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Abstract. The first Ru(II)-catalyzed asymmetric cyclopropanation of diacceptor diazophosphonates with olefins is reported. The Ru(II)-Pheox complex 7e was found to be an efficient catalyst for the asymmetric cyclopropanation of α-cyano diazophosp honate with styrene under mild conditions to give the corresponding chiral diacceptor cyclopropylphosphonate products in high yields (up to 99%) with excellent diastereoselectivities (up to 99/1 dr). However, the enantioselectivity was difficult to control by the C_1-symmetric catalyst (up to 68% ee).

INTRODUCTION

The chiral cyclopropylphosphonates are important structural motifs in a variety of biologically interesting natural products and pharmaceutical targets [1-10]. Therefore, several methods have been developed for the construction of optically active cyclopropylphosphonate derivatives over the past two decades [11]. Among the developed methods, the transition-metal-catalyzed asymmetric cyclopropanation of olefins with monoacceptor diazophosphonates is the most efficient method for the direct and stereoselective synthesis [12]. Particularly, high stereocontrolled syntheses of cyclopropylphosphonates have been achieved using chiral copper(I), ruthenium(II), and rhodium(II) catalysts. However, despite these considerable advances, the asymmetric cyclopropanation of diacceptor diazophosphonates is still challenging due to the diacceptor diazophosphonate is less reactive to form metal carbene intermediate like other diacceptor diazo compounds. To date, only one example of the asymmetric cyclopropanation of α-cyano diazophosphonates by using Rhodium(II) catalyst has been reported and the other metal catalysts remain unexplored [12]. Because the resulting chiral diacceptor cyclopropane compounds are of considerable potential synthetic value, the development of a general and efficient catalytic system for the reaction is highly desirable [12].

In recent years, we reported the Ru(II)-Pheox catalyzed highly stereoselective cyclopropanation of monoacceptor diazophosphonates with various olefins including electron-deficient olefins such as α,β-unsaturated carbonyl compounds and vinyl carbamates [13]. In the course of our studies on the catalytic asymmetric cyclopropanation, we attempted the cyclopropanation of diacceptor diazophosphonates. Herein, we report the first Ru(II)-catalyzed asymmetric cyclopropanation of α-cyano diazophosphonate with olefins.

EXPERIMENTAL SECTION

Generally, all reactions were performed under an atmosphere of argon unless otherwise noted. Dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co., Inc. Acetonitrile was purchased from Wako Pure Chemical Industries, Ltd. All reactions were monitored by thin layer chromatography (TLC), glass plates pre-coated with silica gel Merck KGaA 60 F254, layer thickness 0.2 mm. All the starting materials are commercially available and were used after purification. The products were visualized by irradiation with UV light or by treatment with a

