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Enantioselective glyoxylate-ene reaction using a novel spiro bis(isoxazoline) ligand in copper catalysis

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Abstract—Novel chiral spiro bis(isoxazoline) ligands **3** and **4** are synthesized from an optically active olefin. The Cu(II)-spiro bis(isoxazoline) complex prepared in situ from $Cu(OTf)_2$ and **3** promoted the glyoxylate-ene reaction in high yield and moderate enantioselectivity (up to 70%).

1. Introduction

The search for novel chiral ligands is one of the most challenging tasks in asymmetric catalysis.[1] The development of chiral spiro ligands for asymmetric induction is particularly interesting since the spiro skeleton has unique chirality and displays unusual reactivity.[2,3] For example, we reported a novel chiral spiro bis(isoxazoline) ligand [SPRIX] **1** containing a spiro[4.4]nonane skeleton (Fig. 1). These spiro ligands promoted the Pd-catalyzed asymmetric Wacker-type cyclization of alkenyl alcohols,[2b] intramolecular aminocarbonylation of alkenyl amines and tosylamides,[2c] and intramolecular cyclization of 2-alkynoates.[2d] Recently, we reported the synthesis of chiral spiro bis(isoxazole) ligands **2**.[4a] Herein, we report a new design and synthesis of chiral spiro bis(isoxazoline) ligands **3** and **4** starting from enantiomerically pure olefin derivative **11**. The complex generated from **3** and $Cu(OTf)_2$ efficiently promoted the asymmetric

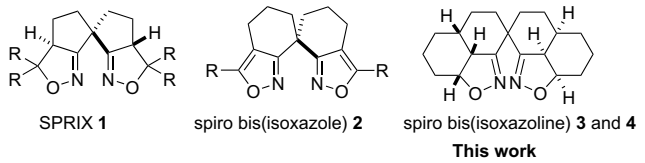
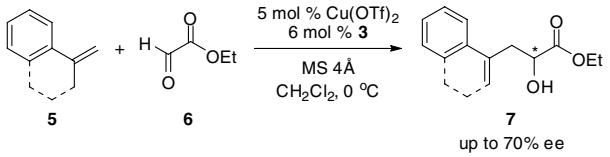


Figure 1. Chiral spiro ligands.



Scheme 1. Cu(II)-Spiro bis(isoxazoline)-catalyzed glyoxylate-ene reaction.

glyoxylate-ene reaction of various olefins **5** with ethyl glyoxylate **6** (Scheme 1).

The carbonyl-ene reaction is an important carbon–carbon bond forming transformation.[5] Yamamoto et al. reported the first example of an asymmetric ene reaction of prochiral aldehydes and alkenes catalyzed by chiral organoaluminum reagents.[6] Mikami and Nakai have reported a catalytic enantioselective ene reaction with glyoxylate esters by using a Ti–BINOL complex.[7,8] Jørgensen[9] and Evans[10] explored the use of Cu(II)–bis(oxazoline) complexes for enantioselective carbonyl-ene reactions; further, numerous reports have been made about the use of bis(oxazoline) as a ligand.[11] However, to the best of our knowledge, bis(isoxazoline) ligands have never been used in the carbonyl-ene reactions.

2. Results and discussion

We decided to start our study with the design of new spiro bis(isoxazoline) ligands **3** and **4**. The perceived conformational rigidity in these ligands is due to the inherent

