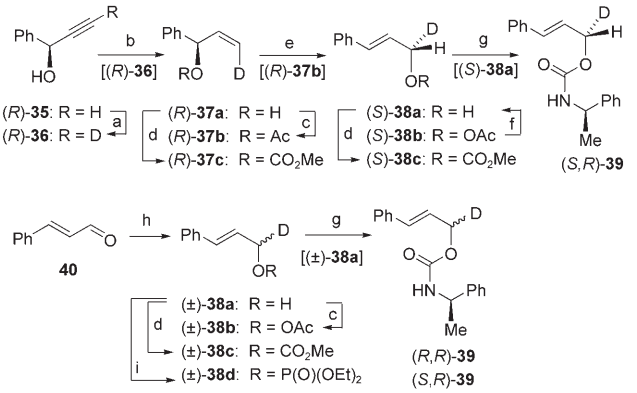
Scheme 6.

through the η^1-complex **33** (with a nonchiral allylic moiety) or via transfer of the allyl unit between Mo centers, as has been identified (in restricted cases) in Pd–allyl chemistry.[2b,41]

Interestingly, experimental evidence accumulated for the related W^0-catalyzed allylic substitution demonstrates that *isolable* η^3 complexes are not involved in the productive part of the catalytic cycle.[3h] As an alternative, one might consider η^1-type intermediates as the active component of the catalytic cycle. If a similar mechanistic picture were to apply to Mo, then **4** and both enantiomers of (±)-**5** would generate the same η^1-complex **33**[42] and the facial selectivity of the subsequent nucleophilic attack would be dictated by the chirality of the ligand. In such a manner, the enantio- and regioselectivity of the reaction should be independent of the identity of the substrate, that is there should be no "memory effect".[43] As can be seen in Table 1, for certain ligands, this is not the case with the linear and branched substrates giving different enantiomeric excesses and regioselectivities. Hughes et al. have reported on memory effects in the analogous reactions involving "Mo-**8**", with an efficient kinetic resolution accompanying the reaction of the racemic branched substrate (±)-**5**.[14] To test for kinetic resolution during the reactions catalyzed by the complexes bearing the C_1-symmetric type ligands described herein, we monitored the *ee* of **5** against conversion (*c*), starting with racemic substrate and employing an internal standard for chiral GC analysis. Nonlinear regression of the relationship of *c* versus *ee* for a series of data obtained with ligand (*S*)-**12c** (VALDY) yielded a selectivity factor, *s*, of 2 in favor of the reaction of (*S*)-**5** versus (*R*)-**5**. The selectivity was substantially lower than that observed with ligand **8**.[14] An analogous experiment with ligand (*R*)-**12a** yielded an *s* value of 3 [in favor of (*R*)-**5**, consistent with the use of the opposite configuration]. These experiments suggest that the slower reacting enantiomers are mismatched in chirality with the

catalyst and, if a memory effect is operating, will be processed with lower selectivity.[44]

In order to address the above mechanistic issues, in particular to elucidate the net stereochemical pathways and modes of stereochemical convergence (Scheme 6), we designed a stereospecific isotopic labeling strategy that would probe for π–σ–π equilibration in Mo–allyl intermediates. To study the pathways involving the branched substrate **5**, we deployed enantiomerically enriched samples of monodeuterated branched methyl carbonate **37c** where the deuterium atom is located in the *cis* position at the allylic terminus distal from the phenyl group (Scheme 7). To study the reac-



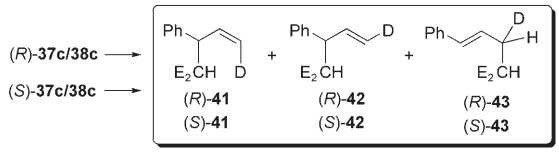
Scheme 7. a) D_2O, K_2CO_3, RT, 1 h; b) i) DIBAL-H, CH_2Cl_2, RT, 10 min; ii) $[Cp_2Zr(H)Cl]$, 0 °C, 10 min; c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25 °C, 3 h; d) $ClCO_2Me$, pyr, CH_2Cl_2, reflux, 18 h; e) 2.5 mol% $[(PhCN)_2PdCl_2]$, $CHCl_3$, 25 °C, 3.5 h; f) K_2CO_3, MeOH, 25 °C, 6 h; g) (*R*)-(+)-PhC(Me)N-CO, DMAP, toluene, reflux overnight; h) $NaBD_4$, MeOH, 0 °C, 10 min; i) $(EtO)_2P(O)Cl$, pyr, CH_2Cl_2, RT, 2 h.

tion of the *achiral* linear substrate **4**, we deployed enantiomers of the linear methyl carbonate **38c** in which the deuterium label at the allylic methylene introduces a stereocenter.

Synthesis of the isotopically labeled substrates was carried out as follows (Scheme 7). In the racemic series, the label was introduced in the first step by base-catalyzed H/D exchange of terminal acetylenic proton of **35**, which afforded the labeled propargyl alcohol **36** (69%; 98% ^2H by ^1H NMR). Hydroxyl deprotonation of the latter product with DIBAL-H, followed by hydrozirconation of the resulting propargylic alkoxide with Schwartz's reagent,[45] afforded the deuterio alcohol **37a** (79%; 98% $[^2H_1]$ by ^1H NMR) with >99% *Z* stereoselectivity as revealed by ^1H NMR spectroscopy [the level of the nondeuterated material was greater than the level of the (*E*)-deuterated product]. The latter alcohol was converted into the corresponding acetate **37b** (72%) and carbonate **37c** (67%). Palladium(II)-catalyzed rearrangement[46] of allylic acetate **37b** afforded the linear isomer **38b** (71%), in which no *Z* isomer was detected by ^1H NMR spectroscopy. The latter acetate **38b** underwent methanolysis to afford alcohol **38a** (70%) that was converted into the corresponding carbonate **38c** (63%) and phosphate **38d** (26%). Alternatively, racemic alcohol **38a** (95% ^2H by ^1H NMR) was obtained from cinnamaldehyde **40** by reduction (93%). Derivatization of alcohol **38a** with enantiopure (*R*)-(+)-α-methyl benzylisocyanate afforded two diastereoisomers of **39** (58%). These were used as a 0% *de* ^1H NMR standard for analysis of enantioenriched samples of **38a** after conversion into **39**, in which the diastereotopic protons at C1 display suitable dispersion [4.71 ppm in the C1-(*R*) diastereoisotopomer and 4.67 ppm in the C1-(*S*) diastereoisotopomer].

The same methodology was employed in the synthesis of enantiomerically enriched substrates **37c** and **38c**. Thus, the starting racemic alcohol (±)-**35** was resolved into enantiomers by Toda's method,[47] to obtain (*R*)-**35** (>95% *ee*) and (*S*)-**35** (>95% *ee*), whose conversion into the *cis*-deuteriated enantiomeric acetates (*R*)-**37b** and (*S*)-**37b** was carried out in analogy to the racemic counterpart (Scheme 7).[48] The Pd^{II}-catalyzed rearrangement of the latter enantiomers proved to occur stereospecifically,[46] affording the terminal acetates (*R*)-**38b** (≥95% *ee*) and (*S*)-**38b** (≥95%). The high enantiomeric excess of these latter samples was confirmed by ^1H NMR analysis of the corresponding carbamates (**39**), prepared from alcohols (*R*)- and (*S*)-**38a**, which in turn were obtained by methanolysis of the enantiomeric acetates **38b**. Alcohols (*R*)- and (*S*)-**38a** were then converted into the corresponding carbonates (*R*)- and (*S*)-**38c**.

With stereospecifically labeled substrates **37c** and **38c** in hand, we then developed a robust methodology for the analysis of the products arising from **37c**/**38c** in the Mo-catalyzed allylic substitution, that is, **41**, **42**, and **43** (Scheme 8),



Scheme 8. E = CO_2Me.

which form a six-component mixture. The analysis was facilitated by use of a chiral liquid crystal matrix (CLCM) consisting of a solution of polybenzyl-L-glutamate in CH_2Cl_2[49] in combination with chiral HPLC.

The anisotropy induced through partial ordering in the liquid crystal matrix causes quadrupolar coupling ($\Delta|\nu Q|$) to be manifested in the $^2H\{^1H\}$ NMR spectrum. By using a chiral matrix of the appropriate concentration and viscosity, the six components can, in principle, be resolved. In the event, the enantiomers of **41** and of **43** were both reasonably well resolved with average $\Delta\Delta|\nu Q|$ of 20 and 33 Hz, respectively. Although the technique did not resolve the enantiomers of **42**, the quadrupolar splitting of (±)-**42** was found to be much smaller ($\Delta|\nu Q| = 49$ Hz) than that of **41** ($\Delta|\nu Q|$ ca. 525 and 544 Hz) and of **43** ($\Delta|\nu Q|$ of ca. 693 and 726 Hz) and thus in a clear window of the $^2H\{^1H\}$ NMR spectrum. By knowledge of the global enantiomeric excess

(ee_g) of branched products (**41** and **42**), as measured by chiral HPLC, one may then deduce the enantiomeric ratio of (*S*)-**42** and (*R*)-**42**. Assignments of each of the five resolved components [that is, (*R*)-**41**, (*S*)-**41**, **42**, (*R*)-**43** and (*S*)-**43**] were made on the basis of reference mixtures (Figure 2). Although the quadrupolar couplings did vary between experiments (±4%) it was found that the changes were proportional across the five resolvable components and therefore spectra can be normalized to a basis set (see Experimental Section for full details). Thus, regioselective W-catalyzed alkylation ([$W(CO)_3(\eta^6\text{-}C_7H_8)$]/bipyridine)[3h] of branched carbonate (±)-**37c** gave *cis*-(±)-**41** with essentially no trace of *trans*-(±)-**42** (Figure 2, spectrum a). An analogous reaction, employing linear carbonate (±)-**38c**, prepared via simple reduction of cinnamaldehyde (**40**, Scheme 7), produced a mixture of (±)-**41** and (±)-**42**, thereby distinguishing **41** (enantiomers resolved) from **42** (Figure 2, spectrum b). To assign **41**, an asymmetric, W-catalyzed alkylation ([$W(CO)_3(\eta^6\text{-}C_7H_8)$]/phosphinoaryl oxazoline)[6] of phosphate (±)-**38d** was performed, which gave

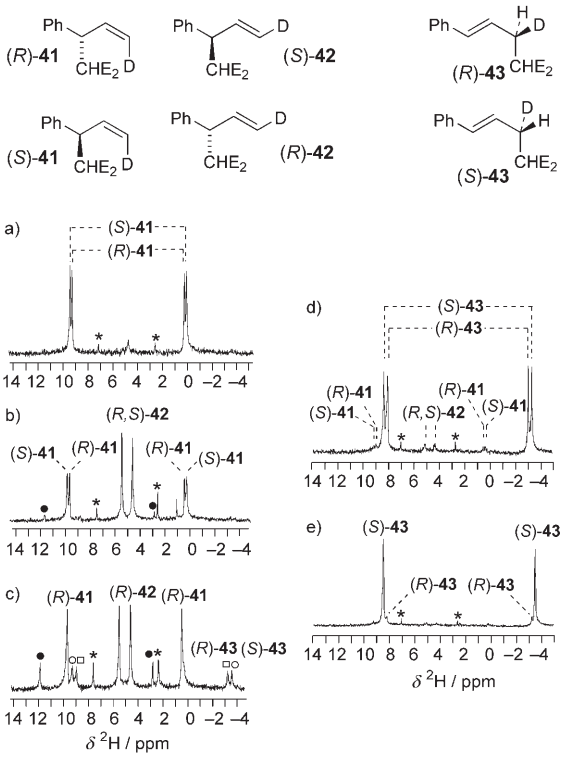


Figure 2. $^2H\{^1H\}$ NMR spectra (61.4 MHz) of reference samples of monodeuterated allylic alkylation products **41**, **42**, and **43** in a chiral liquid crystal matrix (CLCM) consisting of a ca. 5% w/w solution of poly-γ-benzyl-L-glutamate in CH_2Cl_2 at 23°C (*: $CDHCl_2$, ●: $CDCl_3$, ○: (*S*)-**43**, □: (*R*)-**43**). Differential partial ordering effects results in differential quadrupolar splittings ($\Delta|\nu Q|$) see experimental section for full details. Spectrum a, racemic *cis*-deuterated branched isomer [(±)-**41**]; spectrum b, racemic 1:1 mixture of *cis*-[(±)-**41**] and *trans*-[(±)-**42**] deuterated branched isomers; spectrum c, enantiomerically enriched (>90% *ee*) samples of a 1:1 mixture of *cis*-[(*R*)-**41**] and *trans*-[(*R*)-**42**] deuterated branched isomers, together with a small amount of the linear isomer (±)-**43**. Spectrum d, racemic sample of linear isomer [(±)-**43**]; spectrum e, enantiomerically enriched (>90% *ee*) sample of linear isomers (*S*)-**43**.

>90% *ee* samples of branched isomers (*R*)-**41** and (*R*)-**42**, together with some linear isomer (±)-**43** (Figure 2, spectrum c). A regioselective, Pd-catalyzed alkylation of (±)-**38b** afforded racemic linear (±)-**43** (Figure 2, spectrum d) and the analogous stereospecific Pd-catalyzed reaction of (*S*)-**38b** (95% *ee*) furnished enantiomerically enriched linear product (*S*)-**43** (95% *ee*) (Figure 2, spectrum e).

Having established an assay ($^2H\{^1H\}$ NMR in CLCM/chiral HPLC) for all six components of the anticipated product mixture, we tested the individual Mo-catalyzed reactions of the branched and linear ^2H-labeled carbonates (*R*)-**37c**, (*S*)-**37c**, (*R*)-**38c** and (*S*)-**38c** (all ca. 95% *ee* or greater) with $NaCHE_2$. The ligands (*R*)-(−)-**12a** and (*S*)-(+)-**12c** gave complementary results in terms of stereochemical outcome and "memory effect" (see below). Consequently, the discussion below is restricted to the case of (*S*)-(+)-**12c** (VALDY) which, being the more enantioselective ligand, was explored in greater detail. The experiments were conducted using [$Mo(CO)_3(\eta^6\text{-}C_7H_8)$] as the molybdenum source and, in contrast to the reactions reported in Table 1, the procatalyst solution [(*S*)-(+)-**12c** + the Mo source] was not heated before addition of substrate and $NaCHE_2$ in order to avoid decomposition.[50] After complete consumption of the substrate, followed by work-up and purification, the alkylation product mixture (**41**/**42**/**43**) was analyzed by chiral HPLC and $^2H\{^1H\}$ NMR using the CLCM method. The resulting spectra a–d are given in Figure 3.

