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Synthesis of chiral 2-alkyl-8-quinolinyl-oxazoline ligands: reversal of enantioselectivity in the asymmetric palladium-catalyzed allylic alkylation

Xiao-Guang Li [a], Xu Cheng [a], Jun-An Ma [a], Qi-Lin Zhou [a,b,*]

[a] *The State Key Laboratory and the Institute of Elemento-organic Chemistry, Nankai University, Weijin Road 94, Tianjin 300071, People's Republic of China*

[b] *The Open Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*

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Abstract

New chiral 2-alkyl-8-quinolinyl-oxazolines were synthesized from 2-alkyl-8-quinolinecarboxylic acids and enantiomerically pure amino alcohols using a convenient procedure. Enantioselective palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of 2-alkyl-8-quinolinyl-oxazolines provided an alkylation product with an opposite configuration compared to those obtained from unsubstituted quinolinyl-oxazoline ligands.

Keywords: Palladium complexes; Asymmetric catalysis; Chiral ligands; Allylic alkylation

1. Introduction

Chiral heteroaryl-oxazolines have been used as ligands in a number of catalytic enantioselective reactions [1]. Recently, we synthesized 8-quinolinyl-oxazolines **1** as ligands in the copper-catalyzed cyclopropanation of styrene with diazoacetates [2], palladium-catalyzed Heck-type hydroarylation of norbornene with phenyl iodides [3] and the copper-catalyzed allylic oxidation of cyclic olefins with *tert*-butyl perbenzoate [4]. In 1999, Chelucci used ligands **1** in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, and moderate to good enantioselectivities have been achieved [5]. Later, he reported that 4-acridininyl-oxazoline ligands, 2,3-benzo-fused derivatives of **1**, have much lower activities and enantioselectivities in this reaction [6]. These promoted us to report our results in the investigation of 2-alkyl-8-quinolinyl-oxazoline ligands **2** in the palladium-catalyzed allylic alkylation reaction.

* Corresponding author. Fax: +86-22-2350-0011.
E-mail address: qlzhou@public.tpt.tj.cn (Q.-L. Zhou).

2. Results and discussion

2-Alkyl-8-quinolinyl-oxazolines were synthesized from 2-alkyl-8-quinolinecarboxylic acids **3** and enantiomerically pure amino alcohols according to the procedure shown in Scheme 1. Thus, the 2-alkyl-8-quinolinecarboxylic acids **3** were converted to the esters **4** in 70–81% yield. The ester exchange of **4** with amino alcohols provided amides **5** in 51–88% yield. The cyclization of amides **5** with MsCl–Et_3N–DMAP in a mild condition afforded the ligands **2** in 54–88% yield [7].

To investigate the chiral discrimination of ligands **2**, asymmetric palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**6**) was performed. The alkylation reaction was carried out in CH_2Cl_2 using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as precatalyst and the *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) as the base according to Trost's procedure [8]. The results are summarized in Table 1.

Compared to ligands **1**, ligands **2** provided a slightly higher level of enantiocontrol, although the reactions using ligands **2** needed longer reaction time. In contrast,

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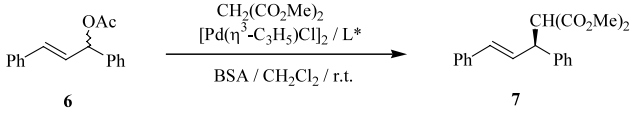
the 4-acridininyl-oxazoline ligands gave much lower enantioselectivities (less than 34% ee) than those obtained with ligands **1** [6]. The effect of the 2-alkyl group (R′) in ligands **2** on the enantioselectivity was examined. When the R group in ligands **2** is benzyl, the influence of the R′ group on the enantioselectivity of the reaction is very limited, resulting in enantiomeric excesses ranging from 66 to 74% (Table 1, entries 7, 11 and 12). However, when R is *tert*-butyl, R′ has a significant effect on the enantioselectivity of the reaction. For example, ligand **2d** (R′ = CH_3) gave 78% ee, whereas ligand **2g** (R′ = *i*-Bu) afforded only 53% ee. It is unexpected and interesting that ligands **2** with *S* configuration yielded the alkylation product **7** with *R* configuration, which is opposite to the configuration of the product given by ligands **1**. This reversal of enantioselectivity was also observed in the reaction with acridininyl-oxazoline ligands [6].



