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Preparation of new chiral bisoxazoline ligands for the catalytic asymmetric intramolecular cyclopropanation of α-diazo-β-keto phenyl sulfone to afford a useful bicyclo[3.1.0]hexane derivative

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ABSTRACT

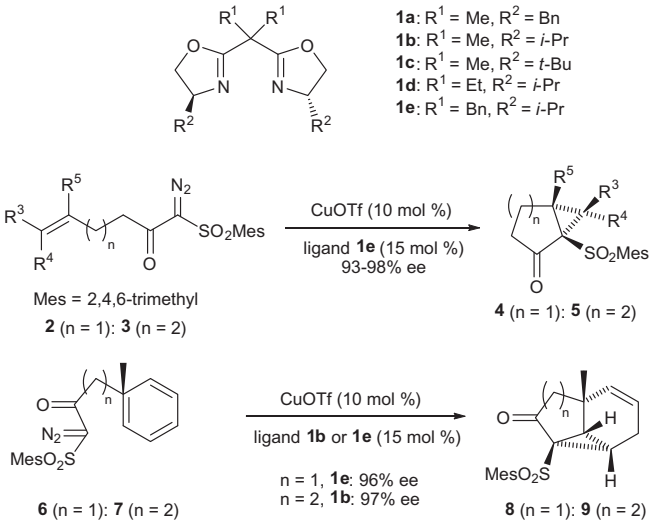
Herein we describe the preparation of novel chiral bisoxazoline ligands with various substituents at the bisoxazoline linkage, for use in the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-keto phenyl-5-hexenyl sulfone to afford a simple, but useful, bicyclo[3.1.0]hexane derivative. The enantioselectivity of the CAIMCP of α-diazo-β-keto phenyl-5-hexenyl sulfone was improved and a product with 84% ee was obtained using 30 mol % of the catalyst, which was prepared in situ by CuOTf and the new bisoxazoline ligand with two 3,5-di-*tert*-butylbenzyl groups at the bisoxazoline linkage. The product was obtained in enantiomerically pure form by a single crystallization, enabling its use as a chiral building block.

1. Introduction

Asymmetric catalysis with chiral metal complexes has attracted considerable attention from synthetic organic chemists in recent years because of its efficiency in producing chiral compounds. Since chiral ligands play a pivotal role in the use of chiral metal complexes, the development of various chiral ligands is an expanding area of research. The C_2-symmetric bisoxazoline ligands that have two oxazoline rings separated by a single carbon atom with two identical substituents can be easily prepared using the requisite chiral amino alcohols. Chiral amino alcohols can be readily derived from commercially available chiral amino acids; hence, a variety of bisoxazoline derivatives have been prepared and extensively utilized in asymmetric catalysis in addition to other chiral ligands.[1]

We have reported the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-keto aryl sulfones, which proceeds in a high yield and with excellent enantioselectivity (Scheme 1).[2] The CAIMCP of α-diazo-β-keto aryl sulfones has been utilized for natural product synthesis,[3] and has promoted related studies, proving the potential utility and wide applicability of the CAIMCP approach.[4] During these studies, it was found that the bisoxazoline ligand with two benzyl groups at the linkage was effective in improving the enantioselectivity of the CAIMCP of α-diazo-β-keto aryl sulfones.[2,3]

Figure 1 shows the proposed transition state models to explain the enantioselectivity of the CAMICP of **2** ($R^3 = R^4 = R^5 = H$) with



Scheme 1. Catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-keto aryl sulfones.

CuOTf and ligand **1e**.[2a] The cyclopropanation occurs preferentially at the *Re*-face (defined by the Cu=C–C arrangement) of the carbene complex, since steric hindrance would be encountered at the *Si*-face. Thus, when the double bond approaches from the *Si*-face, the carbene C atom would become pyramidal in the transition state and the mesityl sulfonyl group would interact unfavorably with both the isopropyl group and the benzyl group of the ligand. Conversely, reaction at the *Re*-face would be preferred

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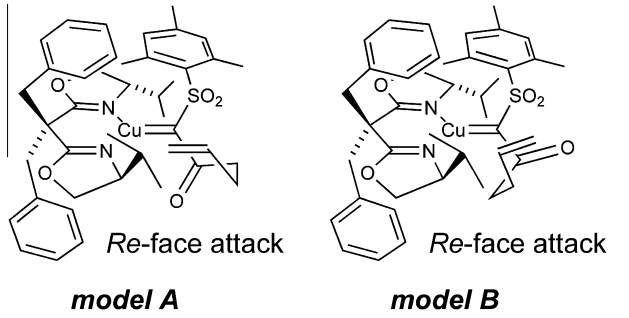


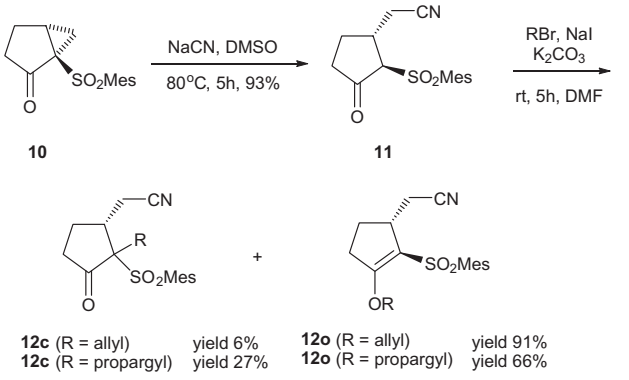
Figure 1. Proposed models A and B for the CAIMCP of **2** ($R^3 = R^4 = R^5 = H$) with ligand **1e** and CuOTf.

because the unfavorable interactions with the mesityl sulfonyl group would be negligible in the transition states arising from model A or model B.