Considering first the product mixtures obtained from the linear substrate **38c** (see spectra a and b in Figure 3), the minor product in both cases is, as expected, the linear isomer **43** (Scheme 9), with the branched products **41**/**42** ob-

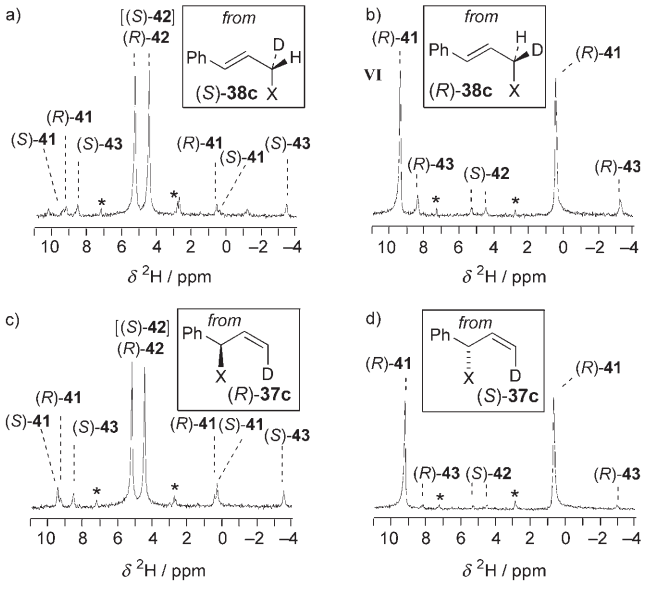
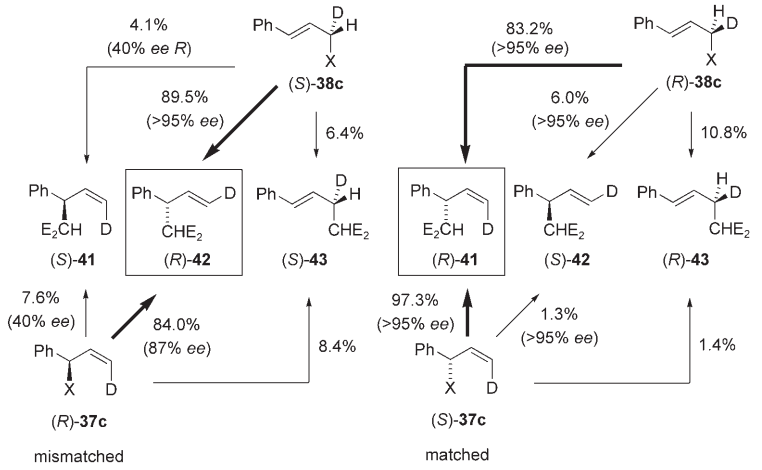


Figure 3. $^2H\{^1H\}$ NMR spectra (61.4 MHz) in a chiral liquid crystal matrix (CLCM) of samples of monodeuterated allylic alkylation products **41**, **42**, and **43** obtained from "Mo-(*S*)-**12c**"-catalyzed allylic alkylation of enantiomerically enriched (>95% *ee*) samples of (*S*)-**38c** (spectrum a); (*R*)-**38c** (spectrum b); (*R*)-**37c** (spectrum c); and (*S*)-**37c** (spectrum d). For product assignments and conditions, see Figure 2.



Scheme 9. Outcome from reactions of (*S*)-**38c**; (*R*)-**38c**; (*R*)-**37c** and (*S*)-**37c** with $NaCHE_2$ catalyzed by Mo/(*S*)-(+)-**12c** (see text for full details) according to analysis by chiral HPLC and $^2H\{^1H\}$ NMR (61.4 MHz) spectroscopy in a chiral liquid crystal matrix (CLCM; see Figure 3). Enantiomeric excesses of **41** and **43** are derived directly from NMR analysis. Enantiomeric excesses of **42** are deduced from the ratio (NMR)/global *ee* (HPLC) of the branched isomers **41**/**42**.

tained in 90–93% *global* enantioselectivity (ee_g, established by HPLC). However, it is immediately evident that the reactions are stereospecific since different sets of products are obtained from (*R*)-**38c** versus (*S*)-**38c** (spectra b and a, respectively). Using the reference spectra (Figure 2, d and e) it can be deduced that the reactions giving the linear products proceed with net retention at the allylic carbon. Thus (*S*)-**38c** gives (*S*)-**43** (Figure 3,a) and (*R*)-**38c** gives (*R*)-**43** (Figure 3, b). Whether the reactions proceed with complete stereofidelity is hard to establish as the low proportion of the linear isomer in the mixtures (7 ± 1%) precludes detection of **43** generated with net inversion of stereochemistry unless it contributes more than about 15% of the linear product and thus greater than about 1% of the overall product mixture. The major product in both cases is the branched isomer (**41**/**42**). Again, a stereospecific outcome is evident as enantiomeric substrates give enantiodivergent double bond geometry in the major component. Thus, (*S*)-**38c** gives the *E*-configured isotopomer (*R*)-**42** as the major product and in >95% *ee*, (Figure 3, a) with a trace of *Z*-configured (*R*)-**41** (the ratio **41**/**42** is ca. 1:22). It should be noted that the configuration and low *ee* value [40% (*R*)] of the minor product **41** arises from the non-enantiopure nature of the substrate [ca. 3% of (*R*)-**38c**]. With the opposite enantiomer of substrate (*R*)-**38c** (Figure 3, b) the double bond geometry of the major product is reversed and *Z*-configured (*R*)-**41** (>95% *ee*) is obtained together with a small proportion of *E*-configured (*S*)-**42** (>95% *ee*). As noted above, the configuration and *ee* of the minor product (**41**/**42** is ca. 14:1) is dependent on the enantiopurity of the substrate ((*R*)-**38c**), which in this case was higher (<1% (*S*)-**38c**) than its enantiomer (*S*)-**38c**. These outcomes demonstrate that the major (branched) isomer of product from the reaction of the linear substrate (compare **4**) is one in which the nucleophile is delivered *syn* to the leaving group with concomitant allylic transposition, or in other words, with overall net *retention* of allylic stereochemistry (Scheme 9).

The reactions of the branched substrates also proceeded, predominantly, by stereospecific processes. *Z*-Configured (*R*)-**37c** gives **41**/**42** in low global ee_g [74% (*R*), HPLC) together with ca. 8% of the linear isomer (*S*)-**43**, with no (*R*)-**43** detected (Figure 3, spectrum c). The stereochemistry of the generation of the linear isomer (*S*)-**43** from branched (*R*)-**37c** thus mirrors the reaction of linear (*S*)-**38c** in that the nucleophile is delivered *syn* to the leaving group, in this case with concomitant allylic transposition (overall "net retention"), as depicted in Scheme 9. The major branched product isomer is *E*-configured **42** [87% *ee* (*R*)] where the double bond geometry has been transposed. The minor branched isomer is *Z*-configured **41** (ratio **41**:**42** ca. 1:11) and is rich in the *S* enantiomer (40% *ee*) and thus of opposite configuration, lowering the global *ee* to 74%. The low enantio- and regioselectivity of the reaction confirms that the slower reacting (*R*)-**5** (see above) is indeed the *mismatched* enantiomer.

The reaction of enantiomeric (*S*)-**37c** gives the highest selectivity of all four substrates, with the branched products **41**/**42** obtained in 95% ee_g [(*R*), HPLC; Figure 3, spectrum d). The linear product **43** represents only 1.4% of the mixture and is of the opposite configuration [(*R*)-**43**] to that obtained from mismatched (*R*)-**37c**. The dominant species from the reaction is the *Z*-configured (*R*)-**41** generated in >95% *ee* (Scheme 9), with only a trace (1.3%) of *E*-configured (*S*)-**42** in which double bond geometry has been transposed.

From the above analysis it is clear that the dominant stereochemical pathways associated with the reaction of both of the enantiomers of the branched substrate **5** as well as the linear substrate **4** are related and are stereospecific. The reaction of the matched branched substrate (*S*)-**5** [(*S*)-**37c**] proceeds with net retention whilst the mismatched branched substrate (*R*)-**5** [(*R*)-**37c**] proceeds with *apparent* inversion (Scheme 9). The deuterium labeling reveals that both processes proceed with overall net retention, which involves an isomerization process at the Mo–allyl stage, resulting in double bond geometry being transposed in the major product from the mismatched substrate. The memory effect arises from this isomerization being incomplete and this then reduces the net global enantiomeric excess. Also of note is that the deployment of (*R*)-**37c** reveals that the reaction of the mismatched substrate (*R*)-**5** does not proceed with complete overall net retention since 8.5% of the

branched product arises from net inversion, a significantly higher level than the minor enantiomer (*S*)-**37c** present in the 95% *ee* substrate (i.e., ca. 2.5%). Experiments in which the unreacted substrate (*R*)-**37c** was recovered and analyzed prior to complete conversion indicate no *cis–trans* scrambling of the ^{2}H label. Furthermore, the *ee* versus *c* relationship observed in the kinetic resolution of (±)-**5** (see above) correlates well with the theoretical curve generated by $s = 1.8 = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$, suggesting that there is little or no inversion of the mismatched substrate during reaction. Control experiments confirmed that neither **4** nor **5** react with $NaCHE_2$ in THF at 60°C over a period of 18 h. To test whether a noncomplexed pre-catalyst, derived from $[Mo(CO)_3(\eta^6\text{-}C_7H_8)]$, might be responsible for a slow background reaction, we tested the reaction of **4** and of **5** with $NaCHE_2$ (E = CO_2Me; 2 equiv) in the presence of 10 mol% of $[Mo(CO)_3(\eta^6\text{-}C_7H_8)]$ in THF at 60°C over a period of 24 h. Only the linear substrate **4** reacted (24% conversion) and gave exclusively the linear product **7**. It therefore seems likely that with the *mismatched* substrate, a small proportion (ca. 5%) of the reaction proceeds via a net inversion process, analogous to stoichiometric examples,[5] and potentially arising from Mo–Mo transfer with inversion as a side reaction.

Having delineated the *net* stereochemical outcome over the complete reaction for the matched and the mismatched manifolds, we then returned to using racemic substrate so that we could study the reaction of interest, that is, how the Mo catalyst "Mo-(*S*)-**12c**" processes *racemic* (±)-**5** to give (*R*)-**6** in high enantioselectivity. By again employing the stereospecific labeling strategy, but using *racemic Z*-configured (±)-**37c**, we were able to track matched and mismatched manifolds simultaneously. The reaction was sampled at various intervals and the conversion and *ee* of the remaining **37c** was determined by chiral GC. This information then allowed the conversions of matched (*S*)-**37c** and mismatched (*R*)-**37c** to be deduced. A simple analysis of the alkene region of the ^{1}H NMR spectrum of the crude product mixture yields the *E*/Z ratio of the ^{2}H label in branched products, and thus the ratio of *E*-configured **42** to *Z*-configured **41**. Since the reaction of matched (*S*)-**37c** gives, over the whole course of reaction, essentially a single branched isotopomer [ca. 98.7% (*R*)-**41**], the ratio of (*S*)-**41**/(*R*)-**42** arising from the mismatched substrate (*R*)-**37c** is readily derived. A plot of conversion against mol fraction product (Figure 4) reveals that in the initial phases of reaction (<30% conversion) the mismatched substrate (*R*)-**37c** is converted predominantly into *Z*-configured (*S*)-**41** (and matched substrate into (*R*)-**41**) and hence reactions proceeds with a low global ee_g which is slightly augmented by the kinetic resolution (s = ca. 2) favoring the matched substrate and generating (*R*)-**41**.

However, after about 30% conversion, the generation of *Z*-configured (*S*)-**41** essentially ceased and the memory effect in the mismatched manifold thus disappeared. The enantiomeric excess of the nascent product from this point on is remarkably high. For example, from 0–46% conversion, the global enantioselectivity for branched products (**41**/**42**) is ee_g = 57% (*R*); in stark contrast, from 46–100% conversion the nascent enantioselectivity is about 96%, with global enantioselectivity at 100% conversion of ee_g = 80% (*R*). The magnitude of the memory effect in the mismatched manifold is controlled by the rate of equilibration of the Mo-intermediates relative to their rate of attack by nucleophile. During the reaction, factors which increase the former or decrease the latter will decrease memory and facilitate greater global enantiomeric excess. Clearly, the nucleophile concentration will drop during reaction. However, the use of two equivalents of $NaCHE_2$ suggests that the cessation of the memory effect is not related to this factor (at 30% conversion $[Nu]_t/[Nu]_0$ is 0.85). A co-product of the reaction is MeONa. This is known to be required to deprotonate the amido functionality, thereby engendering a selective and active molybdate type intermediate,[15b] and would not be present in the first stages of reaction. However, methoxide generated in excess of the catalyst stoichiometry should be protonated by the malonate C-H group of the nascent prod-

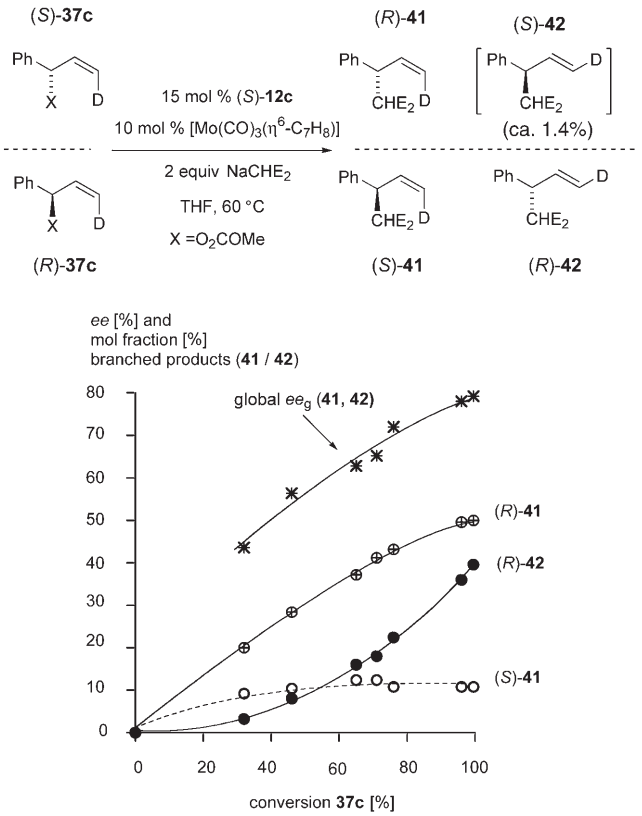


Figure 4. Graph depicting the evolution of a "Mo-(*S*)-**12c**"-catalyzed allylic alkylation of a racemic sample of *cis* monodeuterated branched allylic carbonate **37c** with conversion (by GC analysis with internal standard; *x* axis). The various mol fractions of the branched product isomers [(*R*)-**41**, (*S*)-**41**, and (*R*)-**42**] together with their global enantiomeric excess (ee_g) are plotted on the *y* axis. The quantities of (*S*)-**42** and linear **43**, generated in the reaction, are negligible. Ratios of (*R*)-**41**, (*S*)-**41**, and (*R*)-**42** are deduced from the *ee* and conversion of substrate (**37c**, by GC) and the ^{1}H NMR spectrum of the product mixture (using reactions of the single enantiomers of substrate, Figure 3, as reference).

ucts (**6**/**7**, or in this case **41**/**42**/**43**). Furthermore, in control experiments, deliberate addition of catalytic quantities of MeONa at the start of reaction did not result in increased equilibration and greater global enantiomeric excess.

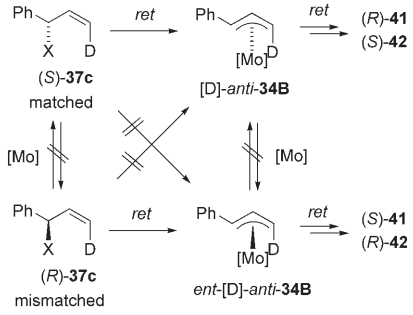
Krska et al.[15b] have identified that a CO source, such as $[Mo(CO)_6]$, is an essential component of the catalytic milieu. Indeed, the isolated Mo allyl complex {[(**8**)Mo(η^3-PhC_3H_4)$(CO)_2$], where **8** is deprotonated at N} only reacts with stoichiometric $NaCHE_2$ in the presence of 2 equiv CO (provided as either $[Mo(CO)_6]$ or as an atmosphere of $CO_{(g)}$) and this process generates **6** (95% *ee*) and [(**8**)$Mo(CO)_4$]Na. The latter complex was demonstrated to be an active carrier for catalysis. In the present system (Figure 4) the CO source must be co-generated during the formation of the active catalyst from the substrate, ligand, and Mo precursor. As the reaction is conducted at 60°C, the CO sources required for turnover, for example, $CO_{(g)}$ or $[Mo(CO)_6]$, will be slowly purged from reaction; the former by out-gassing, the latter by precipitation or sublimation. Reduced levels of CO source would lead to slower turnover with decreased rate of nucleophilic attack. Such a phenomenon would facilitate greater equilibration and thus reduced memory effect.