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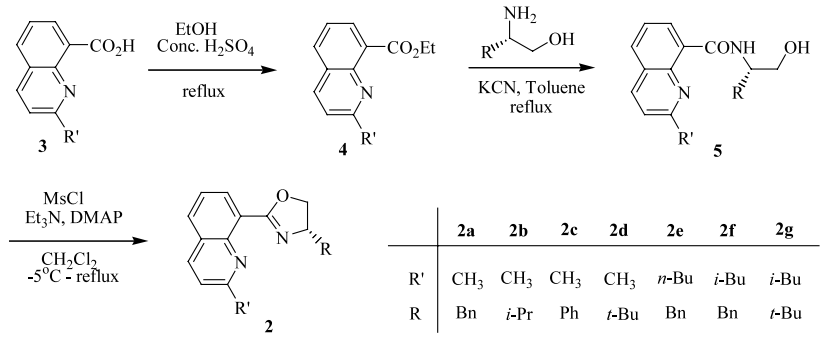
According to the generally accepted mechanism of palladium-catalyzed allylic alkylation, the enantioselectivity of the reaction is determined by the regioselectivity in the attack of nucleophile to one of the two allylic termini in the 1,3-diphenyl-η^3-allylpalladium(II) intermediate [9]. There are a number of possible allylpalladium complex intermediates in the solution. Among them, the intermediate **8** is the most predominant one, and has been demonstrated by ^{1}H-NMR [10]. As shown in Scheme 2, there are two pathways, a and b, for the nucleophile to attack the allylic termini giving the alkylation products with *S* and *R* configuration individually. From the absolute configuration of the product



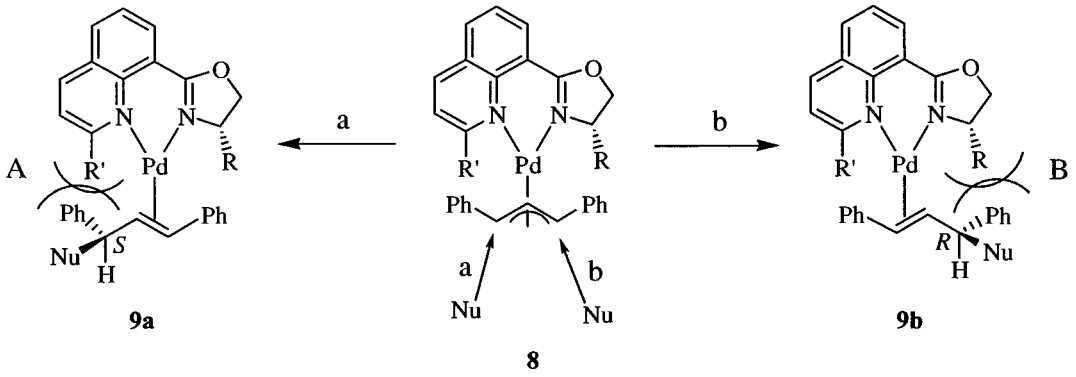
	2a	2b	2c	2d	2e	2f	2g
R′	CH_3	CH_3	CH_3	CH_3	*n*-Bu	*i*-Bu	*i*-Bu
R	Bn	*i*-Pr	Ph	*t*-Bu	Bn	Bn	*t*-Bu

Scheme 1.

Table 1
Enantioselectively allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate [a]

Entry	Ligand	Time (h) [b]	Yield (%) [c]	ee (%) [d]	Conf. [e]
1	**1a** (R′ = H, R = Bn)	3	98	69 [f]	*S*
2	**1b** (R′ = H, R = *i*-Pr)	0.5	96	42 [g]	*S*
3	**1c** (R′ = H, R = Ph)	1	88	59 [g]	*S*
4	**1d** (R′ = H, R = *t*-Bu)	2	94	77 [g]	*S*
7	**2a** (R′ = CH_3, R = Bn)	41	95	66	*R*
8	**2b** (R′ = CH_3, R = *i*-Pr)	60	86	76	*R*
9	**2c** (R′ = CH_3, R = Ph)	64	96	64	*R*
10	**2d** (R′ = CH_3, R = *t*-Bu)	50	79	78	*R*
11	**2e** (R′ = *n*-Bu, R = Bn)	51	96	73	*R*
12	**2f** (R′ = *i*-Bu, R = Bn)	60	67	74	*R*
13	**2g** (R′ = *i*-Bu, R = *t*-Bu)	46	99	53	*R*

[a] Reaction condition: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand (10 mol%), 1,3-diphenyl-2-propenyl acetate (0.4 mmol), $CH_2(CO_2Me)_2$ (1.2 mmol), BSA (1.2 mmol) and KOAc (3.5 mol%) in dichloromethane (4 ml) at room temperature.
[b] Time for completion of reaction.
[c] Isolated yields.
[d] Determined by HPLC using a chiral column (DIACEL Chiracel OD, at 254 nm, *n*-hexane–2-propanol = 99:1, 0.9 ml min^{-1}, t_R = 15.3 min, t_S = 16.8 min).
[e] Assigned by comparison of specific rotation with that in the literature (Ref. [12]).
[f] Data are taken from literature (Ref. [10]).
[g] Data are taken from literature (Ref. [5]).



