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Unexpected reversal of the enantioselectivity using chiral quinolylmethyl- and acridininyloxazolines as ligands for asymmetric palladium-catalyzed allylic alkylation

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Abstract

New chiral quinolylmethyloxazolines and acridininyloxazolines were prepared and assessed in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. The introduction of a benzo-fused substituent on the pyridine ring not containing the chiral backbone resulted in the switch of the expected chiral sense of enantioselection of the reaction. Enantiomeric excesses up to 78% were obtained.

1. Introduction

Chiral oxazolinylpyridines have been used recently as ligands for enantioselective palladium-catalyzed allylic substitutions affording high enantiomeric excesses.[1] We have prepared the chiral oxazolinylpyridines **1** and **2** (Scheme 1) having different substituents (alkyl, aryl, electron-donating and -withdrawing groups) on the pyridine and oxazoline rings and disclosed their cross effects on the catalytic activity and stereoselectivity of this reaction (steric control and electronic control).[1a,b] Next, in search of a ring-size control of this reaction, taking into account the importance that this parameter has on the stereoselectivity of a catalytic process,[2] we obtained the pyridylmethyloxazolines **3** and the quinolyloxazolines **4**, which form a six-membered chelate ring.[3] While the values obtained with **4** were reasonably better than those obtained with the corresponding pyridyloxazolines **1**, those found with **3** were unexpectedly worse.

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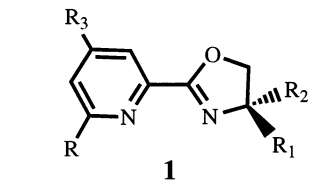
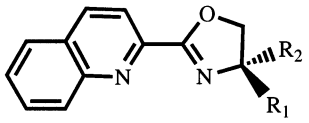
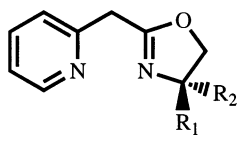
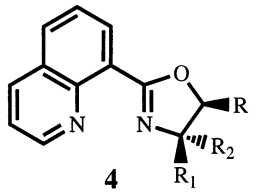


Ligand:	% ee (conf.)
1a: R=R$_3$= H, R$_1$= H, R$_2$= *i*-Pr	24 (*S*)
1b: R=R$_3$= H, R$_1$= Ph, R$_2$= H	55 (*R*)
1c: R= Me, R$_1$= H, R$_2$= *i*-Pr, R$_3$= H	70 (*S*)
1d: R= Me, R$_1$= Ph, R$_2$= H, R$_3$=H	74 (*R*)
1e: R= Me, R$_1$= H, R$_2$= *t*-Bu, R$_3$=H	91 (*S*)
1f: R= Me, R$_1$= H, R$_2$= *t*-Bu, R$_3$= MeO	93 (*S*)

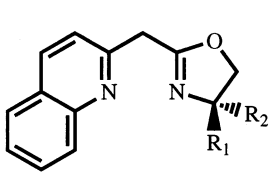


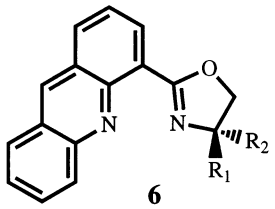
Ligand:	% ee (conf.)
2a: R$_1$= H, R$_2$= *i*-Pr	62 (*S*)
2b: R$_1$= Ph, R$_2$= H	68 (*R*)
2c: R$_1$= H, R$_2$= *t*-Bu	92 (*S*)





Ligand:	% ee (conf.)
3a: R$_1$= H, R$_2$= i-Pr	9 (*S*)
3b: R$_1$= Ph, R$_2$= H	16 (*R*)
4a: R=H, R$_1$= H, R$_2$= i-Pr	42 (*S*)
4b: R=H, R$_1$= Ph, R$_2$= H	59 (*R*)
4c: R=H, R$_1$= H, R$_2$= t-Bu	77 (*S*)
4d: R=Ph, R$_1$= H, R$_2$= i-Pr	43 (*S*)
4e: R=Ph, R$_1$=H, R$_2$= CH_2SiPh_2(t-Bu)	65 (*S*)
4f: R=H, R$_1$= CH_2Ph, R$_2$= H	69 (*R*)