The enantioselectivity of the CAIMCP of **2** ($R^3 = R^4 = R^5 = H$) with CuOTf and ligand **1e** is well explained by model A, because the transition state via model B would be energetically unfavorable due to steric repulsion between the terminal alkene and the carbene complex.

In these models, the mesityl sulfonyl group and the benzyl group of the ligand have crucial roles in the enantioselective discrimination. Thus, the high enantioselectivities observed in the CAIMCP using the mesityl sulfones and ligand **1e** are suitably explained by the increase in unfavorable interactions.

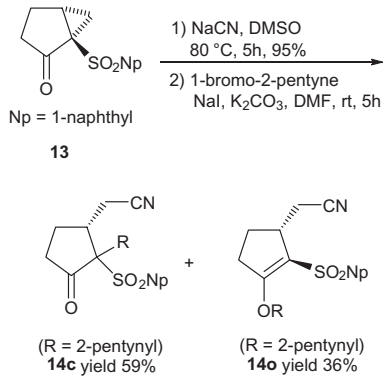
As described above, the use of a bulky mesityl sulfone improves the enantioselectivity of the CAIMCP.[2] However, it makes the transformation of products difficult due to the bulky mesityl sulfone.[3c] For example, the attempted C-allylation and propargylation of compound **11** (Scheme 2), which was derived from the ring-opening reaction of **10** with sodium cyanide, afforded *O*-alkylated products **12o** as the major products.[3c]



Scheme 2. Reaction of **10** with sodium cyanide and subsequent alkylation with 1-bromo-2-pentyne.

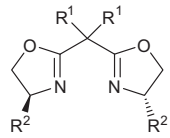
As shown in Scheme 3, however, this problem has been overcome by changing mesityl sulfone **10** to 1-naphthyl sulfone **13**, which generates the *C*-alkylated product **14c** as the major product.[3c] Nonetheless, the preparation of α-diazo-β-keto 1-naphthyl sulfone requires the use of 1-naphthyl sulfone, which is widely unavailable. The use of α-diazo-β-keto phenyl sulfone is more practical because it can be readily prepared using the commercially available methyl phenyl sulfone. Therefore, an improvement in the enantioselectivity of the CAIMCP of α-diazo-β-keto phenyl sulfone is highly desirable.

Table 1 summarizes the CAIMCP of α-diazo-β-keto phenyl sulfone **15**.[2a] The best enantioselectivity was observed for the CAIMCP

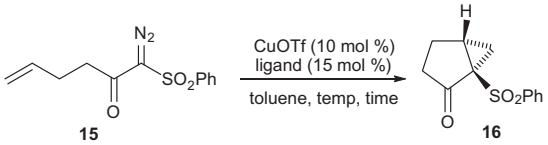


Scheme 3. Reaction of **13** with sodium cyanide and subsequent alkylation with 1-bromo-2-pentyne.

Table 1
CAIMCPs of α-diazo-β-keto sulfone **15** with bisoxazoline ligands **1a–e**



1a: R^1 = Me, R^2 = Bn
1b: R^1 = Me, R^2 = *i*-Pr
1c: R^1 = Me, R^2 = *t*-Bu
1d: R^1 = Et, R^2 = *i*-Pr
1e: R^1 = Bn, R^2 = *i*-Pr



Entry	Ligand	Temp	Time (h)	Yield (%)	ee[a] (%)
1	**1a**	rt	2	67	75
2	**1b**	rt	2	91	65
3	**1c**	50 °C	5.5	61	32
4	**1d**	rt	5.5	67	72
5	**1e**	rt	2	61	73

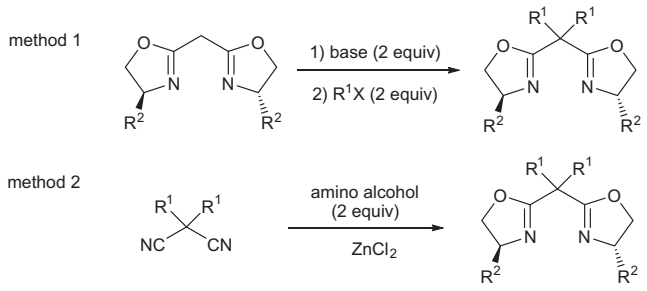
[a] Ee determined by HPLC. For HPLC conditions, see Section 4.

with ligand **1a**, which affords cyclopropane **16** with 75% ee. Compound **16** is one of the simplest bicyclo[3.1.0]hexane derivatives and various transformations are possible, making enantiomerically pure **16** an extremely useful chiral building block. Compound **16** is highly crystalline and can be made in enantiomerically pure form by recrystallization when the ee is high. However, repeated recrystallization was needed to obtain enantiopure **16** because of its relatively low ee. Therefore, we started to investigate a new chiral bisoxazoline ligand that would be effective for the CAIMCP of α-diazo-β-keto phenyl sulfone **15**.

2. Results and discussion

As noted above, the enantioselectivity of the CAIMCP varies with the substituent at the bisoxazoline linkage. Hence, we prepared bisoxazoline ligands with a variety of substituents at the bisoxazoline linkage in order to improve the enantioselectivity of the CAIMCP of **15**.

Several methods have been reported for the preparation of bisoxazoline ligands,[1d–f] and two short and effective methods have been reported as shown in Scheme 4. One is the alkylation of bisoxazoline ligands possessing no substituents at the bisoxazoline linkage (method 1).[5] The other is bisoxazoline formation by the reaction of 2 equiv of amino alcohol with a disubstituted malononitrile in the presence of an acid (method 2).[6]



Scheme 4. Alkylation of bisoxazoline ligands with no substituents at the bisoxazoline linkage (method 1) and bisoxazoline formation by the reaction of an amino alcohol with a substituted malononitrile (method 2).