Scheme 2.

obtained with ligands **2**, we know that the nucleophile preferentially attacks the allylic terminus *trans* to the quinoline nitrogen, i.e. pathway b. This selectivity can be explained by a late transition state related to the steric interaction between ligand and allyl in a product like the Pd(0)–olefin complex [6,9d,11]. According to this model, the pathway of the nucleophile depends on the relative strength of steric interactions A and B. When R′ is hydrogen, the steric interaction B is stronger than A, and the Pd(0)–olefin complex **9a** is more stable than **9b**, providing the alkylation product with *S* configuration (pathway a). However, when R′ is an alkyl group, the steric interaction A is stronger than B, and the complex **9b** becomes more stable than **9a**, giving the product with *R* configuration (pathway b). In the case of ligand **2g**, the bulk *tert*-butyl on the oxazoline ring decreased the difference between the steric interactions A and B, leading to a lower enantioselectivity.

In conclusion, 2-alkyl-quinolinyl-oxazoline ligands have been synthesized, and the substituents on position 2 of the quinoline ring can tune the configuration of product in the palladium-catalyzed alkylation reaction, which could be explained by a late transition state.

3. Experimental

3.1. General

Dichloromethane was distilled from CaH_2. Chloroform was distilled from anhydrous $CaSO_4$. The 2-alkyl-8-quinolinylcarboxylic acids were prepared according to the Doebner–Miller method [13]. All optically pure amino alcohols were prepared by reduction of the corresponding commercially available amino acids with $NaBH_4/H_2SO_4$ in THF [14]. IR (film): selected bands in cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 or 300 Hz): δ in ppm (TMS), J in Hz. EIMS: selected peaks, m/z (%).

3.2. Synthesis of ethyl 2-alkyl-8-quinolinecarboxylate **4**

3.2.1. Synthesis of ethyl 2-methyl-8-quinolinecarboxylate (**4a**)

3.2.1.1. General procedure. A mixture of 2-methyl-8-quinolinecarboxylic acid (**3a**) (2.0 g, 10.7 mmol), anhydrous EtOH (35 ml) and concentrated sulfuric acid (0.8 ml) was heated under reflux for 3 days. After the solvent was evaporated under reduced pressure, the residue was dissolved in $CHCl_3$ (50 ml) and washed with saturated $NaHCO_3$ (3×20 ml) and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give 1.86 g (8.65 mmol, 81%) of **4a** as a pale orange solid, which was used directly for the next step without further purification. M.p. 56–58 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 1H), 7.83 (d, $J = 7.3$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 8.7$ Hz, 1H), 4.49 (q, $J = 7.1$ Hz, 2H), 2.72 (s, 3H), 1.42 (t, $J = 7.2$ Hz, 3H). TLC (PE–EtOAc = 2:1): $R_f = 0.50$.

3.2.2. Synthesis of ethyl 2-butyl-8-quinolinecarboxylate (**4b**)

Pale yellow oil, 70% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, $J = 8.4$ Hz, 1H), 8.00–7.80 (m, 2H), 7.48 (t, $J = 8.1$ Hz, 1H), 7.30 (d, $J = 9.0$ Hz, 1H), 4.51 (q, $J = 7.2$ Hz, 2H), 2.96 (t, $J = 7.8$ Hz, 2H), 1.95–1.75 (m, 2H), 1.60–1.35 (m, 5H), 0.96 (t, $J = 7.8$ Hz, 3H). TLC (PE–EtOAc = 6:1): $R_f = 0.55$.

3.2.3. Synthesis of ethyl 2-isobutyl-8-quinolinecarboxylate (**4c**)

Pale yellow oil, 81% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 7.2$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 7.2$ Hz, 1H), 4.51 (q, $J = 7.2$ Hz, 2H), 2.84 (d, $J = 6.9$ Hz, 2H), 2.38–2.20 (m, 1H), 1.44 (t, $J = 7.2$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 6H). TLC (PE–EtOAc = 6:1): $R_f = 0.55$.