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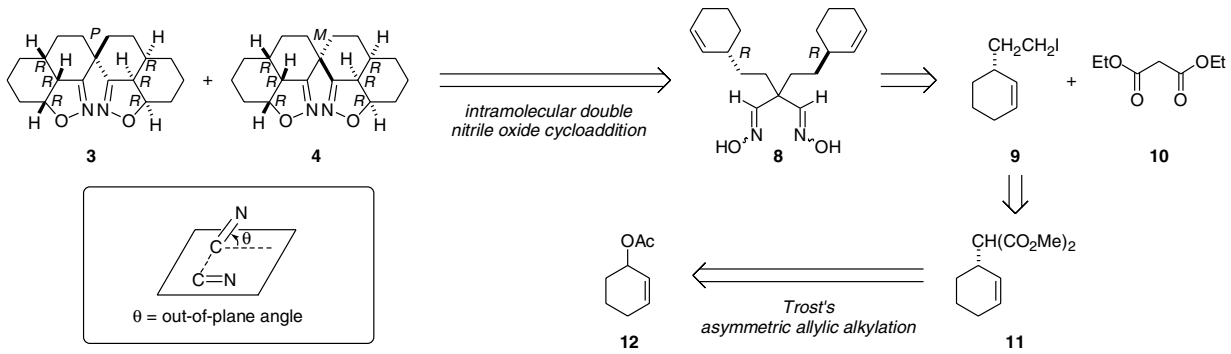
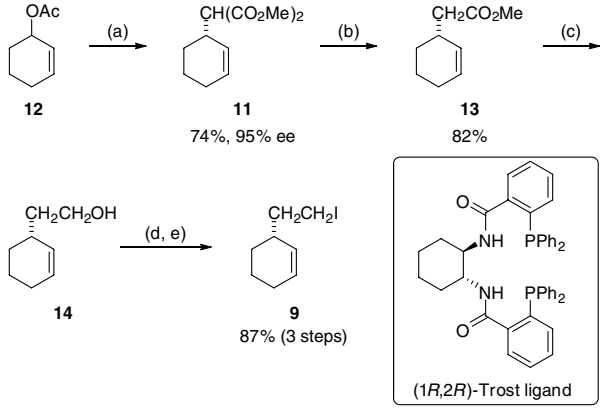


Scheme 2. Synthetic strategy for novel spiro bis(isoxazoline) ligands.

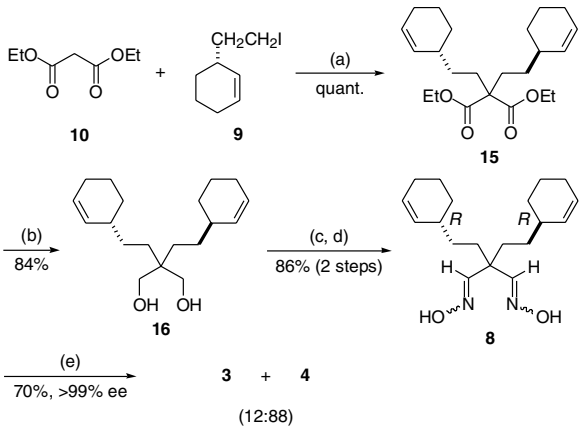
fused-ring system. It was envisioned that these ligands could be prepared using the intramolecular double nitrile oxide cycloaddition of **8**.[12] The molecular modeling calculation using MM2 showed that diastereomer **3** has a short N–N atomic distance (3.04 Å) and a small out-of-plane angle between the two C=N bonds (59.8°) as compared to diastereomer **4**, which showed an N–N atomic distance and out-of-plane angle between the two C=N bonds of 4.09 Å and 89.5°, respectively. As shown in the retrosynthetic analysis (Scheme 2), the key intermediate **8** can be prepared by the alkylation of diethyl malonate **10** with a chiral alkylating reagent (*R*)-3-(2-iodoethyl)cyclohexene **9**; this reagent can be easily synthesized through the asymmetric allylic alkylation of cyclohex-2-enyl acetate **12**.[13]

In order to prepare the cyclization precursor **8**, beginning, iodide **9** was prepared as shown in Scheme 3. The asymmetric allylic alkylation of **12** produced **11** with 95% ee as reported by Trost.[13] Malonate **11** was treated with an aqueous solution of NaCl (1.1 equiv) and DMSO to obtain methyl (−)-(cyclohex-2-enyl)acetate (**13**) in 82% yield. Reduction with $LiAlH_4$ produced alcohol **14**, which was used directly in the subsequent steps without purification. After mesylation, the crude mesylate was added dropwise to a solution of NaI in acetone at room temperature then followed by reflux overnight to produce the desired (*R*)-3-(2-iodoethyl)cyclohexene **9** in 87% yield from **13** in three steps.

The synthesis of the target spiro bis(isoxazoline) ligands **3** and **4** was completed as shown in Scheme 4. Compound **10** was treated with 2.2 equiv of NaH and 2.2 equiv of **9** successively to obtain diethyl (*R*,*R*)-2,2-bis(2-cyclohex-2-enylethyl)malonate **15** in quantitative yield. Malonate **15** was reduced with $LiAlH_4$ to obtain diol **16** in 84% yield. After Swern oxidation of **16**, the resulting dialdehyde was treated with NH_2OH–HCl in pyridine at 0 °C without further purification. The reaction mixture was then stirred at room temperature for 6 days to produce dioxime **8** in 86% yield over two steps.[14] The treatment of dioxime **8**, which had an (*R*,*R*)-configuration, with 5% aq NaOCl produced 70% yield of the desired spiro bis(isoxazoline) ligands via the intramolecular double nitrile oxide cycloaddition. The two diastereomers **3** and **4** were separated by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/1) in a ratio of 12:88. It is important to note that these chiral spiro bis(isoxazoline) ligands **3** and **4** could be obtained in enantiomerically pure forms simply by column chromatographic separation, and the other diastereomers were not detected. As shown in Scheme 2, the configuration of the spiro chiral center (*P* or *M*) was tentatively assigned by NMR