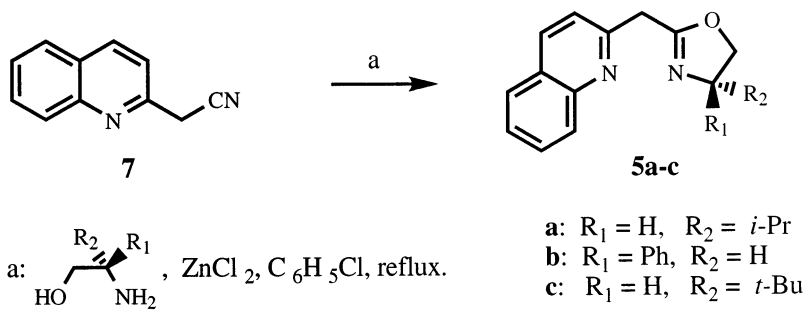
Scheme 1.

In order to obtain a deeper insight into the factors responsible for the enantioselectivity of the reaction, we have prepared and assessed the palladium-catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate, the quinolylmethyloxazolines **5** and acridininyloxazolines **6**, which are the derivatives of **3** and **4** bearing a benzo-fused ring on the pyridine framework. The interest in these new ligands stems from the consideration that the introduction of a substituent on the 6-position of the pyridine of oxazolinylpyridines **1a**,**b** had the effect of increasing the enantioselectivity of the reaction as demonstrated by the results obtained with ligands **2** (Scheme 1).

2. Results and discussion

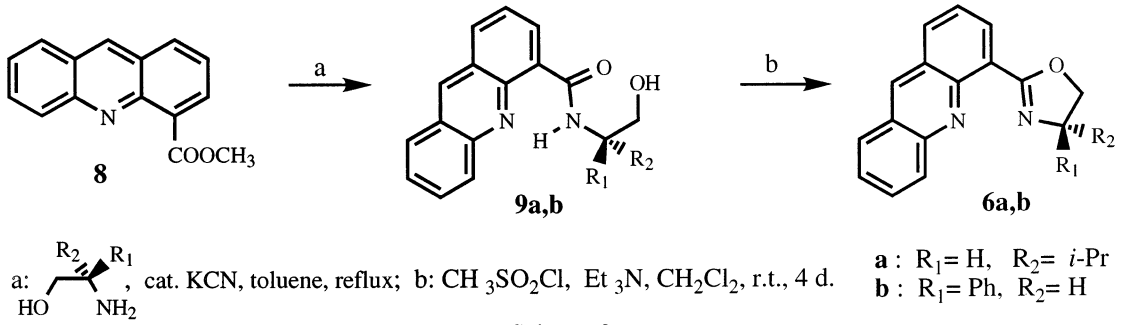
2.1. Synthesis of ligands

Quinolylmethyloxazolines **5a**,**c** were prepared in moderate yields (42–57%) by heating a chlorobenzene solution of 2-cyanomethylquinoline **7** with the pertinent amino alcohol under reflux in the presence of a catalytic amount of zinc chloride[4] (Scheme 2).



Scheme 2.

For the synthesis of acridininyloxazolines **6** the protocol involving the sequence amide–mesylate–oxazoline was evaluated[5] (Scheme 3). Thus, 4-acridinecarboxylic acid methyl ester **8** was heated under reflux with the appropriate amino alcohol in the presence of a catalytic amount of potassium cyanide[6] to give the corresponding amides **9a**,**b** in almost quantitative yield. Finally, the acridineoxazolines **6a**,**b** were obtained directly in moderate overall yields (50–74%) by reaction of **9a**,**b** with methanesulfonyl chloride and triethylamine in a methylene chloride solution. Ligands **6** were unstable compounds and upon standing at room temperature for some days underwent ring opening to give the corresponding amides.



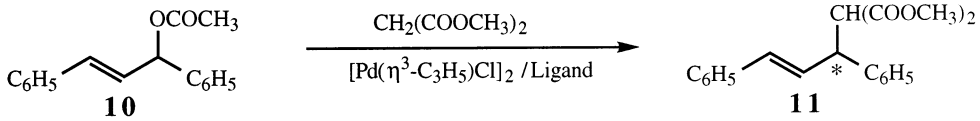
Scheme 3.