3.3. Synthesis of 2-alkyl-8-quinolinecarboxamides **5**

3.3.1. (1′S)-N-(1′-Benzyl-2′-hydroxyethyl)-2-methyl-8-quinolinecarboxamide (**5a**)

3.3.1.1. General procedure. A mixture of ethyl 2-methyl-8-quinolinecarboxylate (**4a**) (3.01 g, 14 mmol), L-phenylalaninol (2.75 g, 18.2 mmol) and KCN (303 mg, 4.67 mmol) in toluene (50 ml) was heated under reflux until the ester disappeared. After cooling to room temperature (r.t.), water (20 ml) was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (2×30 ml). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by flash column chromatography on silica gel with PE–EtOAc (1:2) to give 3.94 g (12.3 mmol, 88%) of **5a** as a white solid. M.p. 96–98 °C. $[\alpha]_D^{20}$ −142.0 (*c* 0.4, EtOH). IR: 3355m, 3158w, 3064w, 2940m, 2875w, 1952w, 1883w, 1732w, 1631s, 1563s, 1496w, 1384m, 1358m, 1278w, 1235w, 1078m, 1037m. ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 11.87 (d, $J = 6.7$ Hz, 1H), 8.74 (d, $J = 7.3$ Hz, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.32–7.15 (m, 6H), 4.60–4.40 (m, 1H), 3.90–3.70 (m, 2H), 3.39 (broad, 1H), 3.20–3.05 (m, 2H), 2.64 (s, 3H). EIMS: 320 (1, M^+), 289 (13), 230 (15), 229 (75), 211 (9), 171 (25), 170 (100), 143 (28), 115 (39), 91 (10). TLC (PE–EtOAc = 1:2): $R_f = 0.49$. Anal. Calc. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.78; H, 6.76; N, 8.99%.

3.3.2. (1′S)-N-(1′-Isopropyl-2′-hydroxyethyl)-2-methyl-8-quinolinecarboxamide (**5b**)

White solid, 56% yield. M.p. 115–117 °C. $[\alpha]_D^{20}$ −21.0 (*c* 0.4, EtOH). IR: 3345m, 3180w, 3035w, 2958w, 2926w, 2875w, 1953w, 1911w, 1864w, 1644s, 1617m, 1594m, 1548s, 1460m, 1386w, 1369m, 1285m, 1080m. ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 11.78 (d, $J = 6.3$ Hz, 1H), 8.78 (d, $J = 7.3$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 7.3$ Hz, 1H), 7.60 (t, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 1H), 4.25–4.00 (m, 1H), 3.90–3.70 (m, 3H), 2.77 (s, 3H), 2.30–2.10 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.3$ Hz, 3H). EIMS: 241 (35), 170 (100), 143 (26), 142 (16), 115 (39), 43 (18), 41 (17), 31 (27), 27 (13). TLC (PE–EtOAc = 1:2): $R_f =$ 0.40. Anal. Calc. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.70; H, 7.38; N, 10.26%.

3.3.3. (1′S)-N-(1′-Phenyl-2′-hydroxyethyl)-2-methyl-8-quinolinecarboxamide (**5c**)

White solid, 60% yield. M.p. 149–150 °C. $[\alpha]_D^{20}$ −147.5 (*c* 0.4, EtOH). IR: 3372m, 3209w, 3027w, 2998w, 2926w, 2875w, 1950w, 1870w, 1732w, 1643s, 1605m, 1594m, 1546s, 1489m, 1455m, 1431m, 1278w, 1070m. ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 12.46 (d, $J = 5.2$ Hz, 1H), 8.79 (d, $J = 6.3$ Hz, 1H), 8.14 (d, $J = 8.5$ Hz, 1H), 7.91 (d, $J = 5.2$ Hz, 1H), 7.60–7.24 (m, 7H), 5.55–5.30 (m, 1H), 4.20–4.00 (m, 2H), 3.90–3.70 (m, 1H), 2.65 (s, 3H). EIMS: 276 (20), 275 (48), 171 (13), 170 (100), 143 (22), 142 (13), 115 (23). TLC (PE–EtOAc = 1:1): $R_f = 0.40$. Anal. Calc. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 73.98; H, 5.52; N, 9.14%.