solution of phosphomolybdic acid, a solution of a KMnO$_4$ or a solution of p-anisaldehyde. Column chromatography was performed using silica gel (Merck, Art. No.7734). ^{1}H NMR (500 MHz, 400 MHz), ^{13}C NMR (100 MHz) and ^{31}P NMR (161 MHz) spectra were recorded on JEOL JNM-ECX500, JEOL JM-ECS400 spectrometer. Chemical shifts are reported in ppm (δ) relative internal tetramethylsilane (0.00 ppm) in CDCl$_3$. Phosphorous chemical shifts are reported in ppm (δ) relative to 85% H$_3$PO$_4$ as an external standard (0.00 ppm). Optical rotations were performed with a JASCO P-1030 polarimeter at the sodium D line (1.0 ml sample cell). DART mass (positive mode) analyses were performed on a LC-TOF JMS-T100LP.
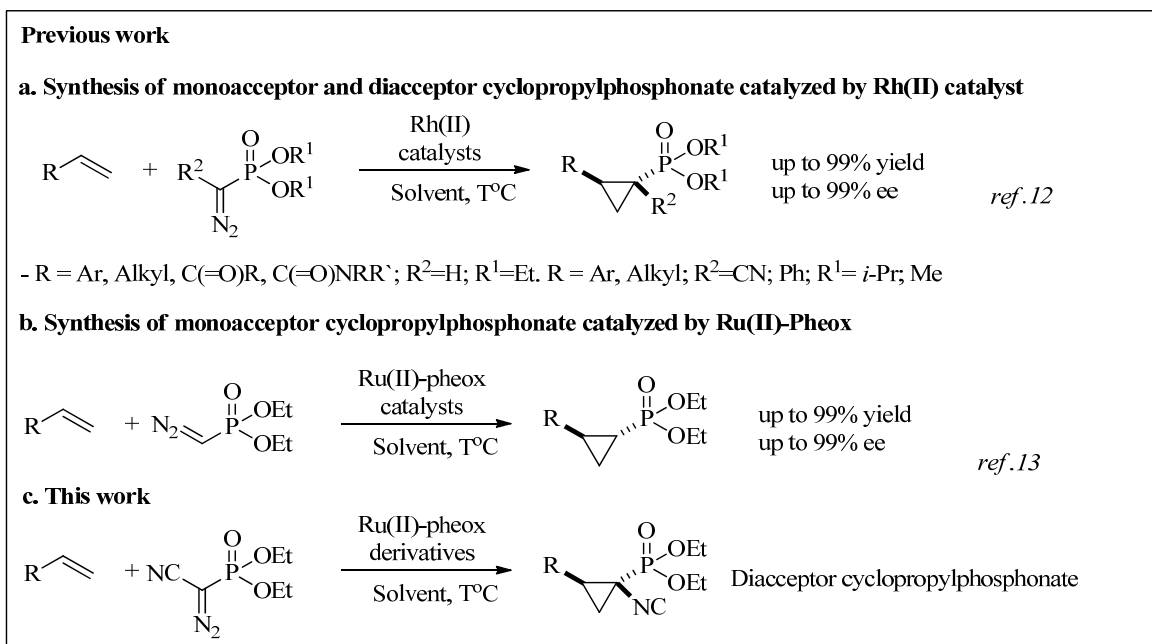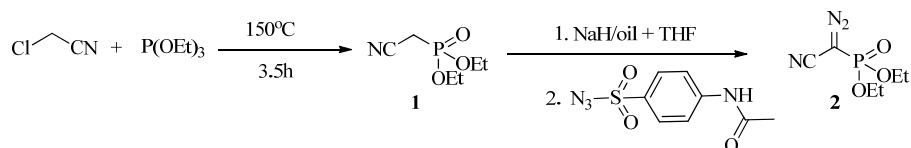

Previous work

a. Synthesis of monoacceptor and diacceptor cyclopropylphosphonate catalyzed by Rh(II) catalyst

ref.12

- R = Ar, Alkyl, C(=O)R, C(=O)NRR`; R^2=H; R^1=Et. R = Ar, Alkyl; R^2=CN; Ph; R^1= *i*-Pr; Me

b. Synthesis of monoacceptor cyclopropylphosphonate catalyzed by Ru(II)–Pheox

ref.13

c. This work

FIGURE 1. Research background

Synthesis of α-cyanophosphonate

Phosphonoacetonitrile diethyl ester (1): 906 mg (12 mmol) triethyl phosphite were heated to 150 °C. 997 mg (6.0 mmol) chloroacetonitrile were added at 150 °C over a period of 3.5h. Yield: 75%.

(Diethyl cyano(diazo)methyl)Phosphonate (2): Phosphonoacetonitrile diethyl ester (1) (442.8 mg, 2.5 mmol) was dissolved in 10 mL of dry toluene and NaH (150 mg, 3.75 mmol) was added portion wise, after stirred for 1 h at the 0°C, a solution of p-ABSA (620 mg, 2.5 mmol) in 25 mL of dry THF was added dropwise. Then, the reaction mixture was stirred at room temperature for 24 h, after the reaction was completed (monitored by TLC analysis), 50 mL petroleum ether was added, then the precipitate was filtered off, and the filter cake was washed with ether (3 x 50 mL), the filtrate was evaporated and the residue was purified by column chromatography on silica gel (Hex/EA = 2:1 to 2:1), give the 2 as yellow liquid, yield 92%. ^{1}H NMR (CDCl$_3$, 500MHz): δ 4.32-4.16 (m, 4H, OCH$_2$CH$_3$), 1.41 (t, 6H, OCH$_2$CH$_3$). ^{13}C NMR (CDCl$_3$, 125MHZ): δ 108.5, 64.6, 36.1, 16.0. ^{31}P NMR (CDCl$_3$, 202 MHz): δ 9.3. IR (neat) 2221, 2120, 1271, 1010, 984.