Both of these methods for synthesizing bisoxazoline ligands require only three steps from commercially available materials. However, as described later, when the alkylation reagent is bulky, method 1 was found to be relatively low-yielding.[7] On the other hand, we found that the desired bisoxazolines could be efficiently prepared by method 2, even when the substituent of the malononitrile was bulky. The efficiency of method 2 could be attributed to the fact that the chelate formed by the generated bisoxazoline with zinc chloride would be a driving force to in increasing the yield. In addition, our preliminary experiments indicated that the reaction of malononitrile with relatively bulky alkylating reagents afforded the corresponding product in a good to excellent yield. Hence, method 2 was employed to prepare bisoxazolines.

In order to compare the data obtained by the CAIMCP of **15** using ligands **1b**, **1d**, and **1e** with those that would be obtained using new chiral ligands, L-valinol was used for step B in the preparation of new bisoxazoline ligands. Thus, bisoxazoline ligands with isobutyl **1f**, cyclohexyl **1g**, phenethyl **1h**, cyclohexanediyl **1i**, substituted benzyls **1j**–**p**, and 2-naphthylmethyl **1q** groups at the bisoxazoline linkage were prepared (Table 2).

The alkylation of malononitrile (step A) proceeded smoothly when using either alkylbromide or alkyliodide with DBU to afford the di-alkylated products **17f**–**q** in good yield (from 67% to quantitative yield).[8] The yield of the subsequent bisoxazoline formation depended on the type of substituent on the malononitrile derivatives. Thus, the yield of step B was 96% in the case of the 2-naphthylmethyl group, and 19% and 17% in the cases of cyclohexylmethyl and 3,5-di-*tert*-butylbenzyl groups, respectively. The low yields were attributed to the steric hindrance derived from the bulky substituents at the bisoxazoline linkage.

Another research group has also reported on the preparation of ligand **1q** by method 1.[7] However, the yield of the alkylation step was 55%, which was lower than the overall yield (66%, two steps) of **1q** by method 2 (Table 2). This result could indicate that method 2 is more effective than method 1 for the preparation of bisoxazoline ligands with bulky substituents at the bisoxazoline linkage.

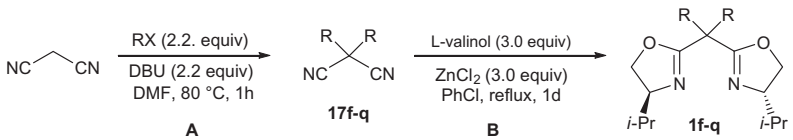
Table 3 shows the results of the CAIMCPs of **15** with **1f**–**q**. All the CAIMCPs of **15** were completed within three hours and the absolute configurations of all of the products were the same as those shown in Table 1. The ee obtained from the use of the ligand with ethyl groups **1d** (72% ee, Table 1) was almost the same as those obtained using the ligands with *i*-butyl **1f** (70% ee), *c*-hexylmethyl **1g** (72% ee), and cyclohexanediyl **1i** (71% ee) groups. The ee obtained from the use of the ligand with a *c*-hexylmethyl group **1g** (72% ee) is the same as that obtained when using the ligand with a benzyl group **1e** (72% ee). This result could indicate that the effect of the benzyl group on the enantioselectivity of the CAIMCP could be attributed to the steric bulkiness. However, the benzene ring is capable of π–π interactions with the aryl sulfonyl group of the substrate and so this could also play a part.

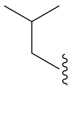
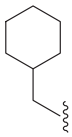
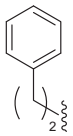
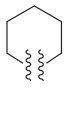
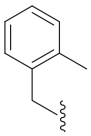
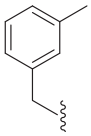
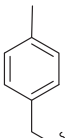
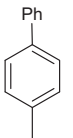
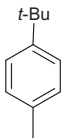
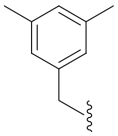
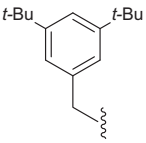
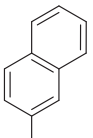
Since a phenethyl group is more bulky than an ethyl group, the ee of the product obtained by use of the ligand with a phenethyl group **1h** was expected to be higher than that observed in the reaction with the ligand with an ethyl group **1d** (72% ee, Table 1). However, this was found to not be the case and the ee was slightly lower with the use of **1h** (67% ee).

The ee values observed in reactions with the use of ligands with *m*-tolyl **1k** (72% ee), *p*-tolyl **1l** (72% ee), *p*-phenylbenzyl **1m** (72% ee), and *p*-*tert*-butylbenzyl **1m** (74% ee) are almost the same as those observed in the reaction using the ligand with a benzyl group **1e** (73% ee, Table 1). However, the ee slightly increased with the use of the ligand with 3,5-dimethylbenzyl group **1o** (76% ee), and the ee increased significantly to 81% ee in the case of the ligand with the 3,5-di-*tert*-butylbenzyl group **1p**. Interestingly, the ee decreased with the use of the ligand with an *o*-tolyl group **1j** (63% ee), indicating that the ee could be altered not only by the bulkiness, but also by the position of the substituents on the benzene ring.