3.3.4. (1′S)-N-(1′-tert-Butyl-2′-hydroxyethyl)-2-methyl-8-quinolinecarboxamide (**5d**)

White solid, 72% yield. M.p. 138–139.5 °C. $[\alpha]_D^{20}$ −10.8 (*c* 0.4, EtOH). IR: 3354m, 3165w, 3035w, 2962w, 2919w, 2868w, 1947w, 1908w, 1869w, 1777w, 1639s, 1590m, 1563s, 1431m, 1394w, 1369m, 1221w, 1084m. ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 11.83 (d, $J = 6.3$ Hz, 1H), 8.80 (d, $J = 7.3$ Hz, 1H), 8.16 (d, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.60 (t, $J = 7.3$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 4.20–3.90 (m, 2H), 3.80–3.60 (m, 2H), 2.77 (s, 3H), 1.14 (s, 9H). EIMS: 256 (9), 255 (32), 229 (48), 211 (6), 171 (19), 170 (100), 143 (24), 142 (17), 115 (28). TLC (PE–EtOAc = 1:1): $R_f = 0.40$. Anal. Calc. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.77; H, 7.61; N, 9.70%.

3.3.5. (1′S)-N-(1′-Benzyl-2′-hydroxyethyl)-2-butyl-8-quinolinecarboxamide (**5e**)

White solid, 73% yield. M.p. 114–117 °C. $[\alpha]_D^{20}$ −115.8 (*c* 0.4, EtOH). IR: 3352m, 3151w, 3027w, 2955w, 2926w, 2860w, 1953w, 1911w, 1743w, 1627s, 1588m, 1563s, 1539s, 1496m, 1360m, 1135m, 1093m, 1046m. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 11.97 (d, $J = 6.6$ Hz, 1H), 8.80 (dd, $J = 7.2$ and 1.5 Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 7.92 (dd, $J = 8.1$ and 1.5 Hz, 1H), 7.61 (t, $J = 7.8$ Hz, 1H), 7.37–7.18 (m, 6H), 4.65–4.50 (m, 1H), 4.00–3.80 (m, 2H), 3.80–3.65 (m, 1H), 3.30–3.05 (m, 2H), 2.94 (t, $J = 7.8$ Hz, 2H), 1.90–1.70 (m, 2H), 1.50–1.30 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H). EIMS: 362 (1, M^+) 331 (21), 271 (87), 253 (9), 213 (26), 212 (100), 185 (7), 169 (8), 142 (10), 115 (19), 91 (11). TLC (PE–EtOAc = 1:1): $R_f = 0.40$. Anal. Calc. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.86; H, 7.25; N, 7.70%.

3.3.6. (1′S)-N-(1′-Benzyl-2′-hydroxyethyl)-2-isobutyl-8-quinolinecarboxamide (**5f**)

White solid, 54% yield. M.p. 129–131 °C. $[\alpha]_D^{20}$ −116.8 (*c* 0.4, EtOH). IR: 3353m, 3136m, 3013w, 2955m, 2917m, 2866m, 1965w, 1910w, 1869w, 1776w, 1627s, 1563s, 1489m, 1454m, 1358m, 1336m, 1198w, 1136m, 1092m, 1046m. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 11.97 (d, $J = 6.6$ Hz, 1H), 8.80 (d, $J = 7.2$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.61 (t, $J = 7.8$ Hz, 1H), 7.37–7.18 (m, 6H), 4.60–4.45 (m, 1H), 3.90 (d, $J = 11.1$ Hz, 1H), 3.77 (d, $J = 4.8$ Hz, 1H), 3.20–3.00 (m, 3H), 2.77 (d, $J = 6.9$ Hz, 2H), 2.20–2.00

(m, 1H), 0.95 (d, $J = 6.6$ Hz, 6H). EIMS: 362 (0.7, M^+), 331 (11), 271 (73), 213 (22), 212 (100), 185 (16), 169 (20), 142 (22), 115 (24), 91 (35). TLC (PE–EtOAc = 1:1): $R_f = 0.57$. Anal. Calc. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.35; H, 7.06; N, 7.53%.