Synthesis of 3,4,5 methoxy Ru(II)-pheox catalyst
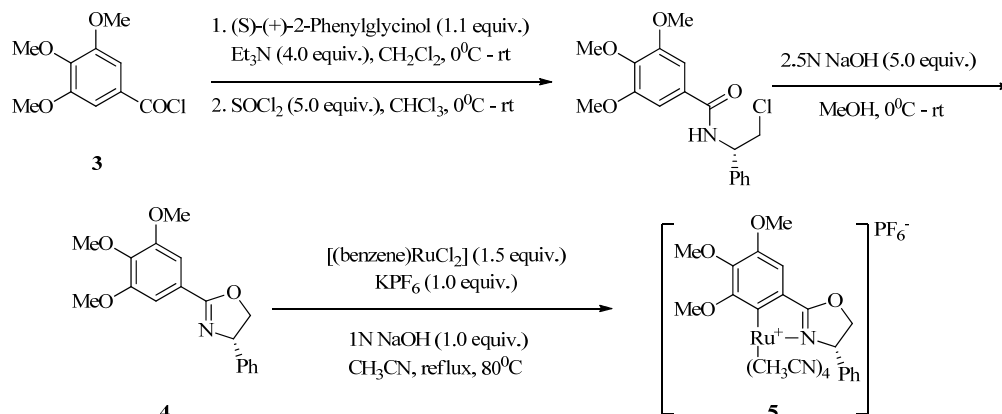
To a mixture of (S)-(+)-2-phenylglycinol (603.6 mg, 4.4 mmol, 1.1 equiv.) and triethylamine (2.28 mL, 16 mmol, 4 equiv.) in CH_2Cl_2 (5 mL), a solution of 3,4,5-trimethoxybenzoyl chloride 3 (922.56 mg, 4 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) was added dropwise with magnetic stirring at 0^oC. After the stirring for 24h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and treated with $SOCl_2$ (1.45 mL, 20 mmol, 5 equiv.) at 0^oC. After stirring for 12 h at room temperature, the solvent and excess $SOCl_2$ were removed under reduced pressure. Sat. $NaHCO_3$ (aqua) (40 mL) was added to the residue with stirring for 10 min. the organic product was extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using a sonicate, the solid residue was dissolved in methanol (15 mL) and 2.5 N NaOH (aqua) (640 mg, 16 mmol, 4 equiv.) was added slowly at 0^oC, then the reaction mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum, followed by addition of water (25 mL) and CH_2Cl_2 (3 x 25 mL) for extraction. The solvent was evaporated under vacuum to afford (S)-4-phenyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole 4 (1250 mg, 4 mmol, 99% yield). αD31.7= -9.1928 (c 0.97, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.9 (s, 9H), 4.26 (t, J = 8.41 Hz, 1H), 4.78 (dd, J1 = 8.41 Hz, J2=10.32 Hz, 1H), 5.37 (dd, J1 = 8.03 Hz, J2=10.32 Hz, 1H), 7.26-7.33 (m, 2H), 7.33-7.38 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.33, 60.99, 70.31, 75.10, 105.71, 122.83, 126.85, 127.78, 128.87, 141.02, 142.38, 153.14, 164.55 ppm. 19F ($CDCl_3$) δ -153.73, -149.61, -138.17, -133.92 ppm. IR (neat) 3388, 2940, 2148, 1956, 1639 cm^{-1}, HRMS (DART) cal. for $C_{16}H_{15}NO_2$ [M+H]+: 314.1387 found: 314.1385. A two necked round bottom flask (100 ml) fitted with a magnetic stirring bar and a reflux condenser was charged with (S)-4-phenyl-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole 4 (125.34 mg, 0.4 mmol, 1 equiv.), [$RuCl_2$(benzene)]$_2$ (100.36mg, 0.2 mmol, 0.5 equiv.), and KPF_6 (294.4 mg, 1.6 mmol, 4 equiv.). The reaction flask was evacuated and backfilled with argon. Through the side arm CH_3CN (10 mL, degassed) and NaOH (aq.) (16 mg, 0.4 mmol, 1 equiv.) were injected. The suspended reaction mixture was refluxed for 48 h at 80^oC. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with CH_3CN/CH_2Cl_2 (1/10 (v/v)) to give the desired complex 5 (251.5 mg, 0.348 mmol, 87% yield) as a green solid. ^{1}H NMR (400 MHz, CD_3CN) δ 1.94 (s, 6H, CH_3CN), 2.05 (s, 3H, CH_3CN), 2.16 (s, 3H, CH_3CN), 3.66 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.49 (t, J = 6.87 Hz, 1H), 5.11 (m, 2H), 7.03 (s, 1H), 7.33-7.44 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN) δ 0.78, 0.99, 3.09, 60.15, 60.37, 68.20, 78.00, 107.40, 121.83, 127.98, 128.11, 128.41, 129.47, 141.64, 145.38, 149.35, 163.48, 164.57, 174.80 ppm. IR (neat) 3653, 3223, 2934, 2272, 1397, 837 cm^{-1}.