Scheme 3. Synthesis of (*R*)-3-(2-iodoethyl)cyclohexene **9**. Reagents and conditions: (a) dimethyl malonate (3.1 equiv), Cs_2CO_3 (3 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3 mol %), (1*R*,2*R*)-Trost ligand (9 mol %), CH_2Cl_2, 40 °C; (b) NaCl, H_2O, DMSO, 160 °C; (c) $LiAlH_4$, THF, rt; (d) MsCl, NEt_3, CH_2Cl_2, 0 °C; (e) NaI, acetone, reflux.



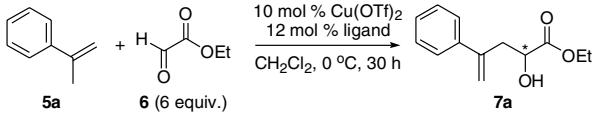
Scheme 4. Synthesis of the target spiro bis(isoxazoline) ligands. Reagents and conditions: (a) NaH, DMSO, rt; (b) $LiAlH_4$, THF, rt; (c) $(COCl)_2$, CH_2Cl_2, DMSO, −78 °C, NEt_3; (d) NH_2OH–HCl, pyridine, 0 °C then rt; (e) 5% aq NaOCl, CH_2Cl_2, rt.

analysis.[15,16] Ligand **3** is stable in air, and to moisture, and even under acidic, basic, and oxidative conditions at room temperature.[17]

After obtaining the new spiro ligands, in order to elucidate their potential as chiral ligands, we examined the asymmetric glyoxylate-ene reaction of α-methyl styrene **5a** with ethyl glyoxylate **6** and compared the catalyst activity with our previously synthesized chiral spiro ligands.[18] The results are shown in Table 1. We were pleased to find that the glyoxylate-ene reaction in the presence of 10 mol % of $Cu(OTf)_2$ and 12 mol % of ligand **3** in CH_2Cl_2 at 0 °C provided the desired product ethyl 2-hydroxy-4-phenyl-4-pentenoate **7a** in 47% yield and 66% ee (entry 2).[19] By comparing entries 1 and 2, it can be seen that spiro ligand **3** accelerated the glyoxylate-ene reaction significantly. As revealed from the MM2 calculations (vide supra), it was not surprising that the use of ligand **4** did not show any enantioselectivity (entry 3). Interestingly, except for *i*-Pr-SPRIX **1b** (R = *i*-Pr), the catalysts formed from ligands **1a** (R = H), **2a** (R = H), and **2b** (R = Me) gave lower ees (entries 4–7). The loading of the catalyst can be reduced to 5 mol % without losing enantioselectivity (entry 8). The counterion effect was examined using the catalyst prepared by mixing $CuBr_2$ (5 mol %), $AgSbF_6$ (10 mol %), and ligand **3** (6 mol %) in CH_2Cl_2.[10] This catalyst showed a higher reactivity but decreased the enantioselectivity (entry 9). Gratifyingly, the use of molecular sieves in the presence of 5 mol % of $Cu(OTf)_2$ and 6 mol % of ligand **3** improved both the yield and ee up to 70% (entry 10). No remarkable effect on the enantioselectivity was observed when the reactions were run at −5 and −10 °C. The reaction conducted at 0 °C was found to be optimal in terms of both yield and ee.

The reaction of **6** with other olefins has been investigated under optimized conditions and the results are summarized in Table 2.[20] The ene reaction of 4-chloro-α-methylstyrene **5b** with **6** produced the corresponding product **7b** with 67% ee, albeit with a poor yield (entry 1). An electron-donating substituent at the *para*-position as in substrate **5c** reduced the enantioselectivity but provided a good chemical yield (70%) (entry 2). The bulky naphthalene substituent in **5d** was well tolerated (entry 3). The olefin substrate can also be adopted into cyclic systems; quantitative yield with moderate ee (64%) was obtained by using **5e** (entry 4).