3.3.7. (1′S)-N-(1′-tert-Butyl-2′-hydroxyethyl)-2-isobutyl-8-quinolinecarboxamide (**5g**)

White solid, 51% yield. M.p. 114–116 °C. $[\alpha]_D^{20}$ −31.3 (*c* 0.4, EtOH). IR: 3317m, 3158m, 3027w, 2958m, 2911w, 2875w, 1961w, 1917w, 1872w, 1637s, 1591m, 1567s, 1543s, 1460m, 1393w, 1382w, 1362m, 1220w, 1084s. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 11.62 (s, 1H), 8.94 (s, 1H), 8.27 (d, $J = 7.5$ Hz, 1H), 7.98 (d, $J = 8.1$ Hz, 1H), 7.68 (t, $J = 7.8$ Hz, 1H), 7.41 (d, $J = 8.1$ Hz, 1H), 4.65–4.45 (m, 1H), 4.28–4.10 (m, 1H), 4.05 (dd, $J = 10.8$ and 2.4 Hz, 1H), 3.80 (t, $J = 9.6$ Hz, 1H), 2.91 (d, $J = 6.9$ Hz, 2H), 2.30–2.10 (m, 1H), 1.14 (s, 9H), 0.99 (t, $J = 7.5$ Hz, 6H). EIMS: 298 (15), 297 (47), 271 (67), 213 (28), 212 (100), 185 (27), 169 (24), 142 (22), 115 (25), 41 (12). TLC (PE–EtOAc = 1:1): $R_f = 0.40$. Anal. Calc. for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 72.33; H, 8.38; N, 8.24%.

3.4. Synthesis of 2-alkyl-8-quinolinyl-oxazoline ligands **2**

3.4.1. (4S)-4,5-Dihydro-2-(2′-methyl-8′-quinolinyl)-4-benzyloxazole (**2a**)

3.4.1.1. General procedure. To a mixture of **5a** (3.2 g, 10 mmol), 4-dimethylaminopyridine (50 mg, 0.4 mmol) and Et_3N (5.39 ml, 39.1 mmol) in CH_2Cl_2 (85 ml) was added methanesulfonyl chloride (4.44 g, 3 ml, 38.7 mmol) at −5 to 0 °C, and the solution was stirred for 40 min at this temperature. Another portion of Et_3N (24.54 ml, 175.6 mmol) was added to the solution, and it was refluxed until the initially formed mesylate disappeared (checked by TLC). After cooling to r.t., the reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $NaSO_4$. After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel (elution with PE–EtOAc = 1:2) to give 2.68 g (8.87 mmol, 88%) of **2a** as a pale yellow solid. M.p. 101–102 °C. $[\alpha]_D^{20}$ −8.0 (*c* 0.8, EtOH). IR: 3020w, 2970w, 2926w, 1947w, 1901w, 1729w, 1671s, 1606m, 1598s, 1569m, 1493m, 1431w, 1355m, 1255m, 1189m, 1129m, 1020m. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 8.04 (d, $J = 8.6$ Hz, 1H), 8.01 (d, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 7.35–7.24 (m, 6H), 4.80–4.65 (m, 1H), 4.50 (dd, $J = 9.4$ and 8.3 Hz, 1H), 4.26 (t, $J = 7.8$ Hz, 1H), 3.34 (dd, $J = 13.6$ and 5.2 Hz, 1H), 2.90 (dd, $J = 13.6$ and 8.4 Hz, 1H), 2.76 (s, 3H). EIMS: 302 (2, M^+), 301 (2, M − 1), 212 (32), 211 (100), 182 (18), 170 (9), 156 (50), 115 (18), 91 (12). TLC (PE–EtOAc = 1:2): $R_f = 0.30$. Anal. Calc. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 78.78; H, 6.30; N, 9.26%.

3.4.2. (4S)-4,5-Dihydro-2-(2′-methyl-8′-quinolinyl)-4-isopropyloxazole (**2b**)

Orange yellow oil, 81% yield. $[\alpha]_D^{20}$ −83.5 (*c* 0.8, EtOH). IR: 3050w, 2958s, 2926m, 2900m, 2872m, 2721w, 1942w, 1898w, 1830w, 1667s, 1614s, 1600s, 1570m, 1500s, 1465m, 1384w, 1357s, 1326m, 1188s, 1129s, 1024s. ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 7.97 (d, $J = 8.7$ Hz, 1H), 7.94 (d, $J = 7.3$ Hz, 1H), 7.82 (d, $J = 8.3$ Hz, 1H), 7.45 (t, $J = 7.3$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 1H), 4.60–4.40 (m, 1H), 4.40–4.15 (m, 2H), 2.69 (s, 3H), 2.05–1.90 (m, 1H), 1.07 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 7.1$ Hz, 3H). EIMS: 255 (1, M + 1), 254 (5, M^+), 212 (15), 211 (100), 183 (11), 182 (10), 170 (13), 156 (53), 115 (19), 43(19), 41(25). TLC (PE–EtOAc = 1:1): $R_f = 0.40$. Anal. Calc. for $C_{16}H_{18}N_2O$: C, 75.79; H, 7.13; N, 11.01. Found: C, 75.15; H, 7.43; N, 10.64%.