Considering the bulkiness and the position of the substituent on the naphthyl group, the ee achieved using the ligand with a 2-naphthyl group **1q** should at least be the same as those obtained by the ligands with an *m*-tolyl **1k** (72% ee) or *p*-tolyl **1l** (72% ee) groups. However, it was found that the ee was lower (67% ee) than that obtained using the ligand with a benzyl group **1e** (73% ee, Table 1). The reason for the low ee cannot therefore be solely

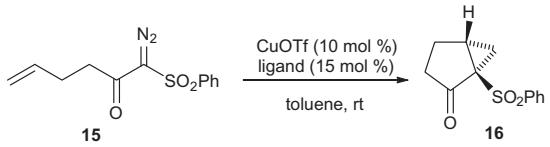
Table 2
Preparation of bisoxazoline ligands **1f**–**q** by method 2

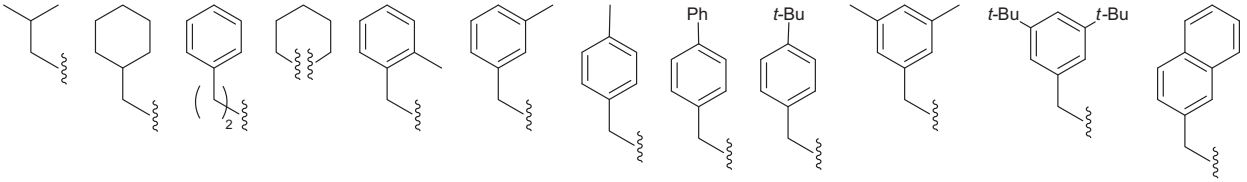


	1f	1g	1h	1i	1j	1k	1l	1m	1n	1o	1p	1q
R												
X	I	Br	Br	Br	Br	Br	Br	Br	I	Br	Br	Br
Step A yield[a] (%)	88	80	67	95	97	94	Quant.	94	83	90	99	69
Step B yield[a] (%)	37	19	75	85	25	86	47	22	40	58	17	96

[a] Isolated yield.

Table 3
The CAIMCP of **15** with bisoxazoline ligands **1f–q**

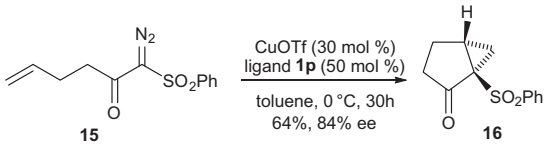


	1f	1g	1h	1i	1j	1k	1l	1m	1n	1o	1p	1q
R								Ph	*t*-Bu		*t*-Bu *t*-Bu	
Time (h)	4	2	1	1	2	2	3	1	2	3	2	3
Yield[a] (%)	90	93	87	79	77	72	63	80	80	74	70	76
ee[b] (%)	70	72	67	71	63	72	72	72	74	76	81	67

[a] Isolated yield.
[b] Ee determined by HPLC. For HPLC conditions, see Section 4.

attributed to the bulkiness of the substituent. As previously mentioned, the ee value obtained using the ligand with a bulky phenethyl group **1h** was lower than that obtained using the ligand with an ethyl group **1d**. Combining these observations suggests that the aromatic ring may have a specific effect on the ee, independent of any effects due to the bulkiness of the substituents.

Since the CAIMCP of **15** with ligand **1p** afforded **16** with 81% ee, the reaction conditions were further optimized. We observed that carrying out the CAIMCP at low temperature could improve the enantioselectivity.[4e] Hence, the reaction of **15** was carried out at 0 °C (Scheme 5). As a result, although the reaction proceeded slowly at 0 °C even when 30 mol % of the catalyst was used, **16** was obtained in 64% yield and 84% ee. The highly crystalline nature



Scheme 5. The CAIMCP of **15** with bisoxazoline ligand **1p** at 0 °C.

of **16** allowed us to obtain an enantiomerically pure compound by a single recrystallization.

3. Conclusion

In conclusion, various novel bisoxazoline ligands possessing bulky substituents at the bisoxazoline linkage have been successfully prepared. We have demonstrated that the bisoxazoline ligands with bulky substituents, including a 3,5-di-*tert*-butylbenzyl group, at the bisoxazoline linkage could be efficiently prepared by the alkylation of malononitrile and subsequent bisoxazoline formation by the reaction of an amino alcohol in the presence of zinc chloride. The ligands prepared were evaluated for the CAIMCP of α-diazo-β-keto-5-hexenyl phenyl sulfone **15**, and a product with 84% ee was obtained using 30 mol % of the catalyst, which was prepared in situ by CuOTf and the new bisoxazoline ligand with two 3,5-di-*tert*-butylbenzyl groups at the bisoxazoline linkage. An enantiomeric excess value of 84% is the highest ee to have been reported so far for the CAIMCP of **15**; the product was made enantiomerically pure by a single crystallization, enabling its use as a chiral building block. The bisoxazoline ligands developed herein as well as their preparation method could be useful for research in the field of asymmetric catalysis.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-270, AL-300, and Lambda 500 spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Chiral HPLC analysis was performed on a JASCO PU-980 and UV-970. Mass spectra and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. MeOH was distilled with a small amount of magnesium and I_2. Benzene, MeCN were distilled from CaH_2, and all other reagents were purchased from Aldrich, TCI, or Kanto Chemical Co. Ltd. 1-Siazo-1-phenylsulfonyl-5-hexene-2-one **15** was prepared according to the procedure reported in the literature.[2a]

4.2. Preparation of dialkylated malononitriles 17f–q

Dialkylated malononitriles **17f–q** were prepared by the alkylation of malononitrile according to the reported procedure.[8] **17h**,[8a] **17i**,[8b] and **17l**[8a] are known compounds.