Conclusion

C_1-symmetric bispicolinamide ligands that bear a single stereogenic center in the linking 1,2-diaminoethane framework between two amide groups can, with the correct choice of substituent, facilitate Mo-catalyzed allylic alkylation of branched and linear cinnamyl-type substrates (cf **4** and **5**) with very high asymmetric induction and regioselectivity for the branched isomer of product (cf. **6** and **7**). Such ligands are readily derived from α-amino acids, for example, valinol (cf. **12c**), which are often available in both enantiomeric forms, thereby allowing access to either enantiomer of products of type **6**, where the Ar ring can be varied. Of the ligands studied, where R = Ph, Bn, *i*Pr, and *t*Bu, the valinol-derived ligand VALDY **12c** (R = *i*Pr) emerged as the most selective, while the closely related *tert*-leucine-derived ligand **12d** (R = *t*Bu) proved significantly poorer. This outcome mirrors the relationship between the amino-acid precursor and the activity/enantio- and regioselectivity observed in the analogous reactions catalyzed by W complexes bearing diphenylphosphinoaryl oxazoline ligands, where an *i*Pr substituent was found to be optimum and a *t*Bu substituent to give rather poor results.[6]

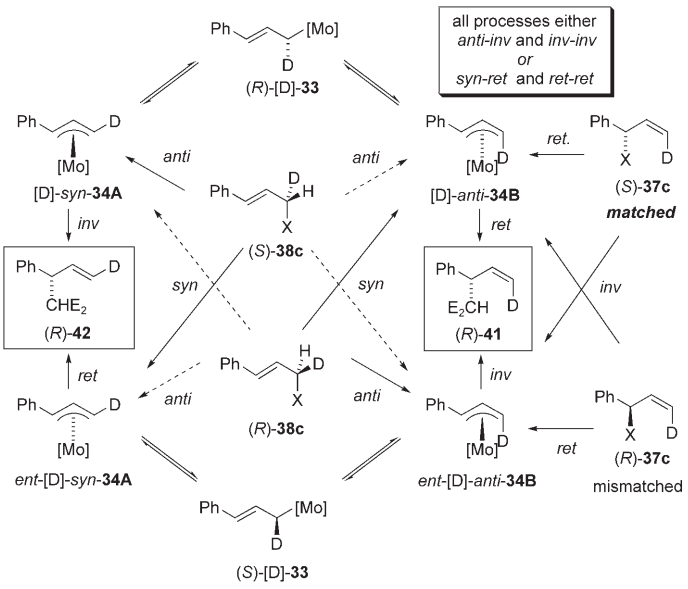
A systematic study of the structural components of ligands of type **12** demonstrates that only one of the amide groups need be picolinic in nature, the other can be a simple amide such as benzamide (cf. **13**, **14**). However, in such cases the stereogenic center is best located distal to the picolinamide on the diaminoethane linker and catalytic activity is reduced somewhat. Ligands not possessing two amide groups are less active and only poorly selective (cf. **16**, **17**). As has also been reported by Trost and Hughes et al.,[15a] at least one of the amido groups must be secondary such that deprotonation to generate an anionic ligand, and thus molybdate species, is possible. All of the above suggests that the ligands that are highly effective, such as VALDY **12c**, coordinate in a tridentate mode. This is fully consistent with the X-ray crystal structures and NMR-derived solution structures for Mo complexes bearing ligands **8**[15] and **11**,[16] which are in many ways analogous to those described herein. The detection of a nonlinear effect (Figure 1) indicates that two, or more, ligands may be accommodated at the Mo center. However, in view of the intermediacy of allylic complexes and the tridentate ligand requirements, complexes bearing two or more ligands are likely to be in equilibrium with the catalytic cycle rather than on it and may thus act as reservoirs.

Compared with analogous transformations involving Pd, where there has been extensive mechanistic investigation and the processes by which stereochemical convergence of chiral but racemic substrates are known in intimate detail, very little is known about asymmetric Mo-catalyzed allylations. The design and deployment of a stereospecific isotopic labeling technique, in which racemic and enantiomerically enriched substrates **37** and **38** are reacted and then the products **41**, **42**, and **43** analyzed by $^2H\{^1H\}$ NMR in a chiral liquid crystal matrix (CLCM), has allowed three important mechanistic features to be deduced. Firstly, the reactions are stereospecific and proceed with net retention of stereochemistry of the linear and both enantiomers of the branched substrates. These results demonstrate that the mismatched and matched branched substrates do not undergo enantiodivergent reactions on generation of the Mo–allyl intermediate and that there is no significant transfer of the allyl group (*inv*) between Mo centers, as exemplified for a retention based mechanism in Scheme 10.



Scheme 10.

Secondly, the reactions of the linear and both enantiomers of the branched substrates [**4** and (±)-**5**] all generate the same dominant regioisomer and enantiomer of product (Scheme 11), therefore the mechanism facilitates stereochemical and regiochemical convergence through equilibration of intermediates, for example, of type **34**. However, incomplete equilibration is evident (Figure 4), which then leads to a memory effect. This memory effect reduces enan-



Scheme 11.

tio- and regioselectivity in the manifold arising from mismatched branched substrate (*R*)-**5**, but is attenuated as reaction proceeds. The same manifold is also partially accessed by the linear substrate through imperfect enantiofacial selectivity on generation of the Mo–allyl intermediates (see dashed lines in Scheme 11). Thirdly, the involvement of the terminal allylic alkene carbon in the reaction of the branched substrates confirms that allyl Mo intermediates, in which the C3-allylic carbon is Mo-bound, must be involved in the generation of branched product from branched substrate. It is tempting to suggest that the regioselectivity arises from attack of an η^1-Mo allyl species, which is bound through the C3-allylic carbon (cf. **33** in Schemes 6 and 11). The asymmetric induction would arise then through diastereo-facial selectivity in an S_N2'-like reaction. However, if the allylic moiety were bound *trans* to the anionic amido moiety of the ligand, as would be consistent with the data of Krska and Hughes et al.[15] (see **C**), then there should be no memory effect since all precursors should lead to the same intermediate **33**, in which the allyl unit itself is achiral.[51] It therefore appears more likely that η^3-Mo allyl intermediates are involved. Of course, the equilibration of such intermediates may well involve η^1-bound Mo species, as outlined in Scheme 11, and the regioselectivity of the attack of the nucleophile on η^3 intermediates will undoubtedly be influenced by the complex electronic and steric parameters associated with pseudo-octahedral geometry, as well as the possibility of distorted η^3-binding modes.[42,52]

The net retention of stereochemistry observed in the linear/matched branched manifolds and the apparent inversion in the mismatched manifold, is indicative that either an *anti*/*inv–inv* sequence or a *syn*/*ret–ret* sequence is *exclusively* operative across all manifolds. There are clear analogies with reactions catalyzed by ligand **8**, where crystallographic and NMR data of [**8**·Mo(η^3-PhC_3H_4)$(CO)_2$] lead to the conclusion that an *inv–inv* sequence[32] would lead to the wrong sense of asymmetric induction. The alternative *ret–ret* mechanism, in which reductive elimination after attack of the nucleophile at the Mo center, or *syn*-attack of a "σ enyl" intermediate at the benzylic carbon, can be envisaged and would be consistent with our earlier demonstration of a *ret–ret* mechanism in a related Mo-catalyzed allylation reaction.[4] Although we have been unable to isolate intermediates from the present system, by employing the labeling techniques we have described, it should now be possible to find a suitable system whereby intermediates can be observed and identified and the *ret–ret* versus *inv–inv* issue addressed on the basis of NMR analysis.[32]

Moreover, a key outcome of the study reported herein, is that irrespective of whether the *anti*/*inv–inv* sequence or the *syn*/*ret–ret* sequence is operative, we have confirmed that diasteroisomeric intermediates are able to interconvert via a π–σ–π mechanism, involving diastereofacial exchange of the Ph–allyl moiety. Without this process, asymmetric catalysis of the allylic alkylation of cinnamyl substrates by "Mo(**12**)" would be limited to the linear substrates **4**, with kinetic resolution the only opportunity for asymmetric induction with the branched substrates **5**. This latter situation is exactly what was observed with the analogous reactions catalyzed by W complexes,[3h,7] which are thus much more limited in scope.

Experimental Section

General methods: Melting points were determined on a Kofler block and are uncorrected. The NMR spectra were recorded in $CDCl_3$, ^1H at 250, 270 or 400 MHz and ^{13}C at 62.9 or 100.6 MHz with $CDCl_3$ (δ 7.26, ^1H; δ 77.0, ^{13}C) as internal standard; 2D techniques were used to establish the structures and to assign the signals. ^2H NMR measurements were performed on a 400 MHz (^1H) spectrometer equipped with a selective 5 mm deuterium probe operating at 60 MHz. Conventional ^2H NMR spectra were run in CH_2Cl_2, using $CDCl_3$ (ca. 1%) as internal reference. ^2H NMR (60 MHz, CH_2Cl_2, 22 °C): δ ($CDHCl_2$) = 5.32 ppm, δ ($CDCl_3$) = 7.30 ppm. ^2H NMR spectra run in a chiral liquid crystal matrix were calibrated against the natural abundance $CDHCl_2$ doublet centered at δ 5.32 ppm. The deuterium content was determined by ^1H NMR and confirmed by ^{13}C NMR. The IR spectra were recorded for a solution in chloroform between NaCl plates unless otherwise stated. The EI and/or CI mass spectra were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. The GC-MS analysis was performed with RSL-150 column (25 m × 0.25 mm). The X-ray data were collected at 183 K on an Siemens Smart CCD diffractometer equipped with LT-2 low-temperature device and using $Mo_{K\alpha}$ radiation (λ = 0.71069 Å, graphite monochromator). Full sphere of reciprocal sphere was scanned by 0.3° steps in ω with a crystal-to-detector distance of 3.97 cm. Data were processed using SMART and SAINT software (Siemens AXS, Madison, Wisconsin, 1995) and empirically corrected for absorption and other effects using SADABS [G. M. Sheldrick, University of Göttingen (Germany), **1996**]. The structure was solved by direct methods and refined by full-matrix least-square technique using program suite SHELXTL [SHELXTL, version 5.10, Bruker AXS Inc., Madison, Wisconsin, **1997**]. Allylic substitution reactions were performed under an atmosphere of dry argon in oven-dried glassware at least twice evacuated and filled with argon. Solvents and solutions were transferred by syringe–septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before

use as follows: diethyl ether from lithium aluminum hydride, tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane from calcium hydride or alternatively were obtained freshly from an Anhydrous Technologies drying train. Where appropriate, tetrahydrofuran and dichloromethane were de-gassed (freeze–thaw cycles) and then saturated with nitrogen prior to use. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. $[(EtCN)_3Mo(CO)_3]$ and $[(\eta^6\text{-}C_7H_8)Mo(CO)_3]$ were prepared according to the literature procedures;[24] additionally a sample of $[(\eta^6\text{-}C_7H_8)Mo(CO)_3]$ was purchased from Strem Chemical Co. D_2O (>99.5% ^2H) was purchased from Cambridge isotope laboratories. $NaB[D_4]$ was purchased from Sigma-Aldrich; PBLG (polybenzyl-L-glutamate) (DP = 564) was purchased from Sigma. $[W(CO)_3(\eta^6\text{-}C_7H_8)]$ was synthesized according to a modified literature procedure.[53] All allylic carbonates are known compounds[3c] and were prepared by stirring the corresponding allylic alcohols with methyl chloroformate in pyridine followed by a standard workup. Yields are given for isolated product showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. Enantiopurity of the products was determined by HPLC on Diacel Chiralpak AD, Chiracel OJ, or Chiralcel OD-H using a hexane/2-propanol mixture as an eluent, or by ^1H NMR with [D]-Eu(hfc)$_3$ (for the ratios, see the individual experiments). Chiral GC was carried out with capillary columns FS-HYDRODEX β-3P.

(1*R*)-(−)-1,2-Bis[(2-pyridinylcarboxamido]-1-phenylethane [(*R*)-(−)-(12a)]: Phenylglycine amide (*R*)-(−)-**23a** was obtained by aminolysis of hydrochloride of (*R*)-(−)-phenylglycine methyl ester **22a** (2.30 g, 70%). ^1H NMR (CD_3OD): δ = 4.70 (s, 1H, CH), 5.06 (s, 4H, 2×NH_2), 7.53–7.70 (m, 5H, Ph); MS (ES): *m*/*z*: 173 $[M+Na]^+$, 151 $[M+H]^+$, in agreement with the literature data.[17] It was reduced with $LiAlH_4$ in THF at reflux for 18 h to afford diamine **24a** (620 mg, 45%). ^1H NMR: δ = 1.37 (brs, 4H, 2×NH_2), 2.81 (dd, *J* = 12.6, 7.1 Hz, 1H, 2-C*H*H), 2.92 (dd, *J* = 12.6, 5.3 Hz, 1H, 2-CH*H*), 3.89 (dd, *J* = 7.1, 5.3 Hz, 1H, 1-CH), 7.23–7.34 (m, 5H, Ph); MS (ES): *m*/*z*: 137 $[M+H]^+$, in agreement with the literature data.[18]

A solution of diamine **24a** (500 mg, 4.1 mmol) in pyridine (8 mL) was added to a solution of α-picolinic acid (1.0 g, 8.13 mmol) and $(PhO)_3P$ (2.52 g, 8.13 mmol) in pyridine (20 mL) at 80°C and the mixture was heated at 100°C overnight. The cooled solution was carefully poured into water (30 mL) and the resulting mixture was extracted with CH_2Cl_2 (2× 40 mL). After drying over $MgSO_4$ and removal of the solvent, the crude product was purified by chromatography on a silica gel column (15× 2.5 cm) with ethyl acetate as an eluent to give (*R*)-(−)-**12a** (880 mg, 62%) as a white solid. M.p. 166–168°C; $[\alpha]_D^{20} = -22.2$ (*c* = 1.4, $CHCl_3$); ^1H NMR: δ = 4.00 (m, 2H, CH_2), 5.44 (dd, *J* = 13.8, 7.8 Hz, 1H, CH), 7.26–7.49 (m, 7H, Ph + Py + Py′), 7.80 (tt, *J* = 7.8, 1.5 Hz, 2H, Py + Py′), 8.16 (t, *J* = 7.1 Hz, 2H, Py + Py′), 8.38 (brt, *J* = 4.5 Hz, 1H, NH), 8.50 (d, *J* = 4.8 Hz, 1H, Py), 8.57 (d, *J* = 4.6 Hz, 1H, Py′), 8.80 (brd, *J* = 8.0 Hz, 1H, NH); ^{13}C NMR: δ = 44.9 (CH_2), 54.6 (CH), 122.7 (Py, Py′, CH), 126.6 (Py, Py′, CH), 127.1 (Ph, 2×CH), 128.3 (Ph, CH), 129.3 (Ph, 2×CH), 137.6 (Py, Py′, CH), 140.0 (Ph, C), 148.5, 148.6 (Py, Py′, CH), 150.1 (Py, Py′, C), 164.9 (2×CO); IR (neat, KBr): $\tilde{\nu}$ = 3380 m, 2990 m, 1675 s, 1590 m, 1570 m, 1505 s, 1465 m, 1430 cm^{-1} m; MS (ES): *m*/*z*: 369 $[M+Na]^+$, 347 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{20}H_{19}N_4O_2$: 347.15080; found: 347.15082.

Crystal data for (*R*)-(−)-12a: $C_{20}H_{18}N_4O_2$, *M* = 346.38; colorless crystals were obtained from a CH_2Cl_2 solution; orthorhombic, space group $P2_12_12_1$; *a* = 5.8672(1), *b* = 16.0079(1), *c* = 18.134(1) Å, *V* = 1703.14(3) Å^3, *Z* = 4, ρ_{calcd} = 1.351 g cm^{-3}, μ = 0.090 mm^{-1}. A total of 24002 reflections were measured, 3539 of them unique (R_{int} = 0.0495), with 2847 having $I > 2\sigma(I)$. All 3539 reflections were used in the structure refinement based on F^2 by full-matrix least-squares techniques with hydrogen atoms calculated in theoretical positions, riding during refinement on the respective pivot atom (253 parameters). Final R_F = 0.040, R_w = 0.095 on F^2 for observed data. The estimated error in bond lengths is 0.002 Å.