## Procedure for Ru(II)-Pheox catalyzed cyclopropanation using a-cyano diazophosphonate
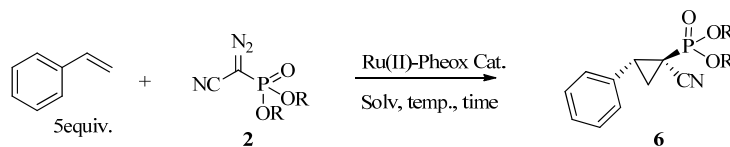
The solution of diazophosphonate (2) (0.2 mmol) in CH_2Cl_2 (1.0 mL) was slowly added to a mixture of Ru(II)-Pheox catalyst (3.8 mg, 0.006 mmol) and olefins (1.0 mmol) in CH_2Cl_2 (1 ml) for 4h under argon atmosphere at room temperature. After the addition completed, the reaction mixture was then stirred for 1h at room temperature. The progress of the reaction was monitored by TLC. Upon completion, solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc/n-Hexane to give desired product. The trans/cis ratio was determined from the crude lH NMR spectra, and the ee value was determined by chiral HPLC analysis.

This compound 6 was prepared according to the typical procedure for asymmetric cyclopropanation reactions between styrene (104.2 mg, 1.0 mmol) and diethyl cyano diazomethylphosphonate 2 (35.6 mg, 0.2 mmol). The resulting mixture was purified by silica gel column chromatography with EtOAc/n-Hexane as an eluent to give the desired product in 99% yield as yellow oil, trans/cis = >99:1. 1H NMR (CDCl3, 500 MHz): δ 4.32-4.16 (m, 4H, OCH_2CH_3), 1.41 (t, J = 7.1 Hz, 6H, OCH_2CH_3). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 108.5, 64.6, 36.1, 16.0. 31P NMR (CDCl$_3$, 202 MHz): δ 9.3. IR (neat) 2221, 2120, 1271, 1010, 984.