3.4.3. (4S)-4,5-Dihydro-2-(2′-methyl-8′-quinolinyl)-4-phenyloxazole (**2c**)

Orange yellow oil, 80% yield. $[\alpha]_D^{20}$ −71.5 (*c* 0.8, EtOH). IR: 3054w, 3028w, 2964w, 2917w, 1952w, 1891w, 1822w, 1733w, 1667s, 1614s, 1600s, 1571m, 1498s, 1472w, 1453m, 1433m, 1356s, 1324m, 1185s, 1130s, 1022s. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 8.07 (t, $J = 8.7$ Hz, 1H), 8.06 (dd, $J = 7.5$ and 1.5 Hz, 1H), 7.90 (dd, $J = 8.4$ and 1.5 Hz, 1H), 7.64–7.56 (m, 2H), 7.52 (t, $J = 7.8$ Hz, 1H), 5.53 (dd, $J = 10.2$ and 7.5 Hz, 1H), 4.94 (dd, $J = 9.9$ and 8.1 Hz, 1H), 4.45 (t, $J = 7.8$ Hz, 1H), 2.82 (s, 3H). EIMS: 289 (8, M + 1), 288 (43, M^+), 287 (6, M − 1), 258 (58), 257 (44), 184 (65), 170 (100), 115 (17), 91 (41), 89 (34). TLC (PE–EtOAc = 1:1): $R_f = 0.50$.

3.4.4. (4S)-4,5-Dihydro-2-(2′-methyl-8′-quinolinyl)-4-tert-butyloxazole (**2d**)

Pale purple oil, 80% yield. $[\alpha]_D^{20}$ −114.3 (*c* 0.8, EtOH). IR: 3054w, 2955w, 2897w, 2860w, 1947w, 1905w, 1840w, 1670s, 1614m, 1598m, 1564m, 1497m, 1392w, 1360m, 1292m, 1256m, 1185m, 1129m. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 8.02 (d, $J = 8.7$ Hz, 1H), 7.95 (dd, $J = 7.2$ and 1.5 Hz, 1H), 7.84 (dd, $J = 8.1$ and 1.8 Hz, 1H), 7.47 (dd, $J = 8.1$ and 7.2 Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 4.51 (dd, $J = 10.5$ and 8.7 Hz, 1H), 4.39 (t, $J = 8.1$ Hz, 1H), 4.19 (dd, $J = 10.2$ and 7.8 Hz, 1H), 2.73 (s, 3H), 1.08 (s, 9H). EIMS: 269 (1, M + 1), 268 (3, M^+), 211 (100), 170 (13), 156 (36), 115 (14), 41 (24), 29 (27). TLC (PE–EtOAc = 1:1): $R_f = 0.50$. Anal. Calc. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.43. Found: C, 75.69; H, 7.78; N, 9.68%.

*3.4.5. (4S)-4,5-Dihydro-2-(2′-butyl-8′-quinolinyl)-4-benzyloxazole (**2e**)*

Orange yellow oil, 78% yield. $[\alpha]_D^{20}$ −22.6 (*c* 0.8, EtOH). IR: 3058w, 2955s, 2928s, 2870m, 2859m, 1946w, 1887w, 1810w, 1658s, 1612s, 1600s, 1570m, 1498s, 1464m, 1454m, 1358s, 1181m, 1129s, 1005m. ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 8.02 (d, $J = 8.6$ Hz, 1H), 7.93 (dd, $J = 7.7$ Hz, 1H), 7.81 (t, $J = 8.3$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 1H), 7.35–7.23 (m, 6H), 4.80–4.60 (m, 1H), 4.48 (t, $J = 8.9$ Hz, 1H), 4.26 (t, $J = 7.8$ Hz, 1H), 3.33 (dd, $J = 13.6$ and 5.2 Hz, 1H), 3.05–2.90 (m, 3H), 1.95–1.70 (m, 2H), 1.45–1.25 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). EIMS: 344 (1, M^+), 343 (0.8, M − 1), 302 (16), 254 (24), 253 (100), 181 (11), 168 (14), 156 (16), 91 (47). TLC (PE–EtOAc = 1:1): $R_f = 0.60$. Anal. Calc. for $C_{23}H_{24}N_2O$: C, 79.48; H, 7.02; N, 8.13. Found: C, 79.48; H, 7.54; N, 7.85%.