CCDC-291520 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*S*)-(+)-1,2-Bis(2-pyridinylcarboxamido)-3-phenylpropane [(*S*)-(+)-(12b)]: (*S*)-Phenylalanine amide (*S*)-**23b** was obtained by aminolysis of hydrochloride of (*R*)-(−)-phenylalanine methyl ester (*S*)-**22b** (2.00 g, 74%). ^1H NMR: δ = 1.40 (brs, 2H, 2-NH_2), 2.73 (dd, *J* = 13.7, 9.6 Hz, 1H, 3-CH*H*), 3.28 (dd, *J* = 13.7, 4.1 Hz, 1H, 3-C*H*H), 3.62 (dd, *J* = 9.6, 4.1 Hz, 1H, 2-CH), 5.65 (brs, 2H, 1-NH_2), 7.28 (m, 5H, Ph); MS (ES): *m*/*z*: 187 $[M+Na]^+$, 165 $[M+H]^+$, in agreement with literature data.[17] A 1M solution of borane•THF complex in THF (50 mL) was added dropwise to a suspension of the latter amide (*S*)-**23b** (1.72 g, 10.5 mmol) in THF (25 mL) at 10°C. The mixture was stirred for 1 h at room temperature and than heated at reflux (70°C) for 5 h. The solution was cooled with ice, methanol (15 mL) was then added, and the mixture was stirred overnight. The solvent was removed in vacuo; 6M HCl (150 mL) was added, the mixture was heated at reflux (110°C) for 4 h, and then evaporated to dryness in vacuo. The residue was extracted with methanol (2× 50 mL); the methanolic solution was evaporated, the residue was treated with 1M aqueous KOH (150 mL), and then extracted with CH_2Cl_2 (4× 100 mL). The combined organic extracts were dried over K_2CO_3 and the solvent was evaporated to give the corresponding diamine (*S*)-**24b** (1.20 g, 76%) as a yellow oil. $[\alpha]_D^{20} = +8.2$ (*c* = 2.0, $CHCl_3$); ^1H NMR: δ = 1.14 (brs, 4H, 1-NH_2 + 2-NH_2), 2.36 (m, 2H, 3-CH_2), 2.64 (m, 2H, 1-CH_2), 2.79 (m, 1H, 2-CH), 7.15 (m, 5H, Ph); MS (ES): *m*/*z*: 151 $[M+H]^+$, in agreement with the literature data.[54] A solution of the latter diamine (*S*)-**24b** (1.20 g, 8 mmol) in pyridine (12 mL) was added to a solution of α-picolinic acid (1.97 g, 16 mmol) and $(PhO)_3P$ (4.96 g, 16 mmol) in pyridine (20 mL) at 80°C and the mixture was heated at 100°C overnight. The cooled solution was carefully poured into water (30 mL) and the resulting mixture was extracted with CH_2Cl_2 (2×40 mL). After the organic solvent was dried over $MgSO_4$ and removal of solvent in vacuo, the crude product was purified by chromatography on a silica gel column (15×2.5 cm) with ethyl acetate as an eluent to afford (*S*)-(+)-**12b** (1.59 g, 55%) as pale yellow solid. M.p. 117–118°C; $[\alpha]_D^{20} = +1.3$ (*c* = 2.1, $CHCl_3$); ^1H NMR: δ = 2.99 (dd, *J* = 14.0, 7.1 Hz, 1H, 3-C*H*H), 3.11 (dd, *J* = 14.0, 6.7 Hz, 1H, 3-CH*H*), 3.73 (m, 2H, 1-CH_2), 4.61 (m, 1H, 2-CH), 7.20–7.38 (m, 7H, Ph + Py + Py′), 7.77 (tt, *J* = 7.8, 1.6 Hz, 2H, Py + Py′), 8.14 (dd, *J* = 7.4, 6.7 Hz, 2H, Py + Py′), 8.40, 8.42 (2×brs, 2×1H, 2×NH), 8.50 (m, 2H, Py + Py′); ^{13}C NMR: δ = 39.2 (CH_2), 43.0 (CH_2), 51.8 (CH), 122.5, 122.6 (Py, Py′, 2×CH), 126.5 (Py, Py′, 2×CH), 127.0 (Ph, CH), 129.0 (Ph, 2×CH), 129.7 (Ph, 2×CH), 137.6, 137.6 (Py, Py′, 2×CH), 137.9 (Ph, C), 148.5, 148.6 (Py, Py′, 2×CH), 150.06, 150.09 (Py, Py′, 2×C), 165.0, 165.5 (2×CO); IR: $\tilde{\nu}$ = 3375 m, 2930 m, 1663 s, 1595 w, 1575 w, 1465 m, 1430 cm^{-1} m; MS (ES): *m*/*z*: 383 $[M+Na]^+$, 361 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{21}H_{21}N_4O_2$: 361.16645; found: 361.16653.

(*S*)-(+)-1,2-Bis(2-pyridinylcarboxamido)-3-methylbutane [(*S*)-(+)-(12c)]: The title compound was prepared in the same way as described above for (*R*)-(−)-**12a**. (*S*)-Valinamide hydrochloride (*S*)-**23c** (2.50 g, 16.4 mmol) was reduced with $LiAlH_4$ (1.90 g, 50 mmol) in THF (50 mL) to give diamine (*S*)-**15c** (1.05 g, 63%) as a yellow oil.[55] A solution of the latter diamine (*S*)-**24c** (1.05 g, 10.3 mmol) in pyridine (10 mL) was treated with α-picolinic acid (2.58 g, 21.0 mmol), $(PhO)_3P$ (6.52 g, 21.0 mmol) in pyridine (30 mL) and the reaction mixture was stirred at 100°C overnight to afford (*S*)-(+)-**12c** as white crystals (2.70 g, 84%). M.p. 94–95°C (MeOH); $[\alpha]_D^{20} = +353.0$ (*c* = 2.1, MeOH); ^1H NMR (CD_3OD): δ = 1.24, 1.27 (2×d, *J* = 7.0 Hz, 2×3H, 2×Me), 2.20 (m, 1H, 3-CH), 3.80 (dd, *J* = 13.5, 9.4 Hz, 1H, 3-C*H*H), 3.96 (dd, *J* = 13.7, 4.1 Hz, 1H, 1-CH*H*), 4.40 (m, 1H, 2-CH), 7.65–7.75 (m, 2H, Py + Py′), 8.05–8.22 (m, 4H, Py + Py′), 8.72, 8.83 (2×m, 2×1H, Py + Py′); ^{13}C NMR δ 19.1, 20.4 (2× Me), 32.3 (3-CH), 42.7 (CH_2), 55.8 (2-CH), 123.4, 123.6 (Py, Py′, 2×CH), 128.1, 128.2 (Py, Py′, 2×CH), 139.1, 139.2 (Py, Py′, 2×CH), 150.07, 151.1 (Py, Py′, 2×CH), 151.2 (Py, Py′, 2×C), 165.0 (2×CO); IR: $\tilde{\nu}$ = 3380 m, 2960 m, 1660 s, 1592 w, 1572 w, 1460 w, 1430 cm^{-1} w; MS (ES): *m*/*z*: 335 $[M+Na]^+$, 313 $[M+H]^+$; HRMS (FAB): *m*/*z*: calcd for $C_{17}H_{21}N_4O_2$: 313.16645; found: 313.16649.

(*S*)-(+)-1,2-Bis(2-pyridinylcarboxamido)-3,3-dimethylbutane [(*S*)-(+)-(12d)]: *N*-Methylmorpholine (630 μL, 5.730 mmol, 4.1 equiv) was added to a suspension of dihydrochloride of (*S*)-3,3-dimethyl-1,2-butanediamine **24d**[21] (264 mg, 1.396 mmol, 1.0 equiv), α-picolinic acid (347 mg, 2.819 mmol, 2.0 equiv), and 1-hydroxybenzotriazole (380 mg, 2.812 mmol, 2.0 equiv) in dry CH_2Cl_2 (20 mL) under nitrogen. The mixture was cooled to 0 °C and a solution of *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride (594 mg, 3.098 mmol, 2.2 equiv) in dry CH_2Cl_2 (20 mL) was added over a period of 3 min. The mixture was stirred at 0 °C to room temperature for 16 h to obtain a clear solution. The solvent was evaporated in vacuo; the residue was purified by flash chromatography on a silica gel column (15×2.5 cm) with an ethyl acetate/methanol 96:4 to afford pure (*S*)-(+)-**12d** as an oil that slowly solidified (200 mg, 44 %). $[\alpha]_D^{20} = +84$ (*c* = 0.61, CH_2Cl_2); ^{1}H NMR: δ = 1.10 [s, 9H, $(CH_3)_3C$], 3.60 (ddd, *J* = 13.8, 10.8, 6.2 Hz, 1H, one H of $CHCH_2$), 3.87 (ddd, *J* = 13.8, 5.4, 3.3 Hz, 1H, one H of $CHCH_2$), 4.22 (dt, *J* = 10.6, 10.6, 3.2 Hz, 1H, $CHCH_2$), 7.33 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, arom.), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, arom.), 7.75 (dt, *J* = 7.7, 7.7, 1.7 Hz, 1H, arom.), 7.80 (dt, *J* = 7.7, 7.7, 1.7 Hz, 1H, arom.), 8.08 (dt, *J* = 7.8, 0.9, 0.9 Hz, 1H, arom.), 8.14 (dt, *J* = 7.8, 0.9, 0.9 Hz, 1H, arom.), 8.21 (br d, *J* = 10.6 Hz, 1H, NH), 8.31 (m, 1H, NH), 8.47 (dq, *J* = 4.8, 0.8, 0.8, 0.8 Hz, 1H, arom.), 8.56 (dq, *J* = 4.8, 0.8, 0.8, 0.8 Hz, 1H, arom.); ^{13}C NMR: δ = 27.0 (CH_3)$_3$C, 34.8 (CH_3)$_3C$, 41.0 (CH_2), 58.0 (CH), 122.4 (CH), 122.7 (CH), 126.3 (CH), 126.5 (CH), 137.4 (CH), 137.6 (CH), 148.5 (CH), 148.5 (CH), 150.0 (s, C), 150.2 (s, C), 165.4 (s, 2×C=O); IR: $\tilde{\nu}$ = 3376 w, 3019 vw, 3006 m, 2967 m, 1670 s, 1592 w, 1570 m, 1528 s, 1465 m, 1434 m, 1370 w, 1291 vw, 1240 w, 1160 vw, 1088 vw, 1041 vw, 998 w, 908 w, 818 cm^{-1} vw; HRMS (EI): *m*/*z*: calcd for $C_{18}H_{22}N_4O_2$: 326.17423; found: 326.17428.

(*R*)-(−)-1-(2-Pyridinylcarboxamido)-2-benzamido-1-phenylethane [(*R*)-(−)-(13)]: A solution of diethyl diazoacetate (1.44 g, 8.25 mmol) in THF (20 mL) was added dropwise to a suspension of hydroxyamide (*R*)-(−)-**26** (2.0 g, 8.25 mmol), phthalimide (1.21 g, 8.25 mmol) and triphenylphosphine (2.16 g, 8.25 mmol) in THF (40 mL) and the mixture was stirred at room temperature overnight. The mixture was then concentrated in vacuo and Et_2O (20 mL) was added to the residue to form a white precipitate. The precipitate was collected by filtration, washed with Et_2O, and dried in vacuo to afford crude phthalimido derivative (1.60 g, 51 %), which was used in the next step without further purification. ^{1}H NMR: δ = 4.26 (dd, *J* = 14.0, 4.1 Hz, 1H, CH*H*), 4.41 (dd, *J* = 14.0, 9.9 Hz, 1H, C*H*H), 5.79 (td, *J* = 9.4, 4.1 Hz, 1H, CH), 7.44–8.01 (m, 11H, Ph + Py + Ar), 8.22 (d, *J* = 7.8 Hz, 1H, Py), 8.82 (dm, *J* = 4.8 Hz, 1H, Py), 9.04 (br d, *J* = 8.2 Hz, 1H, NH); MS (ES): *m*/*z*: 394 [*M*+Na]$^+$, 372 [*M*+H]$^+$. The latter phthalimido derivative (1.58 g, 4.25 mmol) was dissolved in DMF (10 mL), hydrazine hydrate (250 mg, 5 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was then diluted with water (30 mL), extracted with CH_2Cl_2 (4×20 mL), the organic extracts were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was passed through a short silica gel column (5×2 cm) with a mixture of chloroform/methanol 9:1 to afford crude amine (*R*)-**27** (550 mg, 54 %), which was used in the next step without further purification. ^{1}H NMR: δ = 3.32 (m, 2H, CH_2), 5.38 (dt, *J* = 7.6, 5.3 Hz, 1H, CH), 7.42–7.72 (m, 6H, Ph + Py), 8.02 (td, *J* = 7.6, 1.6 Hz, 1H, Py), 8.38 (d, *J* = 7.8 Hz, 1H, Py), 8.78 (dm, *J* = 4.6 Hz, 1H, Py), 8.95 (br d, *J* = 7.5 Hz, 1H, NH); MS (ES): *m*/*z*: 242 [*M*+H]$^+$. The crude amine **27** (275 mg, 1.14 mmol) was dissolved in CH_2Cl_2 (20 mL) and triethylamine (555 mg, 5.5 mmol) was added, followed by a dropwise addition of a solution of benzoyl chloride (280 mg, 2 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and then water (20 mL) was added. The organic layer was separated and washed successively with water (20 mL), satd aq $NaHCO_3$ (20 mL) and water (20 mL), and dried over $MgSO_4$. The solvent was removed in vacuo and the oily residue was recrystallized on addition of Et_2O (3 mL). The resulting solid was recrystallized from a mixture of hexane/ethyl acetate to give (*R*)-(−)-**13** as white crystals (313 mg, 80 %). M.p. 183–184 °C (CH_2Cl_2/Et_2O); $[\alpha]_D^{20} = -60.0$ (*c* = 1.5, $CHCl_3$); ^{1}H NMR: δ = 3.98 (m, 2H, CH_2), 5.44 (m, 1H, CH), 7.27–7.49 (m, 10H, Ph + Ph′ + Py + NH), 7.77–7.87 (m, 3H, Ph′ + Py), 8.18 (d, *J* = 7.8 Hz, 1H, Py), 8.55 (dm, *J* = 4.8 Hz, 1H, Py), 8.73 (br d, *J* = 7.6 Hz, 1H, NH); IR: $\tilde{\nu}$ = 3360 m, 2960 m, 1658 s, 1485 m, 1460 m, 1435 cm^{-1} m; MS (FAB): *m*/*z* (%): 368 (8) [*M*+Na]$^+$, 346 (56) [*M*+H]$^+$, 307 (17), 289 (11), 211 (13), 154 (100), 136 (69), 105 (48), 102 (55), 89 (20), 77 (22); HRMS (FAB): *m*/*z*: calcd for $C_{21}H_{20}N_3O_2$: 346.1555; found: 346.1554.