Table 1. Screening of chiral spiro ligands for asymmetric glyoxylate-ene reaction

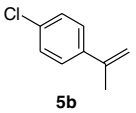
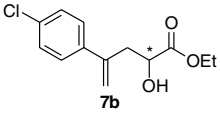
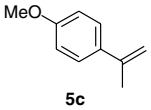
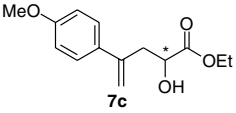
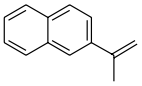
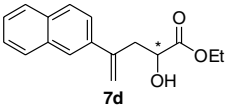
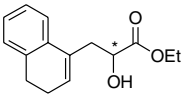


5a **6** (6 equiv.) **7a**

Entry	Ligand	Yield[a] (%)	% ee (configuration)[b]
1	None	30	—
2	**3**	47	66 (*S*)
3	**4**	35	1
4	**1a** (R = H)	58	1
5	**1b** (R = *i*-Pr)	45	51
6	**2a** (R = H)	60	1
7	**2b** (R = Me)	58	14
8[c]	**3**	55	68 (*S*)
9[d]	**3**	70	29 (*S*)
10[c,e]	**3**	83	70 (*S*)

[a] Isolated yield.
[b] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS, hexane/*i*-PrOH = 10/1, flow rate = 0.5 mL/min).
[c] Catalyst loading: 5 mol % of $Cu(OTf)_2$ and 6 mol % of ligand **3**.
[d] The copper catalyst was prepared by pre-mixing $CuBr_2$ (5 mol %), $AgSbF_6$ (10 mol %) and **3** (6 mol %).
[e] In the presence of MS 4 Å.

Table 2. $Cu(OTf)_2$-**3**-catalyzed enantioselective glyoxylate-ene reactions between ethyl glyoxylate and various olefins[a]

Entry	Olefin	Product	Yield[b] (%)	ee[c] (%)
1	 **5b**	 **7b**	23	67
2	 **5c**	 **7c**	70	34
3	 **5d**	 **7d**	48	65
4	 **5e**	 **7e**	>99	64

[a] Reaction conditions: olefin (0.20 mmol), ethyl glyoxylate (6 equiv), $Cu(OTf)_2$ (5 mol %), ligand **3** (6 mol %), MS 4 Å (100 mg), CH_2Cl_2, 0 °C, 30 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS, hexane/*i*-PrOH = 10/1, flow rate = 0.5 mL/min).

3. Conclusion

In conclusion, we have designed and synthesized a new class of chiral spiro bis(isoxazoline) ligands **3** and **4** bearing seven stereocenters. Optical resolutions were not required to obtain these chiral spiro ligands, which could simply be obtained by a normal column chromatography in enantiomerically pure forms; this shows the advantage of the methodology used to prepare these chiral ligands. We have demonstrated the first example of a bis(isoxazoline) ligand accelerated copper-catalyzed enantioselective glyoxylate-ene reaction providing the chiral alkenoates with up to 70% ee. Further investigations to identify the active catalytic species and applications of the spiro ligands in asymmetric catalysis are in progress.

Acknowledgments

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Science, and Technology, Japan. We thank the technical staff of the Materials Analysis Center, The Institute of Scientific and Industrial Research (ISIR), Osaka University, for their technical assistance.