2.2. Palladium-catalyzed allylic alkylation

Allylic substitutions were carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a procatalyst and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room or reflux temperature.[7] The results obtained for these catalytic processes are shown in Table 1.

Quinolylmethyloxazolines **5** gave effective palladium catalysts affording the dimethyl 1,3-diphenylprop-2-enylmalonate **11** in high yield. The introduction of a benzo-fused substituent on the pyridine ring had a tremendous effect on the enantioselectivity of the reaction. Thus, ligands **5a**,**b** afforded much better enantiomeric excess (75 and 78%) than the related ligands **3a**,**b** (9 and 16% ee, Scheme 1). Moreover, ligands **5a**,**b** led to better stereochemical results than those obtained with the benzo-substituted ligands **2a**,**b** (62 and 68% ee) and **2b** in which the quinoline and oxazoline rings are directly connected. Unexpectedly, this trend was not followed by ligand **5c** (52% ee), which afforded a much lower enantioselectivity with respect to **2c** (92% ee).

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]



Entry	Ligand	Temperature	React. time, h	Conv.[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**5a**	Rt	42	100	92	75	*R*
2	**5b**	Rt	48	100	88	78	*S*
3	**5c**	Rt	29	100	77	52	*R*
4	**6a**	Rt	168	0	–	–	–
5	**6a**	Reflux	168	38	N.d.	34	*R*
6	**6b**	Rt	168	0	–	–	–
7	**6b**	Reflux	168	75	45	0	–

[a] Reaction of the ligand (10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(COOMe)_2$ (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5% mol) in CH_2Cl_2 (2 ml) at room or reflux temperature.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] Isolated yields.
[d] Determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent.
[e] The assignment is based on the sign of the specific rotation: Ref. 12.

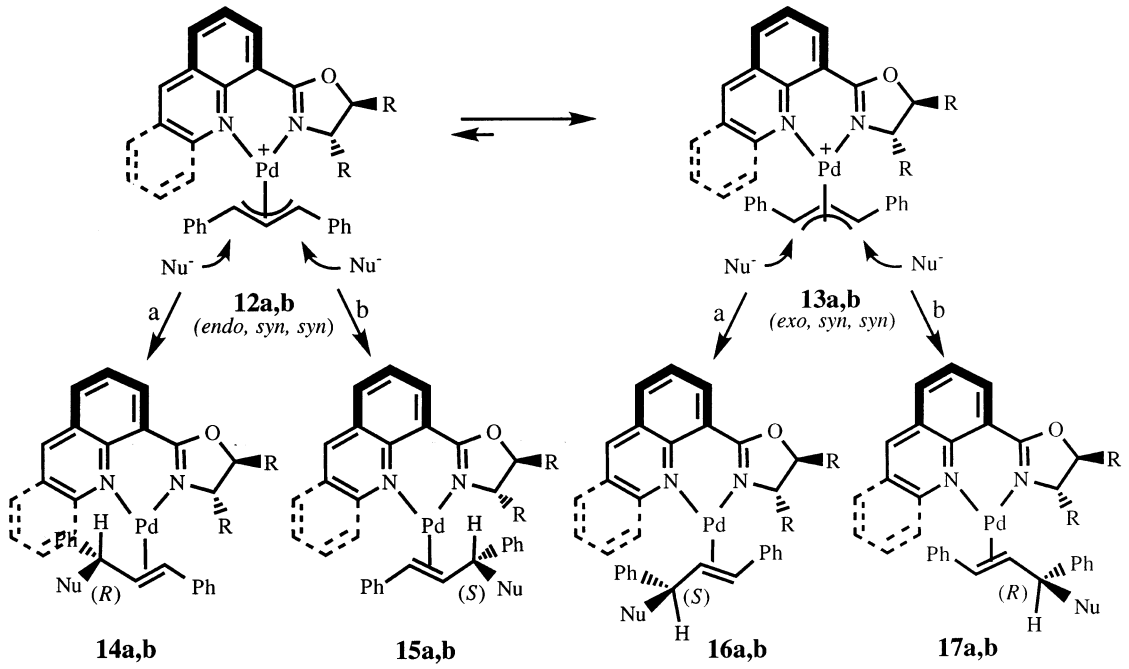
The acridininyloxazolines **6** whose enantioselective ability was expected to be better than that of **5**, because **4** is superior to **3**, was catalytically unreactive at room temperature and afforded only a partial conversion of the starting material after 168 hours at reflux (40°C). Under these reaction conditions a racemic product was obtained with **6b** and a low enantiomeric excess was obtained with **6a**.

