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Resolution-free route to chiral 2,2′-bis(pyridin-2-yl)-1,1′-binaphthyl ligand: photochemical $CpCo(CO)_2$-mediated cycloaddition of enantiopure 2,2′-dicyano-1,1′-binaphthyl with diynes

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Abstract—A resolution-free route to chiral 2,2′-bis(pyridin-2-yl)-1,1′-binaphthyl ligands **2** was developed for the first time based on the photochemical $CpCo(CO)_2$-mediated cycloaddition reaction of enantiopure 2,2′-dicyano-1,1′-binaphthyl **3** with 1,6-heptadiyne, 1,7-octadiyne, 1,8-nonadiyne, and 2,8-decadiyne.

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Chiral nitrogen ligands have recently attracted much attention in metal-catalyzed enantioselective processes, particularly those in which the nitrogen ligands cannot be replaced by more soft and oxidative phosphine ligands.[1] The bis(oxazoline) ligand represented by an architecture **1** is the most frequently employed chiral nitrogen ligand. With respect to neutral, bidentate, sp^2-nitrogen donors, the bis(pyridine) ligand would be a complementary chiral nitrogen ligand in this class. However, its application to chiral catalysts is still in its infancy owing to the difficulties associated with installation of chirality into the planar pyridine units so that extensive efforts have been devoted to the design and synthesis of novel chiral bis(pyridine) ligands.[2]

On the analogy of the highly successful application of BINAP ligand to chiral catalysts, 2,2′-bis(pyridin-2-yl)-1,1′-binaphthyl ligand of general type **2** would be a candidate for novel chiral bis(pyridine) ligands. The simplest ligand **2a** was recently reported by Lloyd-Jones and co-workers.[3] Quite recently, they also synthesized the chloro and methyl substituted analogues derived from **2a** and applied them as chiral ligands to the zinc complex-catalyzed asymmetric allylation of benzaldehyde with allyltributyltin.[4] However, the structural diversity and the synthetic application of these ligands are somewhat limited due in part to the inevitable optical resolution process of the racemic ligand (±)-**2a**. Thus, development of a resolution-free route must be indispensable for wide employment of this novel chiral ligand. As mentioned by Lloyd-Jones, transition metal-catalyzed cross-coupling reactions between optically active binaphthyl electrophiles and 2-metallopyridine reagents or reversal of its cross-coupling polarities would be the most plausible resolution-free route. However, unfortunately, they demonstrated that the steric hindrance of the binaphthyl reagents made it difficult to form the pyridine-to-naphthalene bond in the cross-coupling reactions.[3] Because transition metal-mediated cycloaddition of a nitrile with two alkynes, especially a diyne, is the practical protocol for the construction of pyridine rings, this type of cycloaddition of enantiopure 2,2′-dicyano-1,1′-binaphthyl **3** with a diyne would be an alternative resolution-free route directly accessible to the chiral ligand **2**. We also assumed that the structural diversity of ligating pyridine units would be realized by the cycloaddition of the binaphthyl template **3** with a variety of diynes. The purpose of this communication is to describe the first resolution-free route to the chiral ligand **2** based on the photochemical $CpCo(CO)_2$-mediated cycloaddition reaction of enantiopure **3** with diynes.

The enantiopure dinitrile (*R*)-**3** was prepared in excellent yield with no observable racemization starting from the corresponding enantiopure dicarboxylic acid (*R*)-**4**, which was derived from the optically active dibromide (*R*)-**5** (Eq. 1).[5] In the early stages of this study, we