(*R*)-(−)-1-Benzamido-2-(2-pyridinylcarboxamido)-1-phenylethane [(*R*)-(−)-(14)]: A solution of benzoyl chloride (0.45 mL, 3.8 mmol) in THF (3 mL) was added dropwise at 0 °C to a solution of crude amine (*R*)-**31** (640 mg, 2.65 mmol) in THF (20 mL) and triethylamine (560 mg, 5.5 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 2 h and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL); the organic layer was washed successively with water (20 mL), satd aq $NaHCO_3$ (20 mL) and again water (20 mL) and subsequently dried over $MgSO_4$. The solvent was removed in vacuo and the oily residue was purified by chromatography on a silica gel column (15×2.5 cm) with ethyl acetate/methanol 96:4 to afford pure (*R*)-(−)-**14** as white microcrystals (448 mg, 48 %). M.p. 180–182 °C (MeOH); $[\alpha]_D^{20} = -40.3$ (*c* = 1.1, $CHCl_3$); ^{1}H NMR: δ = 3.71 (ddd, *J* = 14.3, 5.9, 3.5 Hz, 1H, CH*H*), 3.96 (ddd, *J* = 14.3, 9.0, 7.6 Hz, 1H, C*H*H), 5.25 (m, 1H, CH), 7.18–7.42 (m, 9H, Ph + Ph′ + Py), 7.76–7.83 (m, 3H, Ph′ + Py), 8.13–8.16 (m, 2H, Py + NH), 8.41 (br s, 1H, NH), 8.45 (dm, *J* = 4.7 Hz, 1H, Py); ^{13}C NMR: δ = 45.4 (CH_2), 57.3 (CH), 122.7 (CH), 126.8 (CH), 127.0 (CH), 127.6 (CH), 128.0 (CH), 128.9 (CH), 129.2 (CH), 131.8 (CH), 134.1 (C), 137.8 (CH), 140.3 (C), 148.7 (CH), 149.4 (C), 167.2 (CO), 167.3 (CO); IR: $\tilde{\nu}$ = 1664 cm^{-1} s; HRMS (FAB): *m*/*z*: calcd for $C_{21}H_{20}N_3O_2$: 346.1555; found: 346.1554; elemental analysis calcd (%) for $C_{21}H_{19}N_3O_2$: C 73.03, H 5.54, N 12.17; found: C 72.84, H 5.49, N 11.68.

(*R*)-(−)-2-(2-Pyridinylcarboxamido)-2-phenyl-(2-pyridinylmethyl)acetamide [(*R*)-(−)-(15)]: A mixture of (*R*)-2-(pyridine-2-carbamido)-2-phenylacetic acid methyl ester (*R*)-**18** (350 mg, 1.3 mmol), 2-(aminomethyl)-pyridine (700 mg, 6.5 mmol) and ammonium chloride (27 mg, 0.5 mmol) was heated at 85 °C for 2 h. The mixture was cooled to room temperature and treated with CH_2Cl_2 (10 mL) to dissolve the solid; the solution was washed with water (2×15 mL) and the organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was recrystallized by addition of a hexane/ethyl acetate 3:1 (5 mL). The white crystals were collected by filtration, washed with Et_2O, and dried in vacuo to afford (*R*)-(−)-**15** (350 mg, 78 %). M.p. 125–127 °C (decomp); $[\alpha]_D^{20} = -0.2$ (*c* = 1.8, $CHCl_3$); ^{1}H NMR: δ = 4.51 (dd, *J* = 16.3, 5.0 Hz, 1H, CH*H*), 4.63 (dd, *J* = 16.3, 5.3 Hz, 1H, C*H*H), 5.79 (d, *J* = 7.3 Hz, 1H, CH), 7.15–7.62 (m, 9H, Ph + Py + Py′ + NH), 7.79 (td, *J* = 7.6, 1.6 Hz, 1H, Py), 8.10 (dt, *J* = 7.8, 1.0 Hz, 1H, Py), 8.45 (dm, *J* = 5.0 Hz, 1H, Py), 8.58 (dm, *J* = 4.8 Hz, 1H, Py), 8.70 (br d, *J* = 7.3 Hz, 1H, NH); IR: $\tilde{\nu}$ = 3365 m, 2980 m, 1665 s, 1593 m, 1570 m, 1490 s, 1460 m, 1430 cm^{-1} m; MS (ES): *m*/*z*: 369 [*M*+Na]$^+$, 347 [*M*+H]$^+$; HRMS (FAB): *m*/*z*: calcd for $C_{20}H_{19}N_4O_2$: 347.15080; found: 347.15083.

(*R*)-(−)-1-(2-Pyridinylcarboxamido)-2-(2-pyridinylcarboxy)-1-phenylethane [(*R*)-(−)-(16)]: α-Picolinic acid (1.23 g, 10 mmol) was heated at reflux in $SOCl_2$ (10 mL, 137 mmol) at 85 °C for 2 h. The volatiles were removed in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL). The resulting solution was added dropwise to a stirred solution of (*R*)-(−)-phenylglycinol (*R*)-(−)-**25** (0.41 g, 3.0 mmol) and Et_3N (2.02 g, 20 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and then water (20 mL) was added. The organic layer was separated and washed successively with water (20 mL), satd aq $NaHCO_3$ (20 mL), and again water (20 mL), and dried over $MgSO_4$. The solvent was removed in vacuo; Et_2O (5 mL) was added to the oily residue that slowly solidified. The solid was recrystallized from hexane/benzene to give (*R*)-(−)-**16** (0.70 g, 67 %) as white crystals. M.p. 154–155 °C; $[\alpha]_D^{20} = -4.3$ (*c* = 1.9, $CHCl_3$); ^{1}H NMR: δ = 4.75 (dd, *J* = 11.5, 5.0 Hz, 1H, CH*H*), 4.84 (dd, *J* = 11.5, 7.6 Hz, 1H, C*H*H), 5.70 (td, *J* = 8.0, 5.0 Hz, 1H, CH), 7.27–7.52 (m, 7H, Ph + Py + Py′), 7.79 (m, 2H, Py + Py′), 8.04 (d, *J* = 7.8 Hz, 1H, Py), 8.15 (d, *J* = 7.8 Hz, 1H, Py′), 8.56 (d, *J* = 4.8 Hz, 1H, Py), 8.74 (m, 2H, Py′ + NH); ^{13}C NMR: δ = 53.1 (CH), 67.9 (CH_2), 122.7 (Py, CH), 125.7 (Py′, CH), 126.7 (Py, CH), 127.29 (Py′, CH), 127.33 (Ph, 2×CH), 128.5 (Ph, CH), 129.3 (Ph, 2×CH), 137.4 (Py, CH), 137.7 (Py′, CH), 138.6 (Ph, C), 148.0, 150.0 (Py, Py′, C), 148.6, 150.4 (Py, Py′, CH), 164.5, 165.3 (2×CO); IR: $\tilde{\nu}$ = 3375 m, 2985 m, 1735 s (ester),

1675 s (amide), 1585 m, 1570 m, 1500 s, 1465 m, 1430 cm^{-1} m; MS (ES): *m/z*: 370 $[M+Na]^+$, 348 $[M+H]^+$; HRMS (FAB): *m/z*: calcd for $C_{20}H_{18}N_3O_3$: 348.13482; found: 348.13483.

(*R*)-(−)-2-(2-Pyridinylcarboxamido)-2-phenylethane [(*S*)-(−)-(17)]: A solution of α-picolinic acid chloride [prepared from α-picolinic acid (1.23 g, 10 mmol) and $SOCl_2$ (10 mL, 137 mmol) as described for the synthesis of **16**] in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of (*S*)-(−)-α-methylbenzylamine (0.48 g, 4 mmol) and Et_3N (2.02 g, 20 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and then water (20 mL) was added. The organic layer was separated and washed successively with water (20 mL), satd aq $NaHCO_3$ (20 mL) and again water (20 mL), and dried over $MgSO_4$. The solvent was removed in vacuum and Et_2O (5 mL) was added to the oily residue that slowly solidified. The solid material was recrystallized from hexane/benzene to give (*S*)-(−)-**17** as white crystals (0.65 g, 72 %). M.p. 54–55 °C; $[\alpha]_D^{20} = -1.76$ (*c* = 1.8, $CHCl_3$); ^{1}H NMR: δ = 1.62 (d, *J* = 6.9 Hz, 3H, Me), 5.32 (m, 1H, CH), 7.22–7.43 (m, 6H, Ph + Py), 7.82 (td, *J* = 7.8, 1.6 Hz, 1H, Py), 8.19 (dt, *J* = 7.8, 0.9 Hz, 1H, Py), 8.32 (br d, *J* = 6.0 Hz, 1H, NH), 8.53 (dm, *J* = 4.6 Hz, 1H, Py); IR: $\tilde{\nu}$ = 3380 m, 2980 m, 1670 s, 1595 m, 1570 m, 1510 s, 1465 m, 1450 m, 1430 cm^{-1} m; MS (ES): *m/z*: 249 $[M+Na]^+$, in agreement with the literature data.[56]

(*R*)-(−)-2-(2-Pyridinylcarboxamido)-2-phenylacetic acid methyl ester [(*R*)-(−)-(18)]: The title compound was prepared by the same procedure as **16** using hydrochloride of (*R*)-(−)-phenylglycine methyl ester (*R*)-(−)-**22a** (800 mg, 3.97 mmol). The crude product was purified by chromatography on silica gel with hexane/ethyl acetate 3:1 to give (*R*)-(−)-**18** (960 mg, 89 %) as a white solid. M.p. 61–63 °C; $[\alpha]_D^{20} = -76.5$ (*c* = 2.2, $CHCl_3$); ^{1}H NMR: δ = 3.77 (s, 3H, OMe), 5.78 (d, *J* = 7.6 Hz, 1H, CH), 7.27–7.50 (m, 6H, Ph + Py), 7.82 (td, *J* = 7.8, 1.6 Hz, 1H, Py), 8.16 (d, *J* = 7.8 Hz, 1H, Py), 8.58 (d, *J* = 4.8 Hz, 1H, Py), 8.70 (br d, *J* = 6.9 Hz, 1H, NH); IR: $\tilde{\nu}$ = 3380 m, 3000 m, 2975 m, 1742 s (ester), 1675 s (amide), 1591 m, 1570 m, 1496 s, 1465 m, 1430 cm^{-1} m; MS (ES): *m/z*: 293 $[M+Na]^+$, 271 $[M+H]^+$; HRMS (FAB): *m/z*: calcd for $C_{15}H_{15}N_2O_3$: 271.10827; found: 271.10823.

(*R*)-(−)-2-(2-Pyridinylcarboxamido)-2-phenylethan-1-ol [(*R*)-(−)-(26)]: A solution of α-picolinic acid chloride [prepared from α-picolinic acid (1.847 g, 15 mmol) and $SOCl_2$ (10 mL, 137 mmol) as described for the preparation of **16**] in CH_2Cl_2 (5 mL) and the resulting solution was added dropwise to a stirred solution of (*R*)-(−)-phenylglycinol **25** (2.06 g, 15 mmol) and Et_3N (4.04 g, 40 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and then water (20 mL) was added. The organic layer was separated and washed successively with water (20 mL), satd aq $NaHCO_3$ (20 mL), and again water (20 mL), and dried over $MgSO_4$. The solvent was removed in vacuo and Et_2O (5 mL) was added to the oily residue that slowly solidified. The solid was recrystallized from hexane/benzene to give (*R*)-(−)-**26** as white crystals (2.5 g, 69 %). M.p. 115–116 °C (decomp); $[\alpha]_D^{20} = -5.2$ (*c* = 2.6, $CHCl_3$); ^{1}H NMR: δ = 3.07 (t, *J* = 6.2 Hz, 1H, OH), 3.99 (t, *J* = 6.0 Hz, 2H, CH_2), 5.44 (dt, *J* = 7.6, 5.3 Hz, 1H, CH), 7.26–7.44 (m, 6H, Ph + Py), 7.83 (td, *J* = 7.8, 1.6 Hz, 1H, Py), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H, Py), 8.53 (dm, *J* = 4.6 Hz, 1H, Py), 8.70 (br d, *J* = 6.9 Hz, 1H, NH); IR: $\tilde{\nu}$ = 3600 w, 3380 m, 2940 m, 1669 s, 1595 m, 1575 m, 1500 m, 1460 m, 1430 cm^{-1} m; MS (ES): *m/z*: 265 $[M+Na]^+$, 243 $[M+H]^+$; HRMS (FAB): *m/z*: calcd for $C_{14}H_{15}N_2O_2$: 243.11335; found: 243.11330.

(*R*)-(−)-28: Di-*tert*-butyl dicarbonate $[(Boc)_2O]$ (3.27 g, 15 mmol) was added in several portions to a stirred solution of (*R*)-(−)-phenylglycinol **25** (2.06 g, 15 mmol) and Et_3N (4.04 g, 40 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. After addition of water (20 mL), the organic layer was separated and washed successively with water (20 mL), satd aq $NaHCO_3$ (20 mL), and again water (20 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give (*R*)-(−)-**28** as an oily residue that slowly solidified on standing (3.41 g, 96 %). The product thus obtained was used in the next step without further purification. ^{1}H NMR: δ = 1.36 (s, 9H, *t*Bu), 2.27 (br s, 1H, OH), 3.77 (m, 2H, CH_2), 4.71 (m, 1H, PhC*H*), 5.17 (br s, 1H, NH), 7.10–7.31 (m, 5H, Ph) in accordance with the literature.[57]

(*R*)-29: A solution of diethyl azodicarboxylate (1.20 g, 6.89 mmol) in THF (20 mL) was added dropwise to a suspension of crude hydroxyamide (*R*)-(−)-**28** (1.5 g, 6.79 mmol), phthalimide (1.00 g, 6.79 mmol), and triphenylphosphine (1.78 g, 6.79 mmol) in THF (40 mL). The mixture was stirred at room temperature overnight and was then concentrated in vacuo. Et_2O (20 mL) was added to the residue to form a white precipitate. The precipitate was collected by filtration, washed with Et_2O, and dried in vacuo to afford crude phthalimido derivative, which was directly used in the next step without further purification. ^{1}H NMR: δ = 1.27 (s, 9H, *t*Bu), 3.95 (m, 2H, CH_2), 5.13 (m, 1H, PhC*H*), 5.32 (br s, 1H, NH), 7.28–7.47 (m, 5H, Ph), 7.73 (m, 2H, Ar), 7.88 (m, 2H, Ar).

The latter phthalimido derivative was dissolved in ethanol (30 mL), hydrazine hydrate (2 mL, 41 mmol) was added, and the mixture was heated at reflux (80 °C) for 5 h. The mixture was then cooled, diluted with water (30 mL), and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was passed through a short silica gel column (5 × 2 cm) with dichloromethane/methanol 9:1 to afford crude amine (*R*)-**29** (0.77 g, 48 % per two steps), which was used in the next step without further purification. ^{1}H NMR: δ = 1.44 (s, 9H, *t*Bu), 3.01 (m, 2H, CH_2), 4.67 (m, 1H, PhC*H*), 5.33 (br s, 1H, NH), 7.26–7.48 (m, 5H, Ph).

(*R*)-31: Methyl chloroformate (0.38 mL, 4.95 mmol) was added dropwise via syringe to a solution of picolinic acid (610 mg, 4.95 mmol) and Et_3N (0.50 g, 4.95 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 30 min at that temperature, while white precipitate formed during this time. The precipitate was removed by filtration under nitrogen and the filtrate was added dropwise to a solution of the crude amine (*R*)-**29** (0.77 g, 3.27 mmol) and Et_3N (0.50 g, 4.95 mmol) in THF (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and left stirring overnight. Water (30 mL) was added to the mixture, and the product was taken up into CH_2Cl_2 (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was passed through a short silica gel column (5 × 2 cm) with ethyl acetate/methanol 9:1 to afford crude (*R*)-**30** as a white solid (1.05 g, 94 %) which was immediately used in the next step.

The product was dissolved in TFA (2 mL) at room temperature and stirred for 2 h. Volatiles were removed in vacuo to give crude (*R*)-**31** as a yellow oil (640 mg, 86 %), which was immediately used in the next step.