The data obtained with ligands **5** and **6** complete the study undertaken in this reaction with ligands **3** and **4** in the search for a ring-size control by expanding the chelating ring size from five to six; and with ligands **1c–f** and **2** in an attempt to sterically control the reaction by introducing an appropriate substituent on the pyridine ring.

With these kinds of ligands the prevailing configuration obtained in the substitution product **11** is strictly connected to the configuration of the oxazoline stereocenter. However, whereas the ligands **1–4** with (*S*)- or (*R*)-configuration yielded **11** with (*S*)- or (*R*)-enantioselectivity, ligands **5** and **6** unexpectedly gave the alkylation product with the opposite configuration.

Rationalization of the steric course of the nucleophilic substitution is difficult because the accepted mechanism for palladium-catalyzed allylic substitutions, which proceeds through a 1,3-diphenyl-η^3-allyl intermediate, foresees that the nucleophile attacks the allylic termini of two alternative diastereomeric π-allyl palladium complexes both with *syn*, *syn* geometry (other isomers with different geometries could be present, but they are much less stable and so their presence can be disregarded). These isomers may interconvert through various mechanisms and are present at the equilibrium in a different ratio. Scheme 4 depicts the two diastereomeric Pd(η^3-1,3-diphenylallyl) complexes **12a**,**b** (*exo*, *syn*, *syn*) and **13a**,**b** (*endo*, *syn*, *syn*) (*exo* configuration refers to the relative orientation of the central allylic C–H vector pointing away from the *R*-substituent) derived from ligands **4a**,**d**,**e** or **5a**,**c**. The products can be formed via four pathways and the preferred one, according to the stereochemical outcome, arises by

reaction at the allylic carbon *trans* or *cis* to the oxazoline nitrogen of *endo* or *exo* isomers, respectively (path b in **12** or a in **13** for ligands **4a**,**d**,**e**; the opposite positions for ligands **5a**,**c**). In order to decide between these possibilities the assumption of an early transition state, in which the more abundant isomer is the more reactive one, is helpful.[8] From this, in conjunction with the known configuration of the products of allylic substitution, it is deduced that the nucleophile preferentially attacks the carbon *trans* to the oxazoline nitrogen of the *exo* isomer in the case of ligands **4a**,**d**,**e** (a in **13a**) and the carbon *cis* of the same isomer in the case of ligands **5a**,**c** (b in **13a**). In confirmation of these conjectures, Muller et al. have demonstrated (by ^{1}H NMR) that the Pd(η^3-1,3-diphenylallyl) complexes derived from ligands **4d**,**e** principally consist of a mixture of the two diastereomeric palladium complexes **12a** and **13a**.[1d] With these ligands the enantioselectivty of the process rises proportionally with the increment of the ratio between **12a** and **13a**, which increases from 2.5:1 for **4d** to 4:1 for **4e** as the substituent on the oxazoline becomes larger.



Scheme 4.

Therefore, the capacity of the ligand to stabilize one of the two diastereomeric complexes is a crucial point in determining its stereodifferentiating ability. This could be increased by controlling the steric requirement not only of a substituent on the 11-position of the oxazoline, but also by introducing a substituent on the pyridine ring which could assist the chirogenic element to increase the stabilization of the sterically favored diastereomer. This expectation is effectively realized both with ligands forming a five-membered chelate ring such as **1c**,**d**,**2a**,**b** and with those ones forming a six-membered chelate such as **5a**,**b**. In fact both these kinds of ligands display a better effectiveness in the enantioselection than the corresponding unsubstituted counterparts **1a**,**b** and **3a**,**b**, respectively.