Procedure A: To a solution of malononitrile in DMF (30 mL per gram of malononitrile) were added DBU (2.2 equiv) and alkyl halide (2.2 equiv), and the reaction mixture was stirred at 80 °C for 2 h. After the reaction was completed, the reaction mixture was

cooled to room temperature and water (150 mL per gram of malononitrile) and dichloromethane (150 mL per gram of malononitrile) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (150 mL per gram of malononitrile) and the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography to afford the dialkylated malononitrile.

4.2.1. 2,2-Bis(isobutyl)malononitrile 17f

This compound was prepared by Procedure A as described using isobutyl bromide. A colorless liquid (88%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.53 (hexane/ethyl acetate = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.10 (tq, J = 7.0, 6.9 Hz, 2H), 1.83 (d, J = 6.6 Hz, 4H), 1.12 (d, J = 7.0 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 116.2, 47.1, 34.6, 26.3, 22.9; IR (neat) ν_{max} 3061, 2937, 2903, 1469, 1389, 1371, 1173, 1025, 923 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{18}H_{19}N_2$: 179.1548, found: 179.1548.

4.2.2. 2,2-Bis(cyclohexylmethyl)malononitrile 17g

This compound was prepared by Procedure A as described using cyclohexylmethylbromide. A white solid (80%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 20:1): R_f = 0.76 (hexane/ethyl acetate = 4:1); mp 90–92 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.98–1.88 (m, 4H), 1.83–1.63 (m, 12H), 1.42–0.98 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 116.5, 46.1, 35.6, 34.2, 33.5, 25.9; IR (neat) ν_{max} 2920, 2849, 1447, 1379, 1347, 1262, 1006, 971, 895, 843, 700, 572, 470 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{17}H_{27}N_2$: 259.2174, found: 259.2210.

4.2.3. 2,2-Di(2-methylphenylmethyl)malononitrile 17j

This compound was prepared by Procedure A as described using *o*-methylbenzylbromide. A white solid (97%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.55 (hexane/ethyl acetate = 4:1); mp 92–95 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.49–7.41 (m, 2H), 7.34–7.20 (m, 6H), 3.37 (s, 4H), 2.40 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 137.5, 31.3, 130.9, 130.7, 128.9, 126.6, 115.5, 40.2, 39.8, 20.0; IR (neat) ν_{max} 1494, 1448, 1384, 1126, 1032, 772, 754, 734, 425, 667, 448 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{19}H_{19}N_2$: 275.1548, found: 275.1502.

4.2.4. 2,2-Di(3-methylphenylmethyl)malononitrile 17k

This compound was prepared by Procedure A as described above using *m*-methylbenzylbromide. A white solid (94%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.58 (hexane/ethyl acetate = 4:1); mp 124–126 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.33–7.26 (m, 2H), 7.22–7.17 (m, 6H), 3.20 (s, 4H), 2.38 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.8, 132.0, 131.1, 129.7, 128.9, 127.4, 115.1, 43.4, 41.1, 21.5; IR (neat) ν_{max} 1486, 144, 1266, 1099, 791, 751, 731, 708, 436 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{19}H_{19}N_2$: 275.1548, found: 275.1472.

4.2.5. 2,2-Di(4-phenylphenylmethyl)malononitrile 17m

This compound was prepared by Procedure A as described using *p*-phenylbenzylbromide. A white solid (94%) was obtained after purification by silica gel chromatography (chloroform/methanol = 50:1): R_f = 0.40 (hexane/ethyl acetate = 4:1); mp 245–248 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.67–7.59 (m, 8H), 7.55–7.33 (m, 10H), 3.33 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 141.9, 140.3, 130.9, 130.8, 129.0, 127.8, 127.7, 127.2, 115.1, 43.2, 41.3; IR (neat) ν_{max} 1485, 1446, 1007, 831, 767, 738, 725, 696, 671, 548, 499, 408 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{29}H_{23}N_2$: 399.1861, found: 399.1793.

4.2.6. 2,2-Di(4-*tert*-Butylphenylmethyl)malononitrile 17n

This compound was prepared by Procedure A as described using *p*-*tert*-butylbenzyliodide. A white solid (89%) was obtained after purification by silica gel chromatography (chloroform/methanol = 50:1): R_f = 0.35 (hexane/ethyl acetate = 10:1); mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44–7.38 (m, 4H), 7.35–7.30 (m, 4H), 3.21 (s, 4H), 1.33 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.8, 130.1, 129.1, 126.0, 115.2, 43.1, 41.4, 34.7, 31.4; IR (neat) ν_{max} 2959, 2902, 1518, 1505, 1469, 1449, 1360, 1268, 1125, 1106, 1019, 837, 825, 677, 666, 554 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{25}H_{31}N_2$: 359.2409, found: 359.2399.

4.2.7. 2,2-Bis(3,5-dimethylphenylmethyl)malononitrile 17o

This compound was prepared by Procedure A as described using 3,5-dimethylbenzylbromide. A white solid (90%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.73 (hexane/ethyl acetate = 4:1); mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.04–6.96 (m, 6H), 3.14 (s, 4H), 2.33 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.6, 132.0, 130.5, 128.2, 115.2, 43.4, 41.0, 21.4; IR (neat) ν_{max} 2930, 1608, 1468, 1448, 1380, 1308, 1040, 854, 733, 715, 675, 660 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{21}H_{23}N_2$: 303.1861, found: 303.1861.