1,2-Bis(2-pyridinylcarboxamido)ethane (19): $(PhO)_3P$ (5.50 mL, 20.99 mmol, 2.1 equiv) was added to a solution of α-picolinic acid (2.585 g, 21.00 mmol, 2.1 equiv) in dry pyridine (35 mL) under nitrogen. The solution was heated to 85 °C and freshly distilled 1,2-ethylenediamine (670 μL, 10.02 mmol, 1.0 equiv) was added dropwise over a period of 5 min. The reaction mixture was stirred at 100 °C for 24 h and allowed to stand at RT overnight. A white precipitate was separated by suction, washed with water (3 × 20 mL), and dried at RT overnight to obtain **19** as white crystals (2.051 g, 76 %). ^{1}H NMR ($CDCl_3$): δ = 3.75–3.77 (m, 4H, 2 × CH_2), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 2H, arom.), 7.84 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 2H, arom.), 8.20 (d, *J* = 7.8 Hz, 2H, arom.), 8.42 (m, 2H, 2 × NH), 8.56 (br d, *J* = 4.1 Hz, 2H, arom.); ^{1}H NMR ($[D_8]$THF): δ = 3.60–3.62 (m, 4H, 2 × CH_2), 7.42 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 2H, arom.), 7.85 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 2H, arom.), 8.12 (dt, *J* = 7.8, 1.0, 1.0 Hz, 2H, 2H, arom.), 8.53 (dq, *J* = 4.7, 0.9, 0.9, 0.9 Hz, 2H, arom.), 8.67 (m, 2H, 2 × NH); ^{13}C NMR ($CDCl_3$): δ = 39.9 (2 × CH_2), 122.6 (2 × CH-arom), 126.6 (2 × CH-arom), 137.7 (2 × CH-arom), 148.6 (2 × CH-arom), 150.1 (2 × C-2), 165.4 (2 × C=O); ^{13}C NMR ($[D_8]$THF): δ = 40.2 (2 × CH_2), 122.8 (2 × CH-arom), 126.6 (2 × CH-arom), 137.8 (2 × CH-arom), 148.9 (2 × CH-arom), 151.7 (2 × C-arom), 165.0 (2 × C=O); IR: $\tilde{\nu}$ = 3392 w, 3060 vw, 3018 m, 1672 s, 1592 w, 1571 w, 1527 s, 1465 w, 1435 w, 1363 vw, 1288 w, 1240 w, 1161 w, 998 w, 905 cm^{-1} vw.

***N*-Methyl-*N*-{2-[(pyridinyl-2-carboxamido]ethyl}-2-pyridinecarboxamide (20)**: A solution of diamide **19** (200 mg, 0.740 mmol, 1.0 equiv) in dry *N*,*N*-dimethylformamide (7 mL) was added dropwise to NaH (33 mg, 60 % suspension, 0.825 mmol, 1.1 equiv) in dry *N*,*N*-dimethylformamide (5 mL) under nitrogen. The mixture was stirred at 40 °C for 45 min and cooled to room temperature; a white suspension was formed. Methyl iodide (50 μL, 0.803 mmol, 1.1 equiv) was added and the mixture was stirred at room temperature for 2 h, during which period an almost clear sol-

ution was formed. The solvent was removed in vacuo using rotary evaporator and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with water and dried over anhydrous $MgSO_4$. The crude product was repeatedly purified from unreacted **19** and the bismethylated product **21** by flash chromatography on a silica gel column (15×2.5 cm) with ethyl acetate/methanol 98:2 → 80:20, which afforded pure monomethyl derivative **20** as an oil that slowly solidified (77 mg, 37%). ^{1}H NMR (two stereoisomers in a 2:1 ratio): δ = 3.08 (s, 1/3 of 3H, CH_3), 3.11 (s, 2/3 of 3H, CH_3), 3.68–3.80 (m, 4H, 2×CH_2), 7.26 (ddd, J=7.6, 4.9, 1.2 Hz, 1/3 of 1H, arom.), 7.30 (ddd, J=7.3, 4.9, 1.4 Hz, 2/3 of 1H, arom.), 7.32–7.37 (m, 1H, arom.), 7.50 (d, J=7.8 Hz, 1/3 of 1H, arom.), 7.63 (d, J=7.7 Hz, 2/3 of 1H, arom.), 7.65–7.72 (m, 1H, arom.), 7.74–7.80 (m, 1H, arom.), 8.09 (d, J=7.8 Hz, 2/3 of 1H, arom.), 8.12 (d, J=7.8 Hz, 1/3 of 1H, arom.), 8.43 (m, 1/3 of 1H, NH), 8.47 (d, J=4.2 Hz, 2/3 of 1H, arom.), 8.52 (d, J=4.7 Hz, 2/3 of 1H, arom.), 8.63 (d, J=4.5 Hz, 2/3 of 1H, arom.), 9.49 (m, 2/3 of 1H, NH); ^{13}C NMR (two stereoisomers in a 2:1 ratio): δ = 33.9 (CH_3), 37.8 (CH_2), 38.1 (CH_3), 38.3 (CH_2), 47.9 (CH_2), 49.6 (CH_2), 122.4 (CH-arom.), 122.6 (CH-arom.), 123.9 (CH-arom.), 124.8 (CH-arom.), 125.0 (CH-arom.), 125.1 (CH-arom.), 126.4 (CH-arom.), 126.5 (CH-arom.), 137.3 (CH-arom.), 137.6 (CH-arom.), 137.6 (CH-arom.), 148.0 (CH-arom.), 148.5 (CH-arom.), 148.7 (CH-arom.), 148.7 (CH-arom.), 150.6 (C-2), 154.0 (C-2), 165.7 (C=O), 169.4 (C=O) and other signals of a minor isomer overlapped; IR: $\tilde{\nu}$ = 3689w, 3387w, 3018vs, 1669m, 1632s, 1590w, 1569m, 1528s, 1465w, 1434w, 1403w, 1289w, 1238w, 932 cm^{-1}vw; HRMS (EI): m/z: calcd for $C_{15}H_{16}N_4O_2$: 284.12739; found: 284.12733.

***N*-Methyl-*N*-{2-[methyl(2-pyridinyl)carboxamido]ethyl}-2-pyridinecarboxamide (21)**: A solution of diamide **20** (200 mg, 0.740 mmol, 100%) in dry DMF (7 mL) was added dropwise to NaH (65 mg, 60% suspension, 1.625 mmol, 2.2 equiv) in dry DMF (5 mL) under nitrogen. The mixture was stirred at 40°C for 45 min and cooled to room temperature; a white suspension was formed. Methyl iodide (100 μL, 1.606 mmol, 2.2 equiv) was added and the mixture was stirred at room temperature overnight, during which period an almost clear solution was formed. The solvent was removed in vacuo using rotary evaporator and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. The crude product was repeatedly purified from unreacted **19** and the mono-methylated product **20** by flash chromatography on a silica gel column (15×2.5 cm) with ethyl acetate/methanol 80:20, which afforded pure bismethylated derivative **21** as an oil that slowly solidified (82 mg, 37%). ^{1}H NMR (three stereoisomers in a 4:3:3 ratio): δ = 2.84 (s, 3/10 of 6H, CH_3), 2.94 (s, 2/10 of 6H, CH_3), 3.11 (s, 3/10 of 6H, CH_3), 3.19 (s, 2/10 of 6H, CH_3), 3.67–3.82 (m, 4H, 2×CH_2), 7.25–7.30 (m, 2H, arom.), 7.54 (t, J=8.8 Hz, 1H, arom.), 7.62–7.77 (m, 3H, arom.), 8.50 (dt, J=14.5, 14.5, 4.3 Hz, 2H, arom.); ^{13}C NMR (three stereoisomers in a 4:3:3 ratio): δ = 34.6 (CH_3), 35.0 (CH_3), 38.1 (CH_3), 38.3 (CH_3), 45.6 (CH_2), 47.6 (CH_2), 48.4 (CH_2), 49.7 (CH_2), 123.6 (CH-arom.), 124.1 (CH-arom.), 124.5 (CH-arom.), 124.7 (CH-arom.), 124.7 (CH-arom.), 124.9 (CH-arom.), 125.0 (CH-arom.), 125.1 (CH-arom.), 137.3 (CH-arom.), 137.4 (CH-arom.), 137.5 (CH-arom.), 137.6 (CH-arom.), 148.1 (CH-arom.), 148.3 (CH-arom.), 148.5 (CH-arom.), 148.9 (CH-arom.), 154.3 (C-arom.), 154.5 (C-arom.), 154.6 (C-arom.), 155.0 (C-arom.), 169.0 (C=O), 169.1 (C=O), 169.4 (C=O), 169.7 (C=O); IR: $\tilde{\nu}$ = 3018s, 1632vs, 1589w, 1568m, 1495m, 1463w, 1443w, 1425w, 1406m, 1359vw, 1289w, 1240w, 1150w, 1079w, 1046w, 996w, 965vw, 809 cm^{-1}vw; HRMS (EI): m/z: calcd for $C_{16}H_{18}N_4O_2$: 298.14301; found: 298.14298.

(±)-3-[$^2H_1$]-1-Phenylprop-2-yn-1-ol [(±)-(36)]: 1-Phenylprop-2-yn-1-ol (**35**) (1 g, 7.57 mmol) was added to a mixture of D_2O (20 mL) and K_2CO_3 (1.04 g, 7.57 mmol) under nitrogen. After 1 h at room temperature the product was extracted with dichloromethane (3×10 mL). The combined extracts were dried ($MgSO_4$), and evaporated to afford a yellow oil that was purified by distillation (36 mbar, Kugelrohr oven at 140°C) to afford (±)-**36** as a yellow oil (0.70 g, 69%; 98% ^{2}H by ^{1}H NMR). ^{1}H NMR (270 MHz, $CDCl_3$, 22°C, TMS): δ = 7.59–7.49 (m, 2H, CH_{ortho}), 7.43–7.29 (m, 3H, arom. H), 5.44 (s, 1H, 1-H), 2.16 (brs, 1H, OH); ^{13}C NMR (100 MHz, 21°C, TMS): δ = 140.0 (arom. C), 128.7, 128.5, 126.6 (arom. CH), 83.0 [t, ^2J(C,^{2}H)=7.7 Hz, C-2], 77.6 [t, ^1J(C,^{2}H)=38.4 Hz, C-3], 64.4 (C-1); ^{2}H NMR (46 MHz, CH_2Cl_2, 23°C, $CDCl_3$): δ = 2.72 [brs, 3-^{2}H]; MS (EI): m/z (%): 133 (100) [M]$^+$, 116 (30), 105 (40), 89 (10), 84 (20), 80 (10), 77 (60), 74 (11), 66 (8), 63 (20), 54 (44).

(±)-(*Z*)-3-[$^2H_1$]-1-Phenylprop-2-en-1-ol [(±)-(37a)]: DIBAL-H (1M in hexane, 2.62 mL, 2.62 mmol) was added slowly to a solution of 3-[$^2H_1$]-1-phenylprop-2-yn-1-ol [(±)-**36**] (314 mg, 2.36 mmol, 98% ^{2}H) in dichloromethane (4 mL) in a Schlenk tube under nitrogen. The mixture was stirred at room temperature for 10 min before adding to a slurry of Schwartz reagent (676 mg, 2.62 mmol) in anhydrous dichloromethane (20 mL) under nitrogen at 0°C. After 10 min the mixture became pale orange in color. The reaction mixture was quenched by dropwise addition of satd aq $NaHCO_3$, filtered through a plug of silica gel (2.5×1 cm); the solvent was evaporated to afford (±)-**37a** as a colorless oil (253 mg, 79%; 98% ^{2}H by ^{1}H NMR) which was not further purified. Note that the product was contaminated with 1–5% of 3-deuterio-1-phenylpropanol (an over-reduction product), which did not need to be separated for the subsequent synthetic steps. The *Z*/*E* ratio was 99.76:0.24 as shown by ^{1}H NMR. ^{1}H NMR (270 MHz, $CDCl_3$, 22°C, TMS): δ = 7.42–7.24 (m, 5H, arom. H), 6.05 (m, 1H, 2-H), 5.26–5.16 (m, 2H, 3-H, 1-H); ^{13}C NMR (100 MHz, 21°C, TMS): δ = 142.6 (arom C), 140.2 (C-2), 128.7, 128.5, 126.3, (arom CH), 114.8 (t, ^1J(C,^{2}H)=23.9 Hz; C-3), 75.9 (C-1); ^{2}H NMR (46 MHz, CH_2Cl_2, 23°C, $CDCl_3$): δ = 5.54 (brs, 3-^{2}H); MS (EI): m/z (%): 135 (90) [M]$^+$, 149 (5), 119 (15), 116 (100), 105 (30), 92 (27), 84 (57), 77 (35), 71 (5), 63 (9), 56 (11),52 (6).

(±)-(*Z*)-3-[$^2H_1$]-1-Phenylprop-2-enyl acetate [(±)-(37b)]: A solution of (*Z*)-3-[$^2H_1$]-1-phenylprop-2-en-1-ol (±)-**37a** (185 mg, 1.37 mmol, 98% ^{2}H), Et_3N (284 mg, 2.80 mmol), and DMAP (5.6 mg, 0.046 mmol) in dichloromethane (2 mL) at 0°C was slowly treated with a solution of Ac_2O (202 mg, 1.98 mmol) in dichloromethane (0.1 mL) and then allowed to warm to 25°C over a period of 3 h. After quenching with an ice-cold 50% aqueous solution of NH_4Cl (5 mL), the mixture was extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with satd aq NH_4Cl (25 mL), satd aq NaCl and satd aq $NaHCO_3$, before being dried ($MgSO_4$) and then concentrated in vacuo. Chromatography on silica gel (50 g) with hexane/ethyl acetate 4:1 afforded (±)-**37b** as a colorless oil (174 mg, 72%; 98% ^{2}H by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$, 22°C, TMS): δ = 7.49–7.28 (m, 5H, arom H), 6.26 (d, ^3J(H,H)=5.8 Hz, 1H; 1-H), 6.02 (m, 1H; 2-H), 5.23 (d, ^3J(H,H)=10.2 Hz, 1H; 3-H), 2.10 (s, 3H; CH_3); ^{13}C NMR: δ = ($CDCl_3$, 70 MHz, 21°C, TMS): δ = 167.0 (C=O), 138.9 (arom C), 136.2 (C-2), 128.5, 128.1, 127.1 (arom CH), 116.6 [t, ^1J(C,^{2}H)=23.8 Hz, C-3], 75.8 (C-1), 21.2 (CH_3); ^{2}H NMR (46 MHz, CH_2Cl_2, 23°C, $CDCl_3$): δ = 5.18 (brs, 3-^{2}H); MS (EI): m/z (%): 177 (1) [M]$^+$, 143 (6), 132 (32), 116 (23), 107 (30), 91 (10), 84 (62), 79 (52), 56 (42).

(±)-(*Z*)-3-[$^2H_1$]-1-Phenylprop-2-enyl methyl carbonate [(±)-(37c)]: Methyl chloroformate (1.25 mL, 17 mmol) was added dropwise to a solution of (*Z*)-3-[$^2H_1$]-1-phenylprop-2-en-1-ol (±)-**37a** (1.00 g, 7.41 mmol; 98% ^{2}H) and pyridine (5 mL, 70 mmol) in dichloromethane (10 mL) at 0°C and the reaction mixture was heated under reflux for 18 h. After quenching with 50% satd aq NH_4Cl (10 mL), the mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were washed with satd aq NaCl and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded an oil that was purified by chromatography on silica gel (125 g) with hexane/ethyl acetate 6:1, and then distilled (4 mbar, Kugelrohr oven, T=120°C) to afford (±)-**37c** as a colorless oil (960 mg, 67%; 98% ^{2}H/H by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$, 22°C, TMS): δ = 7.40–7.29 (m, 5H, arom. H), 6.09 (d, ^3J(H,H)=6.3 Hz, 1H, 1-H), 6.03 (brm, 1H; 2-H), 5.26 (d, ^3J(H,H)=10.3 Hz, 1H, 3-H), 3.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, 21°C, TMS): δ = 155.0 (C=O), 138.3 (arom C), 135.7 (C-2), 128.6, 128.4, 127.0 (arom CH), 116.9 [t, ^1J(C,^{2}H)=25.0 Hz, C-3], 80.1 (C-1), 54.8 (CH_3); ^{2}H NMR (60 MHz, CH_2Cl_2, 23°C, $CDCl_3$): δ = 5.35 (brs, 3-^{2}H); MS (EI): m/z (%): 193 (22) [M]$^+$, 149 (40), 134 (21), 118 (100), 106 (54), 92 (37), 84 (78), 77 (54), 63 (19). Samples of (*S*)-(−)-**37c** (>95% *ee*) and (*R*)-(+)-**37c** (>95% *ee*) were prepared analogously from the corresponding enantiomerically enriched alcohols **37a** and their *ee* was determined by HPLC on Chiral OJ column employing a mixture of hexane and 2-propanol (93:7) as eluent with UV detection at 220 nm (0.5 mL min^{-1}; t_S=24.5 min, t_R=27.2 min).