Another important element which can be used to improve the enantioselection is the enlargement of the chelating ring size.[2] In fact the increase of the chelating ring size, for instance from five to six, brings the substituent on the stereocenter closer to the allylic termini of the π-allyl palladium complex and it is therefore expected to exert a larger influence on the stereoselectivity of the reaction: this is observed, taking into account ligands without substituents on the pyridine ring, with ligands **4a**,**b** which are better enantioselective catalysts than **1a**,**b**, but not with **3a**,**b** which are worse ligands than **1a**,**b**. It is clear that the enlargement of the chelating ring is an important factor for improving the enantioselection, but is insufficient if it is not joint to the stiffening of ligand framework. For this reason both ligands **4** and **1**, providing rigid structures albeit of different sizes, afford better results than **3**. In the case of **3** the methylene bridge allows the ligand to adopt a preferential conformation in the Pd(η^3-1,3-diphenylallyl) complexes, which minimizes the steric interaction between the chirogenic element on the oxazoline and one of the phenyl groups of the allylic system. This fact reduces the ratio between the *exo* and *endo* isomers and thus the enantioselection.

However, these arguments do not explain either the switch of the side of the nucleophilic attack, which leads to the unexpected reversal of the enantioselection observed for ligands **5**,**6** with respect to **4a**,**c**–**e** or the poor stereoselectivity obtained with the *tert*-butyl substituted oxazoline **5c**.

A possible explanation of the observed selectivity for both ligands **1**–**4** and **5**,**6** can be obtained taking into account a late transition state which relates to the severe steric interactions during the formation of the Pd(0) olefin complexes, which are postulated as the primary products upon nucleophilic attack.[9]

According to this model the evolving pyramidalization of the carbon being attacked by the nucleophile would 'push back' the allylic phenyl group toward the substituent present either on oxazoline or pyridine rings. Therefore, that position of the allylic termini will be favored in which there is sufficient space to avoid the unfavorable steric interaction between the proximal phenyl group of the diphenylallyl moiety and the substituent on either oxazoline or pyridine rings. In the case of ligands without substituents on the pyridine such as **4**, the nucleophilic attack will occur preferentially on the carbon *trans* to the oxazoline nitrogen of the *exo* isomer (from **13a** to **16a**, Scheme 4). The nucleophilic attack will occur preferentially in this position also in the case of ligands with substituents on the pyridine such as **2**, because in the related π-allyl palladium complexes the substituents present on the oxazoline and pyridine rings are further away from the allylic termini and therefore the region of the molecule where there is sufficient space to contain the phenyl of the newly formed tertiary carbon is the same as in the previous one. A strikingly different situation is found with ligands **5** where the nucleophilic attack on the carbon *trans* to the oxazoline nitrogen of the *exo* isomer (from **13b** to **16b**) engenders severe steric interaction between the benzo-fused substituent on the pyridine and the phenyl group forming the new bond. Therefore, the nucleophilic attack will occur preferentially on the carbon *cis* to the oxazoline nitrogen of the *exo* isomer (from **13b** to **16b**). An indirect confirmation of this fact is found with ligand **5c**, which affords a much lower enantioselectivity with respect to **5a**,**b** (52 vs 75–78% ee). This stereochemical result can be explained taking into account the increase in the steric demand of the substituent on the oxazoline produced by the very large *t*-butyl group, reducing the space required for the nucleophilic attack on the *cis* position to the oxazoline nitrogen of the *exo* isomer, which makes the nucleophilic attack on the position *trans* to the oxazoline of the same isomer competitive.

In summary, both early and late transition states lead to the conclusion that the preferred product arises from the more abundant *exo* isomer, but only arguments based on a late transition state explain the stereochemical outcome obtained with all ligands **1**–**6**.

3. Experimental

3.1. General methods

Boiling points are uncorrected. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The ^{1}H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin–Elmer 240 B analyzer. 2-Cyanomethylquinoline **7**[10] and 4-acridinecarboxylic acid methyl ester **8**[11] were prepared following a literature procedure. (*S*)-(+)-2-Amino-3-methyl-1-butanol, (*S*)-(+)-2-amino-3,3-dimethyl-1-propanol and (*R*)-(−)-2-amino-2-phenylethanol were purchased from Aldrich.

3.2. General procedure for the preparation of oxazolinylmethylpyridines **5**

In a 25 ml two-necked flask zinc chloride (14 mg, 0.10 mmol) was melted under high vacuum and cooled under argon. After cooling to room temperature, chlorobenzene (12 ml) was added followed by 2-cyanomethylquinoline (0.34 g, 2 mmol) and the suitable amino alcohol (3.0 mmol). The resulting mixture was heated under reflux for the appropriate time (vide infra) and then the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (6 ml) and the resulting solution was washed with water (3×4 ml). The aqueous solution was extracted with CH_2Cl_2 (6 ml), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by chromatography on a silica gel column (benzene:acetone = 8:2).