4.2.8. 2,2-Bis(3,5-di-*tert*-butylphenylmethyl)malononitrile 17p

This compound was prepared by Procedure A as described using 3,5-di-*tert*-butylbenzylbromide. A white solid (99%) was obtained after purification by silica gel chromatography (chloroform/methanol = 50:1): R_f = 0.48 (hexane/ethyl acetate = 10:0); mp 200–202 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.44–7.42 (m, 2H), 7.24–7.22 (m, 4H), 3.24 (s, 4H), 1.34 (s, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.5, 131.4, 124.8, 122.5, 115.3, 44.3, 41.9, 35.0, 31.5; IR (neat) ν_{max} 2964, 2954, 2903, 2867, 1600, 1476, 1463, 1447, 1363, 1248, 1202, 879, 732, 718, 706 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{33}H_{47}N_2$: 471.3739, found: 471.3739.

4.2.9. 2,2-Bis(2-naphthyl)malononitrile 17q

This compound was prepared by Procedure A as described using 2-(bromomethyl)naphthalene. A white solid (69%) was obtained after purification by silica gel chromatography (chloroform/methanol = 10:1): R_f = 0.29 (hexane/ethyl acetate = 4:1); mp 195–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92–7.81 (m, 8H), 7.57–7.45 (m, 6H), 3.44 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.3, 133.2, 129.8, 129.4, 128.8, 128.0, 127.7, 127.5, 126.7, 126.6, 115.0, 43.6, 41.1; IR (neat) ν_{max} 3056, 2926, 1600, 1509, 1371, 1127, 967, 867, 827, 779, 756, 687, 484 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{25}H_{19}N_2$: 347.1548, found: 347.1576.

4.3. Preparation of bisoxazoline ligands 1f–q

Bisoxazoline ligands **1f–q** were prepared from the corresponding dialkylated malononitriles **17f–q** according to the procedure reported in the literature.[2a] Compounds **1f**[9] and **1q**[8] are known compounds.

Procedure B: To a solution of dialkylated malononitrile in *o*-dichlorobenzene (30 mL per gram of dialkylated malononitrile) were added zinc chloride (3.0 equiv) and L-valinol (3.0 equiv), and the reaction mixture was stirred at 150 °C for 12 h. After the reaction was complete, the reaction mixture was cooled to room temperature. To the reaction mixture were added water (3 mL per gram of dialkylated malononitrile) and ethylenediamine (6 mL per gram of dialkylated malononitrile), and the reaction mixture was stirred at room temperature for 1 h. Water (30 mL per gram of dialkylated malononitrile) and dichloromethane (30 mL per gram of dialkylated malononitrile) was added to the reaction mixture and the aqueous layer was extracted with dichlorometh-

ane (30 mL per gram of dialkylated malononitrile). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography to afford the bisoxazoline ligand.

4.3.1. (*S*)-2-(1,3-Dicyclohexyl-2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)propan-2-yl)-4,5-dihydro-4-isopropyloxazole 1g

This compound was prepared from **17g** by Procedure B as described. A white solid (19%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.68 (hexane/ethyl acetate = 2:1); mp 68–70 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 4.19–4.09 (m, 2H), 3.96–3.85 (m, 4H), 2.05–1.74 (m, 6H), 1.71–1.52 (m, 10H), 1.42–0.88 (m, 12H), 0.94 (d, J = 6.9 Hz, 6H), 0.86 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.2, 71.9, 69.3, 45.0, 39.9, 35.1, 34.0, 33.6, 32.4, 26.6, 26.6, 26.4, 19.0, 17.7; IR (neat) ν_{max} 2954, 2923, 2850, 154, 1470, 1447, 1207, 1169, 1022, 1001, 973, 953, 926 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{27}H_{47}N_2O_2$: 431.3638, found: 431.3600; $[\alpha]_D^{20} = -88.0$ (c 0.55, MeOH).

4.3.2. (*S*)-4,5-Dihydro-2-(3-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-1,5-diphenylpentan-3-yl)-4-isopropyloxazole 1h

This compound was prepared from **17h** by Procedure B as described. A white solid (75%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 4:1): R_f = 0.49 (hexane/ethyl acetate = 2:1); mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32–7.14 (m, 10H), 4.26–4.13 (m, 2H), 4.03–3.92 (m, 4H), 2.67–2.56 (m, 4H), 2.47–2.24 (m, 4H), 1.87–1.72 (m, 2H), 0.96 (d, J = 6.6 Hz, 6H), 0.89 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.8, 142.1, 128.6, 128.4, 125.9, 72.0, 69.9, 46.2, 35.3, 32.6, 30.8, 18.9, 18.0; IR (neat) ν_{max} 2954, 1647, 1217, 1189, 1052, 1030, 971, 936, 754, 698, 502, 478 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{29}H_{39}N_2O_2$: 447.3012, found: 447.3010; $[\alpha]_D^{20} = -64.4$ (c 0.55, MeOH).

4.3.3. (*S*)-4,5-Dihydro-2-(1-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)cyclohexyl)-4-isopropyloxazole 1i

This compound was prepared from **17i** by Procedure B as described. A colorless oil (85%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 2:1): R_f = 0.35 (hexane/ethyl acetate = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.22–4.13 (m, 2H), 4.03–3.93 (m, 4H), 2.17–1.92 (m, 4H), 1.89–1.73 (m, 2H), 1.39–1.72 (m, 6H), 0.93 (d, J = 7.0 Hz, 6H), 0.87 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.3, 43.2, 32.7, 32.4, 25.5, 22.7, 18.8, 17.9; IR (neat) ν_{max} 2954, 2932, 2870, 1655, 1466, 1450, 1344, 1226, 1208, 1124, 1046, 1031, 980, 942, 904 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{18}H_{31}N_2O_2$: 307.2386, found: 307.2386; $[\alpha]_D^{23} = -84.2$ (c 0.70, MeOH).