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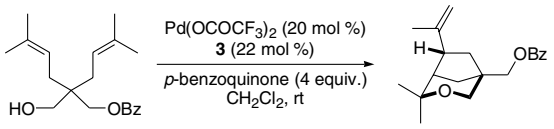
14. *Analytical data for (−)-2,2-bis(2-cyclohex-2-enyl-ethyl)-malonaldehyde dioxime* **8**: White solid. Mp 97–99 °C (hexane–Et_2O). $[\alpha]_D^{26} = -90.0$ (*c* 1.07, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 1.14–1.32 (m, 6H), 1.35–1.58 (m, 2H), 1.64–1.79 (m, 8H), 1.95–1.98 (m, 6H), 5.53 (d, $J = 10.2$ Hz, 2H), 5.67 (m, 2H), 7.39 (s, 2H), 7.78 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5, 25.4, 28.9, 30.3, 33.2, 35.6, 45.6, 127.3, 131.3, 154.5. IR (neat) 3321, 3014, 2922, 2856, 2363, 1649, 1448, 1288, 934, 878, 754, 719, 677 cm^{-1}. FAB-LRMS *m/z*: $[M+H]^+$ 319.0. Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50, N, 8.80. Found: C, 71.69; H, 9.51; N, 8.64.
15. *Analytical data for (P,5aR,5a′R,8aR,8a′R,8bR,8b′R)-4,4′,5,5′,5a,5′a,6,6′,7,7′,8,8′,8a,8′a,8b,8′b-hexadecahydro-3,3′-spirobi[3H-naphtho[1,8-cd]isoxazole]* **3**: Mp 203 °C (decomp.). $[\alpha]_D^{21} = +95.7$ (*c* 0.22, $CHCl_3$). ^1H NMR (270 MHz, CD_2Cl_2) δ 1.00–1.23 (m, 6H), 1.38–1.60 (m, 8H), 1.72–1.91 (m, 6H), 2.06–2.09 (m, 2H), 3.16 (t, $J = 8.8$ Hz, 2H), 4.51 (ddd, $J = 9.4$, 9.3, 7.1 Hz, 2H). ^{13}C NMR (68 MHz, CD_2Cl_2) δ 20.8, 25.6, 27.5, 28.3, 28.7, 32.5, 39.7, 47.5, 78.1, 160.5. IR (neat) 2934, 2853, 2245, 1452, 905, 835, 727, 648 cm^{-1}. FAB-HRMS Calcd for $C_{19}H_{26}N_2O_2$: $[M+H]^+$ 315.2073. Found: 315.2092. *Analytical data for (M,5aR,5a′R,8aR,8a′R,8bR,8b′R)-4,4′,5,5′,5a,5′a,6,6′,7,7′,8,8′,8a,8′a,8b,8′b-hexadecahydro-3,3′-spirobi[3H-naphtho[1,8-cd]isoxazole]* **4**: mp 123–125 °C (EtOH). $[\alpha]_D^{24} = +40.4$ (*c* 1.07, $CHCl_3$). ^1H NMR (270 MHz, CD_2Cl_2) δ 1.17–1.30 (m, 6H), 1.40–1.63 (m, 8H), 1.73–1.80 (m, 2H), 1.96–2.12 (m, 4H), 2.43–2.55 (m, 2H), 3.18 (dd, $J = 8.9$, 6.7 Hz, 2H), 4.52–4.61 (m, 2H). ^{13}C NMR (68 MHz, CD_2Cl_2) δ 19.4, 25.8, 27.3, 27.5, 32.4, 32.7, 39.9, 48.1, 78.1, 160.6. IR (neat) 2924, 2860, 2341, 1450, 1353, 899, 845, 729 cm^{-1}. FAB-LRMS *m/z*: $[M+H]^+$ 315. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33, N, 8.91. Found: C, 72.51; H, 8.44; N, 9.02.

16. The assignment of the absolute configuration of ligands **3** and **4** was based on the different behavior of these ligands to the Pd salt. Thus, mixing of equimolar (*P*)-**3** and $Pd(OCOCF_3)_2$ showed a symmetric ^1H NMR spectrum (CD_2Cl_2) and significant low field shifts of the methyne protons, which indicated an efficient complexation due to the structural geometry, while (*M*)-**4** gave only insoluble material.
17. Acidic conditions: MeOH–aqueous 1 M HCl (1:1) at rt for 24 h. Basic conditions: MeOH–aqueous 1 M NaOH (1:1) at rt for 24 h. Oxidative conditions: MeOH–35% aqueous H_2O_2 (1:1) at rt for 24 h.
18. The Pd-catalyzed asymmetric tandem cyclization of alkenyl alcohol **17** using newly synthesized ligand **3** gave unsatisfactory results. See Refs. 2b, 4a and 11h.



17 **18**

48% yield, 20% ee

19. The absolute configuration of the major enantiomer of **7a** was determined to be *S* by comparing the HPLC profile with the values reported in Ref. 7d.
20. The general procedure for the glyoxylate-ene reaction: A mixture of ligand **3** (0.012 mmol, 6 mol %), $Cu(OTf)_2$ (0.010 mmol, 5 mol %), and MS 4 Å (100 mg) in CH_2Cl_2 (0.56 mL) was stirred at 0 °C for 2 h. To this solution, olefin **5** in 1 M CH_2Cl_2 solution (0.20 mL, 0.20 mmol) and **6** (0.24 mL, 1.2 mmol, 50% toluene solution) were added. After stirring for 30 h at 0 °C, the reaction was quenched by the addition of water, and extracted with ether. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to give product **7**. The enantiomeric excess of the products was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AS, hexane/*i*-PrOH = 10/1, flow rate = 0.5 mL/min).