Absolute configurations were assigned by comparison of HPLC and optical rotation data from **37c** with unlabelled **5**.[3h]

(±)-(*E*)-1-[^{2}H$_1$]-3-Phenylprop-2-en-1-ol (±)-(38a): *Method A:* $NaBD_4$ (501 mg, 12.0 mmol) was added to a solution of (*E*)-3-phenyl-prop-2-enyl aldehyde **40** (1.52 g, 11.5 mmol) in methanol (30 mL) at 0 °C. After 10 min, the reaction was quenched with water and the mixture was diluted with dichloromethane (30 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (20×3 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded (±)-**38a** as yellow crystals (1.44 g, 93 %, 95 % ^{2}H).

Method B: A solution of (*E*)-1-[^{2}H$_1$]-3-phenyl-prop-2-enyl acetate (±)-**38b** (125 mg, 0.706 mmol, 98 % ^{2}H) in methanol (3 mL) was treated with K_2CO_3 (33 mg, 0.24 mmol) and the resulting suspension was stirred at 25 °C for 6 h. After the volatiles were removed in vacuo, the yellow residue was dissolved in Et_2O and the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography on silica gel (50 g) with hexane/ethyl acetate 4:1 afforded (±)-**38a** as a colorless oil (67 mg, 70 %; 98 % ^{2}H by ^{1}H NMR). ^{1}H NMR (270 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.43–7.20 (m, 5H, arom. H), 6.62 (dd, ^3J(H,H) = 15.8, ^4J(H,H) = 1.3 Hz, 1H; 3-H), 6.36 (dd, ^3J(H,H) = 15.8, 5.6 Hz, 1H; 2-H), 4.31 (br m, 1H; 1-H); ^{13}C NMR (100 MHz, 21 °C, TMS): δ = 135.8, 134.1, 128.6, 128.2, 126.7, 124.8 (arom. C, arom. CH, C-3, C-2), 45.2 (t, ^1J(C,^{2}H) = 23 Hz; C-1); ^{2}H NMR (46 MHz, CH_2Cl_2, 23 °C, $CDCl_3$): δ = 4.27 (br s, 1-^{2}H); MS (EI): *m*/*z* (%): 135 (85) $[M]^+$, 118 (35), 116 (60), 106 (45), 103 (22), 92 (100), 89 (7), 86 (62), 84 (93), 80 (15), 78 (75), 65 (12), 63 (20), 56 (17), 52 (15).

(±)-(*E*)-1-[^{2}H$_1$]-3-Phenylprop-2-enyl acetate [(±)-(38b)]: *Method A*: This derivative was prepared in an identical manner to (±)-**37b** but starting from (±)-**38a** as a colorless oil (80 %, 95 % ^{2}H).

Method B: A solution of (±)-(*Z*)-3-[^{2}H$_1$]-1-phenylprop-2-enyl acetate (±)-**37b** (104 mg, 0.59 mmol; 98 % ^{2}H) in chloroform (10 mL) was treated with $[(CH_3CN)_2PdCl_2]$ (3.9 mg, 0.015 mmol, 2.5 mol %). After stirring at 25 °C for 3.5 h, the chloroform was removed in vacuo and the crude product was purified by chromatography on silica gel (50 g) with 4:1 hexane/AcOEt to afford (±)-**38b** as a colorless oil (74 mg, 71 %; 98 % ^{2}H by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.44–7.22 (m, 5H; arom H), 6.64 (d, ^3J(H,H) = 15.7 Hz, 1H; 3-H), 6.27 (dd, ^3J(H,H) = 15.7, 6.2 Hz, 1H; 2-H), 4.71 (br m, 1H; 1-H), 2.11 (s, 3H; CH_3); ^{13}C NMR (100 MHz, 21 °C, TMS): δ = 170.7 (C=O), 136.2 (arom C), 134.2 (C-3), 128.5, 128.0, 126.5 (arom CH), 123.1 C-2), 64.7 (t, ^1J(C,^{2}H) = 23.0 Hz, C-1), 20.9 (CH_3); ^{2}H NMR (46 MHz, CH_2Cl_2, 23 °C, $CDCl_3$) δ = 4.70 (br s, 1-^{2}H), MS (EI): *m*/*z* (%): 177 (25) $[M]^+$, 135 (44), 116 (100), 106 (49), 92 (37), 84 (89), 77 (47), 65 (10), 60 (19); no *Z* isomer was detected by ^{1}H NMR.

(±)-(*E*)-1-[^{2}H$_1$]-3-Phenylprop-2-enyl methyl carbonate [(±)-(38c)]: This compound was prepared in an identical manner to (±)-**37a** but starting from (±)-**38a**. (±)-**38c** was obtained as a colorless oil (63 %; 98 % ^{2}H by ^{1}H NMR). ^{1}H NMR (270 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.43–7.22 (m, 5H, arom H), 6.69 (d, ^3J(H,H) = 15.9 Hz, 1H; 3-H), 6.29 (dd, ^3J(H,H) = 15.9 Hz, 6.6 Hz, 1H, 2-H), 4.78 (br m, 1H; 1-H), 3.82 (s, 3H, CH_3); ^{13}C NMR (68 MHz, 21 °C, TMS): δ = 155.7 (C=O), 136.1 (arom CH), 134.9 (C-3), 128.6, 128.2, 126.7 (arom CH), 122.3 (C-2), 68.0 (t, ^1J(C,^{2}H) = 22.3 Hz, C-1), 54.8 (CH_3); ^{2}H NMR (60 MHz, CH_2Cl_2, 23 °C, $CDCl_3$): δ = 4.76 (br s, 1-^{2}H); MS (EI): *m*/*z* (%): 193 (39) $[M]^+$, 149 (37), 132 (27), 121 (10), 116 (72), 106 (37), 92 (24), 84 (100), 77 (49), 63 (19).

(±)-(*E*)-1-[^{2}H$_1$]-3-Phenylprop-2-enyl diethyl phosphate [(±)-(38d)]: Chlorodiethyl phosphate (1.35 mL, 7.8 mmol) was added to a solution of (*E*)-1-[^{2}H$_1$]-3-phenylprop-2-en-1-ol (±)-**38a** (1.00 g, 7.4 mmol) and pyridine (0.67 mL) in dichloromethane (10 mL) at 0 °C over a period of 5 min and the resulting white slurry was stirred at room temperature for 2 h. The reaction mixture was diluted in Et_2O (10 mL) and washed successively with a 10 % aq HCl solution (5×3 mL), satd aq $NaHCO_3$ (5× 3 mL) and satd aq brine (5 mL). The organic layer was dried ($MgSO_4$); the solvent was evaporated to give a crude oily product that was purified by chromatography on silica gel (125 g) with hexane/ethyl acetate 2:1 to afford (±)-**38d** as a brown oil (0.53 g, 26 %). ^{1}H NMR (270 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.43–7.23 (m, 5H, arom H), 6.68 (d, ^3J(H,H) = 16.1 Hz, 1H, 3-H), 6.30 (dd, ^3J(H,H) = 15.8, 6.2 Hz, 1H, 2-H), 4.68 (br m, 1H, 1-H), 4.14 (dq, ^3J(H,H) = 7.2, ^3J(H,P) = 7.2 Hz; 4H, 2×CH_2), 1.34 (t, ^3J-(H,H) = 7.2 Hz, 6H, 2×CH_3); ^{13}C NMR (100 MHz, 21 °C, TMS): δ = 155.9 (C=O), 133.8 (arom CH), 128.5 (C-3), 128.0, 126.5, 123.4 (arom CH), 123.3 (C-2), 67.5 [t, ^1J(C,^{2}H) = 21.8 Hz, C-1], 63.7 (CH_2), 16.2 (CH_3); ^{2}H NMR (46 MHz, $CHCl_3$, 23 °C, $CDCl_3$): δ = 4.64 (br s, 1-^{2}H); MS (EI): *m*/*z* (%): 271 (45) $[M]^+$, 155 (38), 134 (5), 127 (28), 116 (100), 99 (35), 92 (17), 86 (5), 81 (14), 65 (6).

1-(1*R*,1′*R*)-(*E*)-1-[^{2}H$_1$]-3-Phenylprop-2-en-1-yl 1′-phenylethyl carbamate [(*R*,*R*)-(39)] and 1-(1*S*,1′*R*)-(*E*)-1-[^{2}H$_1$]-3-phenylprop-2-en-1-yl 1′-phenylethyl carbamate [(*S*,*R*)-(39)]: (*R*)-(+)-α-methyl benzylisocyanate (55 mg, 0.370 mmol) was added to a solution of racemic (*E*)-1-[^{2}H$_1$]-3-phenylprop-2-en-1-ol (±)-**38a** (50 mg, 0.370 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (5 mg, 10 %) in toluene (3 mL) and the mixture was heated under reflux overnight. A white solid was obtained on removal of the solvent and washing of the residue with *n*-pentane. Recrystallization from hexane/benzene gave pure carbamate **39** (60 mg, 58 %). M.p. 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C, TMS):[58] δ = 7.41–7.21 (m, 10H, arom H), 6.62 (d, ^3J(H,H) = 15.6 Hz, 1H, 3-H), 6.27 (dd, ^3J(H,H) = 15.1, 5.9 Hz, 1H, 2-H), 5.06 (br s, 1H, N*H* or C*H*-N), 4.92–4.86 (br m, 1H, C*H*-N or N*H*), 4.71 [d, ^3J(H,H) = 5.9 Hz, 1H, (*R*)-1-H], 4.67 [d, ^3J(H,H) = 5.9 Hz, 1H, (*S*)-1-H], 1.48 (d, ^3J(H,H) = 6.3 Hz, CH_3); ^{13}C NMR (100 MHz, 21 °C, TMS): δ = 155.5 (C=O), 143.5 (arom C), 136.3 (arom C), 133.8 (C-3), 128.6, 128.7, 128.5, 127.3, 126.5, 125.9 (arom CH), 123.8 (C-2), 65.1 (t, ^1J(C,^{2}H) = 23.7 Hz, C-1), 50.6 (*C*H-N), 22.4 (CH_3); ^{2}H NMR (60 MHz, CH_2Cl_2, 23 °C, $CDCl_3$): δ = 4.63 (br s, 1-^{2}H); IR (KBr): $\tilde{\nu}$ = 3200–3500 (broad), 1700 cm^{-1}; MS (EI): *m*/*z* (%): 281 (100) $[M]^+$, 117 (82), 105 (100), 91 (31), 84 (44), 77 (31), 65 (6); elemental analysis calcd (%) for $C_{18}H_{19}NO_2$: C 76.84, H 6.81; found: C 76.59, H 6.87.

General procedure for the preparative allylic substitution catalyzed by molybdenum(0): A mixture of $[(EtCN)_3Mo(CO)_3(EtCN)_3]$ (34 mg, 0.1 mmol) and a ligand (0.15 mmol) was dissolved in THF (3 mL). The solution, that instantaneously turned deep red, was heated with stirring at 60 °C for 40 min. The solution was cooled to room temperature and then a solution of the corresponding sodiomalonate (2.0 mmol) in THF (2 mL), generated from dimethyl malonate (or dimethyl methylmalonate) and NaH, and a solution of allylic carbonate (1.0–1.3 mmol) in THF (1 mL) were successively added. Usually, the addition of the reactants was accompanied by a change of color to orange or yellow-brown. The mixture was stirred at 60 °C until the reaction was complete (as evidenced by TLC), then diluted with Et_2O (20 mL), and washed successively with 5 % aqueous $NaHCO_3$ and water. The organic phase was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (15× 2 cm) with hexane/ethyl acetate 9:1. Enantiomeric purity of the products **6** was determined by chiral HPLC using Chiralcel OD-H column (equipped with a silica gel guard column) and hexane/2-propanol 99.5:0.5; UV detection at 220 nm. The retention times were as follows: t_S = 17.4, t_R = 18.7 min. Alternatively, the enantiomeric purity of **6** was determined by ^{1}H NMR with [D]-Eu(hfc)$_3$.

Typical procedure for the asymmetric molybdenum(0)-catalyzed allylic substitution with deuterium-labeled substrates: A mixture of $[Mo(CO)_3(\eta^6\text{-}C_7H_8)]$ (7.1 mg, 26 μmol, 10 mol %) and (−)-(2*S*)-*N*,*N*′-3-methyl-1,2-diaminobutylbis(2-pyridine-carboxamide) (*S*)-**12c** (12.2 mg, 39 μmol, 15 mol %) was dissolved in tetrahydrofuran (0.5 mL) to form a deep-red solution and sodium dimethyl malonate (0.53 mmol) in tetrahydrofuran (1 mL), generated from dimethyl malonate and NaH (60 %), and a solution of the (*Z*)-deuterated branched allylic methyl carbonate (±)-**37c** (50 mg, 0.26 mmol) in tetrahydrofuran (1 mL) were successively added. The mixture was stirred at 60 °C overnight (20 h), then diluted with Et_2O (20 mL), quenched with 5 % aq $NaHCO_3$, and the organic phase was washed with water. The aqueous phase was extracted with dichloromethane and the combined extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (50 g) with hexane/ethyl acetate 6:1. The enantiomeric purity of the product thus obtained was found to be 88 % *ee* by chiral HPLC using a Chiral OJ column with hexane/2-propanol 93:7; UV detection at 220 nm, 0.5 mL min^{-1} (t_S = 31, t_R = 36 min).

Kinetic resolution studies: Samples were taken from the reaction mixture at regular intervals. Each sample was quenched with water, diluted with hexane, then filtered through a plug of silica gel and dried ($MgSO_4$). For each sample the enantiomeric excess and the conversion of substrate was determined by GC (β-column) using (±)-methyl 3-[$^2H_1$]-1-phenylpropyl carbonate as the internal standard. The *cis*/*trans* ratios for the branched product were determined by ^1H NMR spectroscopy. The *s* value was determined by non-linear regression. GC conditions: Capillary columns FS-HYDRODEX β-3P, temperature 120 °C, col. flow: 0.9 mL min^{-1} (t_S = 15.34, t_R = 15.93 min; *t* for internal standard were 14.47 and 14.94 min).