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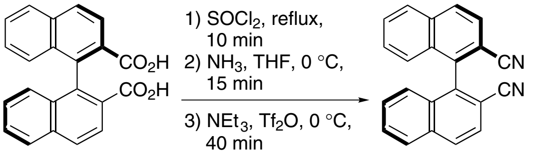
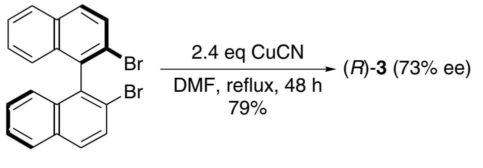
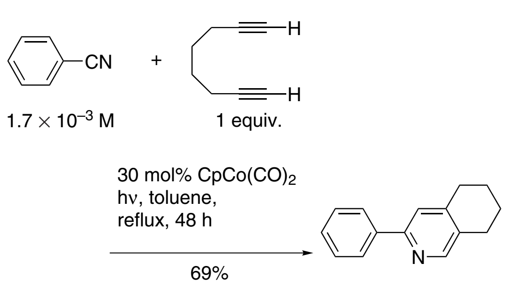
investigated a more straightforward route based on the dicyanation reaction of (*R*)-**5** (Eq. 2). A mixture of (*R*)-**5** (79% ee) and 2.4 equiv of CuCN in DMF was heated to reflux for 48 h to afford the optically active (*R*)-**3** (73% ee) in 79% yield. Though racemization slightly occurred during the cyanation reaction, erosion of enantiopurity was at an acceptable level. In addition, the high yield achieved in this dicyanation reaction was beyond our expectation because Putala and Karák recently reported that the diiodide analogue did not give any cyanation products under the same conditions.[6] However, a more amenable protocol was desired to afford enantiopure (*R*)-**3** because the contamination with the minor enantiomer could not be removed by recrystallization. Actually, we surveyed a variety of solvents (cyclohexane, toluene, EtOH, CH_3CN, *n*-Bu_2O, $Et_2O–CH_2Cl_2 = 10:1$, *i*-$Pr_2O–CHCl_3 = 5:1$) and found no condition that was sufficient to effect an increase in enantiomeric excess of the optically active (*R*)-**3**. The full details of the development of the synthesis of enantiopure (*R*)-**3** starting from (*R*)-**4** are presented in our preceding letter.[5]



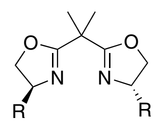
(*R*)-**4** (>99% ee) (*R*)-**3** (>99% ee) (1)



(*R*)-**5** (79% ee) (2)



(3)



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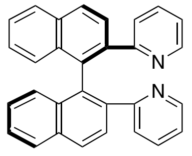
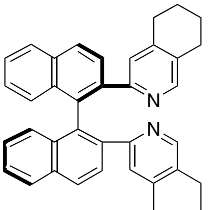
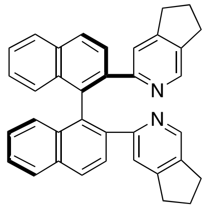


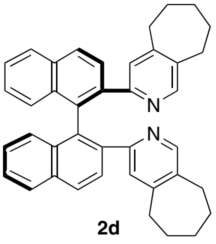
2a



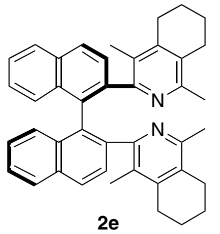
2b



2c



2d



2e

Because Co complexes have proven to be the most effective reagents for the transition metal-mediated cycloaddition of a nitrile and a diyne,[1e,7] our investigation of the preparation of 2,2′-bis(pyridin-2-yl)-1,1′-binaphthyl ligand **2** was based on the $CpCo(CO)_2$-mediated cycloaddition reaction of (*R*)-**3** (>99% ee) with a diyne (Table 1). Initially, the reaction with 1,7-octadiyne was chosen to examine this cycloaddition reaction. To a solution of enantiopure (*R*)-**3** in toluene (1.7×10^{-3} M) was added 180 mol% of $CpCo(CO)_2$ and 6-fold excess of 1,7-octadiyne, and then the reaction mixture was heated to reflux under irradiation using a 200 W tungsten lamp. After 120 h, the dinitrile (*R*)-**3** was completely consumed and the desired ligand (*R*)-**2b** was obtained in 40% yield (entry 1).[8] HPLC analysis of (*R*)-**2b** revealed that the reaction proceeded with complete retention of the axial chirality. On the other hand, both

Table 1. $CpCo(CO)_2$-mediated cycloaddition reaction of (*R*)-**3** with diynes

$$(R)\text{-}\mathbf{3}\ (>99\%\ \text{ee})\ (1.7 \times 10^{-3}\ \text{M}) + \text{Diyne} \xrightarrow[\text{h}\nu,\ \text{toluene, reflux}]{CpCo(CO)_2} (R)\text{-}\mathbf{2}\ (>99\%\ \text{ee})$$

Entry	Reagent	Time (h)	Product	Yield (%)
1	6 equiv 1,7-octadiyne, 180 mol% $CpCo(CO)_2$	120	(*R*)-**2b**	40
2	2 equiv 1,7-octadiyne × 3/48 h, 60 mol% $CpCo(CO)_2$ × 3/48 h	120	(*R*)-**2b**	62
3	2 equiv 1,7-octadiyne × 3/24 h, 60 mol% $CpCo(CO)_2$ × 3/24 h	72	(*R*)-**2b**	70
4[a]	2 equiv 1,7-octadiyne × 3/24 h, 60 mol% $CpCo(CO)_2$ × 3/24 h	72	(*R*)-**2b**	26
5[b]	2 equiv 1,7-octadiyne × 3/24 h, 60 mol% $CpCo(CO)_2$ × 3/24 h	72	(*R*)-**2b**	69
6	2 equiv 1,6-heptadiyne × 3/24 h, 60 mol% $CpCo(CO)_2$ × 3/24 h	72	(*R*)-**2c**	87
7	2 equiv 1,8-nonadiyne × 7/24 h, 60 mol% $CpCo(CO)_2$ × 7/24 h	168	(*R*)-**2d**	9

[a] The reaction was carried out in the absence of light.