*3.4.6. (4S)-4,5-Dihydro-2-(2′-isobutyl-8′-quinolinyl)-4-benzyloxazole (**2f**)*

Orange yellow oil, 54% yield. $[\alpha]_D^{20}$ −27.3 (*c* 0.8, EtOH). IR: 3058w, 3026w, 2954s, 2928m, 2895m, 2867m, 1946w, 1884w, 1814w, 1658s, 1612m, 1600m, 1570m, 1498s, 1464m, 1454m, 1384w, 1359m, 1183m, 1130m, 1005m. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 8.04 (d, $J = 8.4$ Hz, 1H), 7.95 (dd, $J = 7.2$ and 1.2 Hz, 1H), 7.86 (dd, $J = 8.1$ and 1.2 Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 7.35–7.24 (m, 6 H), 4.850–4.65 (m, 1 H), 4.50 (t, $J = 9.0$ Hz, 1H), 4.28 (t, $J = 7.8$ Hz, 1H), 3.33 (dd, $J = 13.8$ and 5.1 Hz, 1H), 2.95–2.85 (m, 3H), 2.40–2.20 (m, 1H), 1.01 (d, $J = 6.9$ Hz, 6H). EIMS: 345 (1, M + 1), 344 (4, M^+), 343 (2, M − 1), 302 (26), 254 (35), 253 (100), 225 (16), 198 (24), 181 (16), 168 (25), 115 (10), 91 (27). TLC (PE–EtOAc = 1:1): $R_f = 0.40$. Anal. Calc. for $C_{23}H_{24}N_2O$: C, 79.48; H, 7.02; N, 8.13. Found: C, 78.64; H, 7.03; N, 7.77%.

*3.4.7. (4S)-4,5-Dihydro-2-(2′-isobutyl-8′-quinolinyl)-4-tert-butyloxazole (**2g**)*

Orange yellow oil, 73% yield. $[\alpha]_D^{20}$ −116.3 (*c* 0.4, EtOH). IR: 3049w, 2954s, 2902m, 2868s, 1935w, 1884w, 1826w, 1667s, 1613m, 1599m, 1572w, 1499s, 1478m, 1464m, 1393w, 1384w, 1356s, 1183m, 1129m, 1013s. ^{1}H-NMR ($CDCl_3$, 300 Hz): δ 8.02 (d, $J = 8.7$ Hz, 1H), 7.92 (dd, $J = 6.9$ and 1.5 Hz, 1H), 7.84 (dd, $J = 8.1$ and 1.5 Hz, 1H), 7.46 (dd, $J = 8.4$ and 7.5 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 4.48 (dd, $J = 10.2$ and 8.7 Hz, 1H), 4.38 (t, $J = 8.4$ Hz, 1H), 4.17 (dd, $J = 10.2$ and 7.8 Hz, 1H), 2.82 (d, $J = 7.2$ Hz, 2H), 2.35–2.15 (m, 1H), 1.06 (d, $J = 4.8$ Hz, 9H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H). EIMS: 311(1, M + 1), 310 (6, M^+), 309 (2, M − 1), 268 (30), 254 (8), 253 (100), 212 (13), 168 (14), 156 (11), 41 (9). TLC (PE–EtOAc = 1:1): $R_f = 0.50$. Anal. Calc. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.69; H, 8.35; N, 8.99%.

3.5. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate

3.5.1. General procedure

[Pd (η^3-C_3H_5) Cl]$_2$ (4 mg, 2.5 mol%) and the ligand (0.04 mmol, 10 mol%) were added into a Shlenck tube containing 2 ml CH_2Cl_2 under nitrogen and the mixture was stirred at 25 °C for 30 min. To this solution, rac-(*E*)-1,3-diphenyl-2-propenyl acetate (0.4 mmol, 100.8 mg) in 2 ml CH_2Cl_2, $CH_2(CO_2Me)_2$ (0.14 ml, 1.2 mmol), BSA (0.3 ml, 1.2 mmol) and KOAc (1.4 mg, 3.5 mol%) were added successively. The resulting mixture was stirred at 25 °C for an appropriate time. After the reaction was completed (determined by TLC), the reaction mixture was diluted with ether (25 ml) and washed with ice-cold saturated aqueous ammonium chloride. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE–EtOAc = 6:1) to give dimethyl 1,3-diphenyl-2-propenylmalonate. The enantiomeric excess was determined by HPLC with DAICEL Chiracel OD (hexane–2-propanol = 99:1).

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