4.3.4. (*S*)-4,5-Dihydro-2-(2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-1,3-di-*o*-tolylpropan-2-yl)-4-isopropyloxazole 1j

This compound was prepared from **17j** by Procedure B as described. A white solid (25%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 20:1): R_f = 0.59 (hexane/ethyl acetate = 2:1); mp 58–60 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.35–7.25 (m, 2H), 7.11–7.01 (m, 6H), 4.13–3.99 (m, 2H), 3.95–3.81 (m, 4H), 3.49 (d, J = 15.0 Hz, 2H), 3.38 (d, J = 15.0 Hz, 2H), 2.16 (s, 6H), 1.80–1.66 (m, 2H), 0.94 (d, J = 6.6 Hz, 6H), 0.84 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.1, 137.6, 136.1, 130.2, 129.7, 126.3, 125.4, 72.1, 69.9, 47.9, 35.8, 32.6, 20.1, 19.2, 18.0; IR (neat) ν_{max} 2960, 2906, 1651, 1463, 1195, 1178, 1055, 1022, 1010, 962, 948, 899, 755, 742 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{29}H_{39}N_2O_2$: 447.3012, found: 447.3021; $[\alpha]_D^{20} = -91.5$ (c 0.55, MeOH).

4.3.5. (*S*)-4,5-Dihydro-2-(2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-1,3-di-*m*-tolylpropan-2-yl)-4-isopropyloxazole 1k

This compound was prepared from **17k** by Procedure B as described. A white solid (86%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.65 (hexane/ethyl acetate = 2:1); mp 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17–7.10 (m, 2H), 7.08–6.99 (m, 6H), 4.21–4.10 (m, 2H), 3.95–3.80 (m, 4H), 3.36 (d, J = 13.9 Hz, 2H), 3.18 (d, J = 13.9 Hz, 2H), 2.30 (s, 6H), 1.74–1.62 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H), 0.82 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.3, 137.1, 136.9, 131.4, 127.7, 127.5, 127.2, 72.0, 69.7, 48.2, 39.2, 32.5, 21.4, 18.9, 17.9; IR (neat) ν_{max} 2963, 2931, 2905, 1662, 1465, 1363, 1185, 1175, 1015, 963, 954, 893, 775, 699, 585 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{29}H_{39}N_2O_2$: 447.3012, found: 447.3012; $[\alpha]_D^{20} = -100$ (c 0.53, MeOH).

4.3.6. (*S*)-4,5-Dihydro-2-(2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-1,3-di-*p*-tolylpropan-2-yl)-4-isopropyloxazole 1l

This compound was prepared from **17l** by Procedure B as described. A white solid (47%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.50 (hexane/ethyl acetate = 4:1); mp 55–58 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.16–7.09 (m, 4H), 7.08–7.01 (m, 4H), 4.23–4.08 (m, 2H), 3.96–3.78 (m, 4H), 3.35 (d, J = 13.9 Hz, 2H), 3.16 (d, J = 13.9 Hz, 2H), 2.30 (s, 6H), 1.78–1.60 (m, 2H), 0.90 (d, J = 6.9 Hz, 6H), 0.82 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$); δ = 166.4, 136.0, 134.0, 130.4, 128.7, 72.1, 69.8, 48.4, 38.8, 32.6, 21.1, 19.1, 18.0; IR (neat) ν_{max} 2958, 2904, 1657, 1515, 1239, 1189, 1173, 1114, 1032, 1014, 986, 962, 952, 857, 809, 711, 563, 543, 486 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{29}H_{39}N_2O_2$: 447.3012, found: 447.3017; $[\alpha]_D^{20} = -92.9$ (c 0.64, MeOH).

4.3.7. (*S*)-2-(1,3-Bis(4-phenylphenyl)-2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)propan-2-yl)-4,5-dihydro-4-isopropyloxazole 1m

This compound was prepared from **17m** by Procedure B as described. A white solid (22%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.26 (hexane/ethyl acetate = 4:1); mp 53–57 °C; ^{1}H NMR (270 MHz, $CDCl_3$); δ = 7.61–7.55 (m, 4H), 7.54–7.39 (m, 8H), 7.37–7.30 (m, 6H), 4.25–4.17 (m, 2H), 3.99–3.85 (m, 4H), 3.48 (d, J = 14.2 Hz, 2H), 3.31 (d, J = 14.2 Hz, 2H), 1.78–1.65 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H), 0.83 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$); δ = 166.3, 141.2, 139.6, 136.2, 131.0, 128.8, 127.2, 127.1, 126.8, 72.1, 70.0, 48.4, 39.1, 32.6, 19.0, 18.0; IR (neat) ν_{max} 2955, 2930, 2895, 2870, 1656, 1486, 1466, 1171, 1022, 1007, 958, 855, 825, 758, 728, 695, 560,520 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{39}H_{43}N_2O_2$: 571.3325, found: 571.3373; $[\alpha]_D^{20} = -20.7$ (c 0.41, MeOH).