[b] Xylene was used as a solvent.

the reaction rate and yield were not satisfactory compared to those of the model reaction of benzonitrile (Eq. 3). We then focused on finding a better condition for this cycloaddition reaction. Because the high dilution condition has been precedented to suppress intermolecular side reactions competitive with the pyridine ring formation, CpCo(CO)$_2$ and 1,7-octadiyne were added portionwise at intervals of 48 h in order to keep the dilution condition higher than that of entry 1 (entry 2). Though the reaction rate was still sluggish, the chemical yield was increased to 62% yield. The shortening addition intervals by half were more effective to improve both the reaction rate (72 h) and yield (70% yield) (entry 3). Along with the high dilution condition, irradiation was also essential in this cycloaddition reaction. In fact, when the reaction was carried out in the absence of light, (*R*)-**2b** was obtained in only 26% yield (entry 4). Elevated reaction temperature had little effect on this cycloaddition reaction at least within a range from toluene to xylene (entry 5). Next, in order to investigate the generality of this cycloaddition reaction, we evaluated use of 1,6-heptadiyne, 1,8-nonadiyne, and 2,8-decadiyne. The reaction with 1,6-heptadiyne afforded the desired ligand (*R*)-**2c** in excellent yield (entry 6). In contrast, the reaction with more flexible 1,8-nonadiyne was much slower than with other terminal diynes and the cycloaddition product (*R*)-**2d** was obtained in only 9% yield (entry 7). 2,8-Decadiyne, which is a dimethyl substituted analogue of highly reactive 1,7-octadiyne, was used with the expectation of incorporation of more sterically demanding substituents than hydrogen in proximity to ligating nitrogen donors of the pyridine rings. However, only a trace of the desired ligand (*R*)-**2e** was detected by mass spectrometry after the dinitrile (*R*)-**3** was completely consumed. These results suggested that the photochemical CpCo(CO)$_2$-mediated cycloaddition reaction of (*R*)-**3** with diynes was sensitive to both the entropy factor and the steric factor of diynes.

In conclusion, we have developed the first resolution-free route to the enantiopure 2,2′-bis(pyridin-2-yl)-1,1′-binaphthyl ligands **2** via the photochemical CpCo(CO)$_2$-mediated cycloaddition reaction of the enantiopure dinitrile **3** with terminal diynes. Application of chiral ligand **2** to catalytic asymmetric syntheses is currently under investigation in our laboratory.

Acknowledgements

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8. (*R*)-**2b** (>99% ee): mp = 95–97 °C; $[\alpha]_D^{20}$ 3.99 (*c* 1.00, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.48–1.74 (m, 8H), 2.04–2.18 (m, 4H), 2.50–2.64 (m, 4H), 6.31 (s, 2H), 7.26 (ddd, $J = 8.7, 6.7, 1.2$ Hz, 2H), 7.38 (d, $J = 8.7$ Hz, 2H), 7.44 (ddd, $J = 8.2, 6.7, 1.2$ Hz, 2H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.91 (d, $J = 8.2$ Hz, 2H), 7.96 (d, $J = 8.5$ Hz, 2H), 8.06 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 22.1, 22.4, 25.7, 28.2, 123.9, 125.7, 126.3, 127.2, 127.8, 127.9, 130.4, 132.7, 133.7, 134.3, 138.5, 144.9, 149.29, 149.31, 154.7; Ms, m/z (%) 516 (M$^+$, 93), 384 (100); HRMS Found: 516.2563. Calcd for $C_{38}H_{32}N_2$: 516.2565. The enantiomeric excess of (*R*)-**2b** was determined by HPLC using a Daicel Chiralcel AD-H (0.46 cm $\phi \times 25$ cm), hexane–*i*-PrOH = 9:1, wavelength: 320 nm, flow rate: 1.0 mL/min, retention time: 9.48 min (*S*), 20.78 min (*R*).