3.3. (S)-2-{[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl]methyl}quinoline **5a**

(*S*)-(+)-2-Amino-3-methyl-1-butanol was used as the amino alcohol. Reaction time: 96 h; 0.132 g (26%); oil; $[\alpha]_D^{25}$ −47.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.04 (t, 2H, J = 8.4 Hz), 7.73 (d, 1H, J = 8.4 Hz), 7.64 (dd, 1H, J = 8.4, 1.2 Hz), 7.44 (m, 2H), 4.19 (m, 1H), 3.99–3.87 (m, 4H), 1.74 (m, 1H), 0.92 (d, 3H, J = 6.6 Hz), 0.84 (d, 3H, J = 6.6 Hz). Anal. calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.14; N, 11.02. Found: C, 75.66; H, 7.19; N, 11.12

3.4. (R)-2-[(4,5-Dihydro-4-phenyloxazol-2-yl)methyl]quinoline **5b**

(*R*)-(−)-2-Amino-2-phenylethanol was used as the amino alcohol. Reaction time: 96 h; 0.27 g (47%); oil; $[\alpha]_D^{25}$ +56.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.12 (dd, 2H, J = 8.1, 7.8 Hz), 7.79 (d, 1H, J = 8.1 Hz), 7.70 (dt, 1H, J = 8.4, 1.2 Hz), 7.51 (m, 2H), 7.36–7.25 (m, 5H), 5.23 (t, 1H, J = 9.3 Hz), 4.63 (dd, 1H, J = 8.7, 1.5 Hz), 4.12 (m, 3H). Anal. calcd for $C_{19}H_{16}N_2O$: C, 79.13; H, 5.60; N, 9.72. Found: C, 79.25; H, 5.51; N, 9.79.

3.5. (S)-2-{[4,5-Dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]methyl}quinoline **5c**

(*S*)-(+)-2-Amino-3,3-dimethyl-1-propanol was used as the amino alcohol. Reaction time: 144 h; 0.26 g (48%); oil; $[\alpha]_D^{25}$ −59.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.05 (dd, 2H, J = 8.4, 2.7 Hz), 7.72 (d, 1H, J = 8.1 Hz), 7.64 (dt, 1H, J = 8.4, 1.2 Hz), 7.44 (m, 2H), 4.15 (m, 1H), 4.02 (m, 3H), 3.88 (m, 1H), 0.89 (s, 9H). Anal. calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.27; H, 7.61; N, 10.27.

3.6. General procedure for the preparation of 4-acridinecarboxamides **9**

A mixture of 4-acridinecarboxylic acid methyl ester **8** (1.19 g, 5 mmol), the suitable amino alcohol (6.5 mmol) and KCN (65 mg, 1 mmol) in toluene (15 ml) was heated under reflux for the appropriate time (vide infra). The solvent was evaporated under reduced pressure and the residue was purified by chromatography on a silica gel column with the indicated eluent if not otherwise stated.

3.7. (S)-N-[2-Hydroxy-1-(1-methylethyl)ethyl]acridine-4-carboxamide **9a**

(*S*)-(+)-2-Amino-3-methyl-1-butanol was used as the amino alcohol. Reaction time: 40 h; the product was obtained by crystallization of the crude reaction mixture from chloroform:petroleum ether; 0.97 g (63%); mp 207–209°C; ^{1}H NMR ($CDCl_3$) δ 8.94 (dd, 1H, $J=7.2$, 1.5 Hz), 8.87 (s, 1H), 8.14 (t, 2H, $J=9.0$ Hz), 8.03 (d, 1H, $J=8.4$ Hz), 7.85 (m, 1H), 7.62 (m, 2H), 4.25 (m, 1H), 3.94 (m, 2H), 3.80 (s broad, 1H), 2.26 (m, 1H), 1.26 (d, 3H, $J=6.9$ Hz), 1.20 (d, 3H, $J=6.9$ Hz). Anal. calcd for $C_{19}H_{19}N_2O_2$: C,74.23; H, 6.23; N, 9.12. Found: C, 74.07; H, 6.54; N, 8.99.