4.3.8. (*S*)-2-(1,3-Bis(4-*tert*-butylphenyl)-2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)propan-2-yl)-4,5-dihydro-4-isopropyloxazole 1n

This compound was prepared from **17n** by Procedure B as described. A white solid (40%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.53 (hexane/ethyl acetate = 4:1); mp 114–116 °C; ^{1}H NMR (270 MHz, $CDCl_3$); δ = 7.29–7.24 (m, 4H), 7.22–7.16 (m, 4H), 4.25–4.09 (m, 2H), 3.95–3.79 (m, 4H), 3.37 (d, J = 14.2 Hz, 2H), 3.21 (d, J = 14.2 Hz, 2H), 1.66–1.52 (m, 2H), 1.29 (s, 18H), 0.85 (d, J = 6.9 Hz, 6H), 0.77 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$); δ = 166.4, 149.3, 134.0, 130.3, 124.9, 72.1, 69.9, 48.3, 38.1, 34.4, 32.5, 31.5, 19.1, 18.0; IR (neat) ν_{max} 2958, 2931, 2905, 2869, 1664, 1512, 1464, 1362, 1268, 1174, 1121, 1009, 981, 965, 840, 817, 600, 584 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{35}H_{51}N_2O_2$: 531.3951, found: 531.3961; $[\alpha]_D^{20} = -59.5$ (c0.43, MeOH).

4.3.9. (*S*)-4,5-Dihydro-2-(2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-1,3-bis(3,5-dimethylphenyl)propan-2-yl)-4-isopropyloxazole 1o

This compound was prepared from **17o** by Procedure B as described. A white solid (58%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 10:1): R_f = 0.53 (hexane/ethyl acetate = 4:1); mp 82–84 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 6.84 (s, 6H), 4.24–4.08 (m, 2H), 3.97–3.81 (m, 4H), 3.31 (d, J = 13.9 Hz, 2H), 3.13 (d, J = 13.9 Hz, 2H), 2.26 (s, 12H), 1.75–1.61 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H), 0.83 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.5, 137.1, 136.9, 128.6, 128.2, 72.2, 69.8, 48.3, 39.2, 32.7, 21.4, 19.1, 18.0; IR (neat) ν_{max} 2956, 2927, 2871, 1662, 1605, 1463, 1366, 1240, 1188, 1175, 1162, 1032, 1011, 962, 950, 931, 890, 847, 697 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{31}H_{43}N_2O_2$: 475.3325, found: 475.3325; $[\alpha]_D^{20} = -89.4$ (c 0.55, MeOH).

4.3.10. (*S*)-2-(1,3-Bis(3,5-di-*tert*-butylphenyl)-2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)propan-2-yl)-4,5-dihydro-4-isopropyloxazole 1p

This compound was prepared from **17p** by Procedure B as described. A white solid (17%) was obtained after purification by silica gel chromatography (hexane/ethyl acetate = 20:1): R_f = 0.73 (hexane/ethyl acetate = 4:1);mp 121–123 °C; ^{1}H NMR (270 MHz, $CDCl_3$); δ = 7.27–7.25 (m, 2H), 7.17–7.16 (m, 4H), 4.17–4.07 (m, 2H), 3.92–3.77 (m, 4H), 3.51 (d, J = 14.5 Hz, 2H), 3.28 (d, J = 14.5 Hz, 2H), 1.66–1.50 (m, 2H), 1.29 (s, 36H), 0.85 (d, J = 6.6 Hz, 6H), 0.76 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$); δ = 166.6, 150.0, 136.3, 124.7, 120.6, 72.1,69.7, 48.1, 39.5, 34.8, 32.6, 31.7, 19.1, 17.7; IR (neat) ν_{max} 2954, 2868, 1670, 1597, 1469, 1362, 1248, 1174, 1023, 1002, 965, 913, 897, 886, 875, 862, 714 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{43}H_{67}N_2O_2$: 643.5203, found: 643.5203; $[\alpha]_D^{20} = -60.9$ (c 0.47, MeOH).

4.4. The catalytic asymmetric intramolecular cyclopropanation of 15 with ligand 1p

A toluene azeotroped $[CuOTf]_2{\cdot}C_6H_6$ (5.0 mg, 0.019 mmol, 10 mol % as CuOTf) was placed in a dried flask (10 mL) under an Ar atmosphere and to this flask was added a solution of toluene azeotroped ligand **1p** (18.8 mg, 0.029 mmol, 15 mol %) in toluene (0.5 mL × 2) via a cannula. The mixture was stirred at room temperature for 0.5 h and then to the light blue solution was added a solution of toluene azeotroped 1-diazo-1-phenylsulfonyl-5-hexene-2-one **15** (50.0 mg, 0.189 mmol) in toluene (0.5 mL × 2) via a cannula. The reaction mixture was stirred at room temperature for 2 h, quenched with an NH_4OH aqueous solution (1 mL), and extracted with ether (10 mL) and CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC (benzene/ethyl acetate = 2:1) to afford (1*R*,5*R*)-1-phenylsulfonyl-2-oxobicyclo[3.1.0]hexane **16** (31.1 mg, 70%, 81% ee) as a white solid. Ee was determined by HPLC (254 nm); Daicel Chiral Cell OD-H 0.46 cm × 25 cm; hexane/isopropanol = 3:1; flow rate = 0.5 mL/min); retention time: 21.3 min for **16**, 23.3 min for *ent*-**16**: R_f = 0.35 (hexane/ethyl acetate = 1:1); mp = 114–115 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23.5} = -62.1$ (c 0.60, $CHCl_3$, 100% ee); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.1 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.56 (dd, J = 8.1, 7.3 Hz, 2H), 3.09–3.01 (m, 1H), 2.33–2.15 (m, 4H), 2.10–1.96 (m, 1H), 1.54 (dd, J = 5.6, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3): δ = 203.2, 139.3, 133.6, 128.8, 128.6, 53.1, 33.6, 31.1, 20.5, 20.3; IR(KBr) ν_{max} 1731, 1446, 1304, 1149, 1034 cm^{-1}; HRMS (FAB): $[M+H]^+$ calculated for $C_{12}H_{13}O_3S$ 237.0585, found 237.0545.

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