Sample preparation for chiral liquid crystal matrix deuterium NMR: The preparation of the sample is very important as it can affect the quality and reproducibility of the NMR spectra. The samples were prepared by the following procedure: PBLG (85–88 mg) was weighed directly into a 5 mm o.d. NMR tube and a solution of the product (16–25 mg) in dichloromethane (400–500 mg) was added. All samples were of the same length (3.3 cm) and were centrifuged in both directions (× 3000 r.p.m). The extent of centrifugation is also an important factor in obtaining good quality NMR spectra. The NMR tube was centrifuged for 1 h in each direction and then 30 min in each direction and then analyzed within 1 h. All NMR spectra were obtained on an Eclipse 400 NMR spectrometer at 23 ± 1 °C. The NMR tube was not spun in the magnet. The absolute values of the quadrupolar coupling vary from experiment to experiment (by up to ca. 4%). Therefore, control experiments were conducted in which the following four parameters were varied within limits that could reasonably be expected under experimental conditions: i) concentration of PBLG, ii) degree of polymerization of the PBLG, iii) analyte concentration, and iv) temperature. These experiments demonstrated that the $\Delta|\nu Q|$ values for the five resolvable components [(*R*)- and (*S*)-**41**, **42**, and (*R*)- and (*S*)-**43**] varied in a directly proportional manner and also that chemical shift anisotropy was negligible. Consequently, $\Delta|\nu Q|$ values can be normalized to allow confident assignment. The following values act as a basis set: (*R*)-**41**, $\Delta|\nu Q|$ = 525 Hz; (*S*)-**41**, $\Delta|\nu Q|$ = 544 Hz; (*R* and *S*)-**42**, $\Delta|\nu Q|$ = 49 Hz; (*R*)-**43**, $\Delta|\nu Q|$ = 726 Hz; and (*S*)-**43**, $\Delta|\nu Q|$ = 693 Hz.

Tungsten(0)-catalyzed allylic substitution

Dimethyl 3-[$^2H_1$]-1-phenyl-2-butene-4,4-dicarboxylate and dimethyl 1-[$^2H_1$]-3-phenyl-1-butene-4,4-dicarboxylate

Method A (asymmetric synthesis): An orange-red solution of [$W(CO)_3$-(η^6-C_7H_8)] (24.4 mg, 0.068 mmol, 10 mol%) and (*S*)-4,5-dihydro-2-[2′-(diphenylphosphino)phenyl]-4-isopropyloxazole (44.1 mg, 0.118 mmol, 17 mol%) in degassed, nitrogen-saturated anhydrous tetrahydrofuran (60 mL), was heated under nitrogen to 60 °C for 15 min, resulting in a homogeneous brown-black solution. After cooling to 25 °C, solid sodium dimethyl malonate (271 mg, 1.76 mmol) was added and the suspension was stirred vigorously at 60 °C for 10 min. The resulting gray-black solution was cooled to 25 °C and (*E*)-1-[$^2H_1$]-3-phenylprop-2-enyl diethyl phosphate (±)-**38d** (183 mg, 0.678 mmol; 95% ^2H) was added by micro syringe. After heating to 60 °C for 18 h, the deep red homogeneous solution was quenched with 50% satd aq NH_4Cl (50 mL) and the mixture was extracted with dichloromethane (50 × 3 mL). The combined extracts were dried ($MgSO_4$) and then filtered through a short plug of silica gel. Evaporation of the solvent afforded an oil that was purified by chromatography on silica gel (100 g) with hexane/ethyl acetate 9:1 and then placed under vacuum (0.1 mbar) to remove traces of dimethyl malonate. This procedure afforded a 4:1 mixture of (*R*)-**41**/**42** (*E*/*Z* 1:1) and (±)-**43** as a colorless oil (91 mg, 54%; 90% *ee*, 95% ^2H).

*Method B [racemic synthesis of (Z)-isomer **41**]*: An orange-red solution of [$W(CO)_3(\eta^6$-$C_7H_8)$] (14.4 mg, 0.04 mmol, 11 mol%) and 2,2′-bipyridine (6.4 mg, 0.04 mmol, 11 mol%) in anhydrous tetrahydrofuran (4.5 mL) was heated under nitrogen to 60 °C for 15 min, resulting in a homogeneous brown-black solution. After cooling to 25 °C, solid sodium dimethyl malonate (140 mg, 0.91 mmol) was added and the suspension was stirred vigorously at 60 °C for 10 min. The resulting gray-black solution was cooled to 25 °C and combined with (*Z*)-1-[$^2H_1$]-3-phenyl-prop-2-enyl methyl carbonate (±)-**37c** (70 mg, 0.36 mmol, 98% ^2H). After heating at 60 °C for 18 h, the deep red homogeneous solution was quenched with 50% satd aq NH_4Cl (10 mL) and the mixture was extracted with dichloromethane (4 × 3 mL). The combined extracts were dried ($MgSO_4$) and then filtered through a short plug of silica gel. Evaporation of the solvent afforded an oil that was purified by chromatography on silica gel (100 g) with hexane/ethyl acetate 12:1 and then placed in vacuo (0.1 mbar) to remove traces of dimethyl malonate, which gave (±)-**41** as colorless oil (71 mg, 79%; 98% ^2H).

Method C (racemic synthesis of a mixture of E/Z *isomers **41**/**42**)*: These compounds were prepared in an identical manner to Method B, but employing (±)-**37c** to give a 24:1 mixture of (±)-**41**/**42** (1:1) and (±)-**43** as a colorless oil (60%; 95% ^2H).

Palladium(0)-catalyzed allylic substitution: A mixture of [Pd(η-C_3H_5)MeCN)$_2$]OTf (3.4 mg, 9.0 μmol) and DPPF (5.0 mg, 9.0 μmol) was dissolved in tetrahydrofuran (1 mL) and the solution was stirred under nitrogen at 25 °C for 15 min to afford a brown solution. A solution of sodium dimethyl malonate (1.42 mmol) in tetrahydrofuran (4 mL), generated from dimethyl malonate (218 mg, 1.42 mmol) and NaH (60%) (57 mg, 1.42 mmol), and a solution of (*E*)-1-[$^2H_1$]-3-phenylprop-2-enyl acetate (±)-**38b** (63 mg, 0.36 mmol) in tetrahydrofuran (4 mL) were successively added. The mixture was stirred at 25 °C for 12 h, then diluted with Et_2O (20 mL), and washed successively with 5% aq$NaHCO_3$ and water. The organic phase was dried ($MgSO_4$) and the crude product was purified by flash chromatography on silica gel (50 g) with hexane/ethyl acetate 4:1 to afford (±)-**43** as a colorless oil (72 mg, 80%; 98% ^2H). The regioselectivity for **43** over **41**/**42** was greater than 95%. An identical procedure using (*S*)-**38b** (>95% *ee*) gave (*S*)-**43** (50%, 98% ^2H, >95% *ee*). The following is the routine (isotropic phase) NMR data for the three racemic ^2H-labeled compounds (obtained from Pd, W or Mo-catalyzed reactions).

(±)-41: ^1H NMR (400 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.33–7.19 (m, 5H, arom H), 5.99 (br m, 1H, 2-H), 5.07 (d, ^3J(H,H) = 10.3 Hz, 1H, 1-H), 4.11 (dd, ^3J(H,H) = 11.0, 8.1 Hz, 1H, 3-H), 3.87 (d, ^3J(H,H) = 11.0, 1H, 4-H), 3.74 (s, 3H, CH_3), 3.49 (s, 3H; CH_3).

(±)-42: ^1H NMR (400 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.33–7.19 (m, 5H, arom H), 5.98 (br dd, ^3J(H,H) = 17.1, 8.3 Hz, 1H, 2-H), 5.07 (d, ^3J(H,H) = 17.1 Hz, 1H, 1-H), 4.11 (dd, ^3J(H,H) = 11.0, 8.3 Hz, 1H, 3-H), 3.87 (d, ^3J-(H,H) = 11.0 Hz, 1H, 4-H), 3.74 (s, 3H, CH_3), 3.49 (s, 3H, CH_3).

(±)-41/42: ^{13}C NMR (75 MHz, 21 °C, TMS): δ = 168.1 (C=O), 167.7, (C=O), 140.1 (arom CH), 138.1 (C-2), 128.6, 127.8, 127.1 (arom CH), 116.5 (t, ^1J(C,^2H) = 21.2 Hz, C-1), 57.3 (C-3), 52.6 (CH_3), 52.4 (CH_3), 49.7 (C-4); ^2H NMR (46 MHz, CH_2Cl_2, 23 °C, $CDCl_3$): δ = 5.06 (br s, 1-^2H); MS (EI): *m*/*z* (%): 249 (2) $[M]^+$, 207 (8), 190 (50), 183(15), 158 (10), 130 (30), 118 (59), 105 (35), 92 (9), 84 (100), 77 (12), 59 (11).

(±)-43: ^1H NMR (400 MHz, $CDCl_3$, 22 °C, TMS): δ = 7.38–7.18 (m, 5H, arom. H), 6.47 (d, ^3J(H,H) = 15.9 Hz, 1-H), 6.14 (dd, 1H; ^3J(H,H) = 15.9, 7.4 Hz, 2-H), 3.74 (s, 6H, 2 × CH_3), 3.52 (d, ^3J(H,H) = 7.5 Hz, 1H, 4-H), 2.77 (br dd, ^3J(H,H) = 7.1, 7.4 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, 23 °C, TMS): δ = 169.2 (C=O), 137.0 (arom C), 132.9 (C-1), 128.5, 127.4, 126.2 (arom CH), 125.3 (C-2), 52.5 (2 × CH_3), 51.6 (C-4), 31.9 [t, ^1J(C,^2H) = 20.0 Hz, C-3]; ^2H NMR (60 MHz, CH_2Cl_2, 23 °C, $CDCl_3$): δ = 2.75 (br s, 3-^2H); MS (EI): *m*/*z* (%): 249 (32) $[M]^+$, 215 (11), 205 (24), 189 (32), 158 (17), 129 (91), 118 (100), 105 (21), 92 (21), 84 (61), 77 (19), 59 (31).

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[26] a) We favor $[(C_7H_8)Mo(CO)_3]$ as it is more air-stable than $[(EtCN)_3Mo(CO)_3]$ and, according to our experience, somewhat easier to prepare in a pure and defined form. Thus, while the preparation of the former complex is straightforward (reflux for 8 h, followed by Soxhlet extraction),[3h] the latter complex is usually contaminated by $[(EtCN)_2Mo(CO)_4]$ so that prolonged reflux (up to 3 d) and repeated recrystallization is often required to obtain the pure species. The complex generated in situ from the latter contaminant and ligand **12a** is very slow in the catalytic reaction, as revealed by control experiments {our results, given in Table 1, were obtained with pure $[(EtCN)_3Mo(CO)_3]$}. b) This behavior seems to suggest that a tridentate coordination of the metal by **12** is required to generate an active catalyst.

[27] With $NaCMe(CO_2Me)_2$, the reaction proved to be much slower and the selectivity lower, but still giving mainly the branched product.[8b]

[28] This outcome corresponds with the difference in A values: 2.8 (Ph) and 1.68 ($PhCH_2$) kcal mol^{-1}: E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 697.

[29] Unfortunately, the A value for *i*Pr (2.21 kcal mol^{-1}) was measured at 27 °C, whereas those for Ph and $PhCH_2$ were obtained at −100 and −71 °C,[28] respectively, so that direct comparison is not straightforward.

[30] High selectivities were also observed for the 2-thienyl and 1-cyclohexenyl analogues of **4** and **5**;[8b] these results are in the same range as the those reported by Trost.[10]

[31] Note that, for instance, α,α′-bipyridine and phenanthroline-type ligands are particularly suitable for Mo^0- and W^0-catalyzed allylic substitution. For selected examples, see the following: a) H. Frisell, B. Åkermark, *Organometallics* **1995**, *14*, 561; b) L. Eriksson, M. P. T. Sjögren, B. Åkermark, *Acta Crystallogr. Sect. C* **1996**, *52*, 77; c) M. P. T. Sjögren, H. Frisell, B. Åkemark, P.-O. Norrby, L. Eriksson, A. Vitagliano, *Organometallics* **1997**, *16*, 942.

[32] Subsequent work involving use of enantiomerically enriched (>90% *ee)* deuterated substrates and analysis of the solution-phase structure and reactivity of deuterated samples of **C** by NMR, has led to the conclusion that **C** is attacked "internally", that is, via a retention pathway, to give the major product enantiomer. With the matched enantiomer of branched substrate the reaction would therefore proceed with overall net retention, via a two-fold retention mechanism [a) G. C. Lloyd-Jones, S. W. Krska, D. L. Hughes, L. Gouriou, V. D. Bonnet, K. Jack, Y. Sun, R. A. Reamer, *J. Am. Chem. Soc.* **2004**, *126*, 702; b) D. L. Hughes, G. C. Lloyd-Jones, S. W. Krska, L. Gouriou, V. D. Bonnet, K. Jack, Y. Sun, R. A. Reamer, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5379], in consonance with our earlier observation of the *ret–ret* pathway.[4] This process could be envisaged to occur by coordination of the nucleophile to the Mo, followed by reductive elimination, or by an S_N2'-like process involving a slipped η^3 complex or a full η^1 complex. The coordinative saturation at the Mo in **C** suggests that the former is unlikely. The intermediacy of a full η^1 complex would not account for a memory effect (see below). For a computational approach to the structure of molybdenum π-complexes, see the following: J. A. R. Luft, Z. X. Yu,

D. L. Hughes, G. C. Lloyd-Jones, S. W. Krska, K. N. Houk, *Tetrahedron: Asymmetry* **2006**, *17*, 716.

[33] a) This result, first reported by us in a preliminary communication,[8a] has now been confirmed by Trost and Hughes,[15b] who reported 77% *ee* (*S*), 43% yield, and 9:1 regioisomer ratio. The minor variation can be tentatively attributed to the slightly different reaction conditions and different Mo precatalayst employed, that is, $[(EtCN)_3Mo(CO)_3]$ and $[(C_7H_8)Mo(CO)_3]$, respectively. b) The reaction catalyzed by Mo·**14** mirrors the result reported by Trost and Hughes[15b] (90% *ee*, 72% yield, and 8:1 regioisomer ratio).

[34] The reaction of cinnamyl carbonate **4** with sodium dimethyl malonate in the presence of [Mo]/**19** proved to proceed with ordinary kinetics, namely with no induction period and no appreciable decomposition or isomerization of products; the reaction was complete within ca 5 h.

[35] The regioselectivities of the catalytic and stoichiometric (in [Mo]/**19**) reaction turned out to differ marginally (83:17 vs 90:10); the catalytic version was faster.

[36] Cinnamyl carbonate **4** and the corresponding bromide provided almost identical results (i.e., regioselectivity and yields) in stoichiometric (in [Mo]/**19**) reactions, (90:10, 36% and 89:11, 39%, respectively). The catalytic reactions cannot be compared since cinnamyl bromide undergoes a non-catalytic reaction, which provides solely the linear product.

[37] 1-Phenyl-but-1-en-3-yl acetate does not react with sodium dimethyl malonate under molybdenum catalysis, showing that molybdenum requires primary allylic esters.

[38] For a dramatic, beneficial effect on *N*-methylation of α-picolinic amide ligands (related to these) in the copper-catalyzed Et_2Zn conjugate addition to enones, see: A. V. Malkov, J. B. Hand, P. Kočovský, *Chem. Commun.* **2003**, 1948.

[39] The good reactivity of ligand **18** lends additional credence to monodeprotonation. Here, in contrast to the other ligands, the three ligating centers must take a meridional arrangement (*mer*) and that could explain the lack of enantioselectivity, which is determined by the turn in the ligand forming facial (*fac*) coordination of the three ligating centers around metal.

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[48] The *ee* values were determined by chiral GC or HPLC; the absolute configurations of the corresponding carbonates **37c** was determined by optical rotation, which then confirms the absolute configuration of the precursors and other products, e.g., the acetate.

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[50] The regio- and enantioselectivities obtained with the D-labeled substrates are slightly lower than those obtained with the unlabelled substrates **4** and **5**. Experiments reported below, employing racemic **37c**, demonstrate how selectivity in the mismatched manifold changes with conversion. A possible origin of this effect is the presence of greater quantities of a CO source, for example, $[Mo(CO)_6]$, in the initial stages of the reaction due to the pro-catalyst formation under ambient temperature conditions. For a full discussion, see the main text.

[51] It is important to note that the memory effect in the reaction of the mismatched enantiomer of branched substrate is not unique to the C_1-symmetric bispicolinamide ligands described herein, but is also prevalent in reactions catalyzed by C_2-symmetric bispicolinamide ligands such as **8**.

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