3.8. (R)-N-(2-Hydroxy-1-phenylethyl)acridine-4-carboxamide **9b**

(*R*)-(−)-2-Amino-2-phenylethanol was used as the amino alcohol. Reaction time: 96 h; chromatographic eluent: petroleum ether:ethyl acetate = 1:3; 1.66 g (97%); mp 177–178°C; ^{1}H NMR ($CDCl_3$) δ 8.96 (d, 1H, $J=7.1$ Hz), 8.87 (s, 1H), 8.14 (d, 1H, $J=7.8$ Hz), 8.02 (dd, 2H, $J=7.3$, 6.6 Hz), 7.81 (m, 1H), 7.62 (m, 4H), 7.47 (m, 2H), 7.38 (m, 1H), 5.51 (m, 2H), 4.15 (m, 2H), 3.77 (s, 1H). Anal. calcd for $C_{22}H_{18}N_2O_2$: C, 77.16; H, 5.3; N, 8.19. Found: C, 77.58; H, 5.51; N, 8.03.

3.9. General procedure for the preparation of oxazolinylquinolines **6**

Methanesulfonyl chloride (0.38 ml, 6.25 mmol) was added to a cold (0°C) solution of quinolinecarboxamides **9a**,**b** (5 mmol) and triethylamine (1.39 ml, 10 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was allowed to warm to room temperature and stirring was continued for 4 days. The solvent was evaporated and the residue was purified by flash chromatography (eluent: petroleum ether:ethyl acetate = 1:3).

3.10. (S)-4-[4,5-Dihydro-4-(1-methylethyl)oxazol-2yl]acridine **6a**

0.42 g (29%); oil; $[\alpha]_D^{25}$ −50.9 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.69 (s, 1H), 8.24 (d, 1H, $J=8.8$ Hz), 8.10 (dd, 1H, $J=7.1$, 1.5 Hz), 8.02 (dd, 1H, $J=8.5$, 1.0 Hz), 7.91 (d, 1H, $J=8.5$ Hz), 7.73 (m, 1H), 7.48 (dd, 2H, $J=8.3$, 7.1 Hz), 4.61 (m, 1H), 4.32 (m, 2H), 2.05 (m, 1H), 1.15 (d, 3H, $J=6.8$ Hz), 1.09 (d, 3H, $J=6.8$ Hz). Anal. calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.37; H, 6.41; N, 9.74.

3.11. (R)-4-(4,5-Dihydro-4-phenyloxazol-2yl)acridine **6b**

0.27 g (17%); oil; $[\alpha]_D^{25}$ +133.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.78 (s, 1H), 8.32 (d, 1H, $J=8.6$ Hz), 8.22 (d, 1H, $J=6.6$ Hz), 8.11 (d, 1H, $J=8.3$ Hz), 7.99 (d, 1H, $J=8.1$ Hz), 7.80 (dd, 1H, $J=8.5$, 6.8 Hz), 7.65–7.53 (m, 4H), 7.46–7.31 (m, 3H), 5.59 (t, 1H, $J=8.1$ Hz), 5.01 (t, 1H, $J=8.4$ Hz), 4.51 (t, 1H, $J=7.8$ Hz). Anal. calcd for $C_{22}H_{16}N_2O$: C, 81.45; H, 4.97; N, 8.64. Found: C, 81.65; H, 4.85; N, 8.82.

3.12. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate: general procedure

A solution of ligand (0.04 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 2.5 mol%) in dry CH_2Cl_2 (2 ml) was stirred at room temperature for 15 min. This solution was treated successively with a solution of rac-(*E*)-1,3-diphenyl-2-propenyl acetate (0.4 mmol) in CH_2Cl_2 (1 ml), dimethyl malonate (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was stirred for the appropriate time (see Table 1) until conversion was complete as shown by TLC analysis (light petroleum:ether = 3:1). The reaction mixture was diluted with ether (25 ml), washed with ice-cold saturated aqueous ammonium chloride. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum:ether = 3:1) to afford dimethyl 1,3-diphenylprop-2-enylmalonate. The enantiomeric excess was determined from the ^1H NMR spectrum in the presence of enantiomerically pure shift reagent Eu(hfc)$_3$; splitting of the signals for one of the two methoxy groups was observed.

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