RESULTS AND DISCUSSION

The cyclopropanation of α-cyano diazophosphonate 2 with styrene using the series of Ru(II)-Pheox complexes and the influence of various solvents were preliminarily described. Firstly, as the results, the cyclopropanation reactions catalyzed by Ru(II)-Pheox catalysts always obtained in excellent yields together with excellent diastereoselectivities (99/1 dr). To describe the screening catalysts, the series of Ru(II)-Pheox complexes which bear different substituents at the phenyl backbone and the oxazoline moiety were investigated as the catalyst for the cyclopropanation. It was observed that the cyclopropanation reactions catalyzed by Ru(II)-Pheox catalyst carrying electron-donating groups at phenyl backbone, in dichloromethane at room temperature were more effective in both yield and enantioselectivity than electron-withdrawing groups at the same position (entries 2 and 3). Therein, the highest enantioselectivity and yield could be received in 63% ee and 99% yield by using Ru(II)-Pheox catalyst, which holds three MeO electron-donating group at phenyl backbone (entry 6). After that, the cyclopropanation reaction also was considered by the effective of 3,4,5-MeO-Ru(II)-Pheox derivatives bearing the substituents at the C4 position of oxazoline ring. The result was found these kinds of catalyst derivative could not improve the enantioselectivity (entries 6 and 7). In contrast, we also examined the cyclopropanation by using chiral Ru(II)-Amm-Pheox complex; however, no cyclopropane product was observed.
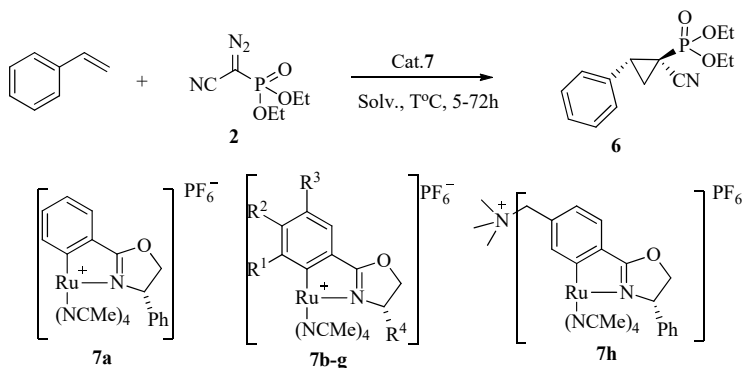
CONCLUSION

Besides, to improve the enatioselectivity of the cyclopropanation of this type diazo compounds, we tried to express the influence of various solvents on the cyclopropanation reaction. However, both the yields and the enantioselectivity had significantly decreases, from 99% to 89% in yield and from 63% to 51% in enantioselectivity (entries 9-12). Moreover, as we can see, 1,4-dioxan also had same effect with dichloromethane, however we still chose dichloromethane as the best solvent in this case because of its low boiling point.

In entry 13, the cyclopropanation reaction was carried out by using catalyst 7e, in dichloromethane at 5 oC and the enantioselectivity could be obtained in 68% ee. This means that the temperature has effected on the

enantioselectivity of this reaction. Thereby, the cyclopropanation reaction will be conducted more with various conditions to improve the enantioselectivity.

In conclusion, we presented the first Ru(II)-catalyzed asymmetric cyclopropanation of diacceptor diazophosphonates with olefins, affording the desired chiral diacceptor cyclopropylphosphonate products in excellent yields and high diastereolectivity with moderate enantioselectivity. The development of catalytic asymmetric cyclopropanation of olefin using diacceptor diazo compounds plays an important role to supply the synthetic intermediates in a vast array of transformations. Based on the results above, we are completely believed that Ru(II)-Pheox derivatives are potential to this reactions, hence, conducting more experiments to improve the enantioselectivity is necessary.

TABLE 1. Optimization of Reaction Conditions

Entry	Catalyst	Solvent	Temp [^{o}C]	Yield [%]b	-ee [%]^c
1	7a	CH_2Cl_2	RT	99	55
2	7b: R3 = NO$_2$, R1 = R2 = H, R4 = Ph	CH_2Cl_2	RT	92	21
3	7c: R3 = OMe, R1 = R2 = H, R4 = Ph	CH_2Cl_2	RT	99	48
4	7d: R1 = R3 = OMe, R2 = H, R4 = Ph	CH_2Cl_2	RT	99	50
5	7e: R1 = R2 = R3 = OMe, R4 = Ph	CH_2Cl_2	RT	99	63
6	7f: R1 = R2 = R3 = OMe, R4 = iPr	CH_2Cl_2	RT	80	32
7	7g: R1 = R2 = R3 = OMe, R4 = tBu	CH_2Cl_2	RT	86	35
8	7h	CH_2Cl_2	RT	0	-
9	7e	Et$_2$O	RT	90	58
10	7e	1,4 Dioxan	RT	89	63
11	7e	THF	RT	93	51
12	7e	Toluene	RT	95	57
13	7e	CH_2Cl_2	5	99	68

[a]Reaction conditions: to a solution of Ru(II)-Pheox (3%) in solvents was added a solution of a-cyanodiazomethyl-phosphonates 2 (0.2mmol) under Ar, [b]Isolated yield, [c]Determined by chiral-phase HPLC analysis.

ACKNOWLEDGEMENTS

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