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Catalytic asymmetric cyclopropanation of alkenes with diazoesters in protic and biphasic media

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Abstract—As a C_2 symmetric hydrophilic chiral ligand, a series of 2,6-bis(oxazolinyl)-pyridines (**pyboxs**) bearing a hydroxyalkyl group on the oxazoline ring has been synthesized from readily available amino acid derivatives. Catalytic asymmetric intermolecular cyclopropanation of electron rich terminal alkenes with diazoesters in the presence of hydrophilic pybox ligand, pybox-*hm* and Ru(II) complex proceeded smoothly in protic or biphasic media to give the corresponding cyclopropanation products in 97:3 to 99:1 *trans*/*cis* ratios and 90 to 97% ee. In the case of the intramolecular cyclopropanation reaction of *trans*-cinnamyl diazoester using Ru(II)(pybox-*he*) complex in biphasic medium gave the corresponding cyclopropane ring fused lactone in 52% ee. Steric tuning of the chiral environment of pybox ligands was simply achieved by using a weak interaction between the solvent and the hydroxyl groups of the chiral ligand. The solubility of the new hydrophilic pybox and Ru(II) complexes in protic solvents is dramatically increased; hence, the efficiency of these catalysts enhanced the rate of cyclopropanation. Furthermore, the active catalyst in the water phase can be re-used several times for the cyclopropanation reaction.

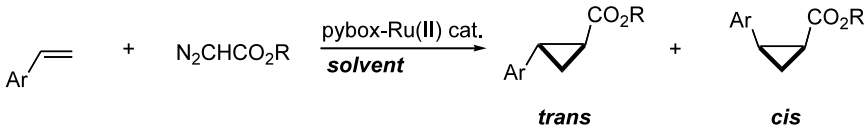
1. Introduction

The Nozaki research group reported the first catalytic asymmetric cyclopropanation reaction in 1966.[2] It is considered that this is one of the most important papers since they used chiral molecular catalysts to induce chirality in an achiral organic molecule. After their historical report, various chiral ligands and their combination with metals for providing optically active organic compounds have been reported.[3] Although there are many examples of cyclopropanation reactions, because of interests in both industry and academia, to the best of our knowledge, there are no reports about the use of protic and/or biphasic solvent systems for the catalytic asymmetric cyclopropanation reaction.[4] In most cases the reaction has been carried out in halogenated and/or organic solvents such as CH_2Cl_2, 1,2-dichloroethane, $CHCl_3$, etc. We report here the design and synthesis of pybox ligands containing hydroxy group moieties and their application for catalytic asymmetric cyclopropanation reactions of terminal electron rich alkenes with a diazoester in protic and/or biphasic media, whose non-halogenated solvent system with environmental concerns complies with recent social demands (Scheme 1).

2. Results and discussion

2.1. Synthesis of ligands

As for the synthesis of functionalized pybox, we recently reported the synthesis of the hydrophilic derivative of pybox, 2,6-bis(4-hydroxymethyloxazolinyl)pyridine **1** (pybox-*hm*), having two hydroxymethyl groups as the symmetric chiral stems of the oxazoline rings.[5] Furthermore, 2,6-bis(hydroxyethyloxazolinyl)pyridine **2a** (pybox-*he*) and 2,6-bis(hydroxy-



Scheme 1. Catalytic asymmetric cyclopropanation.

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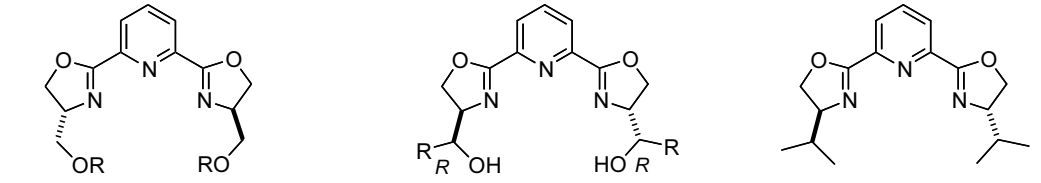
benzyloxazolinyl)pyridine **2b** (pybox-*hbn*) having secondary hydroxy groups were synthesized from an L-threonine derivative and amino alcohol, respectively, as in the synthesis of **1a** (Fig. 1). The synthetic routes are summarized in Schemes 2 and 3. Classical synthetic methods for oxazoline ring formation as a key step can be applied under careful attention for avoiding the side reactions such as dehydration reaction and racemization of stereogenic centers on side chains.[6] **1a**, **2a**, and **2b** were obtained in 54, 51, and 59% total yields, respectively, in four to five steps starting from **3**, which is commercially available.

2.2. Synthesis of Ru(pybox) catalysts

The catalysts were synthesized from pybox ligands and pre-catalyst, $[RuCl_2(p\text{-cymene})]_2$, which can be isolated as its ethylene complex.[7] We isolated Ru(pybox)(ethylene) complexes **13** and **14** for asymmetric cyclopropanation reaction (Scheme 4) As for ethylene complex **14**, deprotection of the hydroxy groups gave complicated mixtures. The complexes of pybox bearing hydroxy groups and Ru(II) was slightly unstable during purification even at low temperature. Ru(pybox-*hm*)(ethylene) and Ru(pybox-*hbn*)(ethylene) complexes could not be isolated because of their instability. In these cases, ethylene atmosphere can be applied to prepare Ru(pybox)(ethylene) complex in situ. The complexation with ethylene and its purification process is sometimes useful for achieving good reactivity and selectivity compared to the preparation of the catalyst in situ.

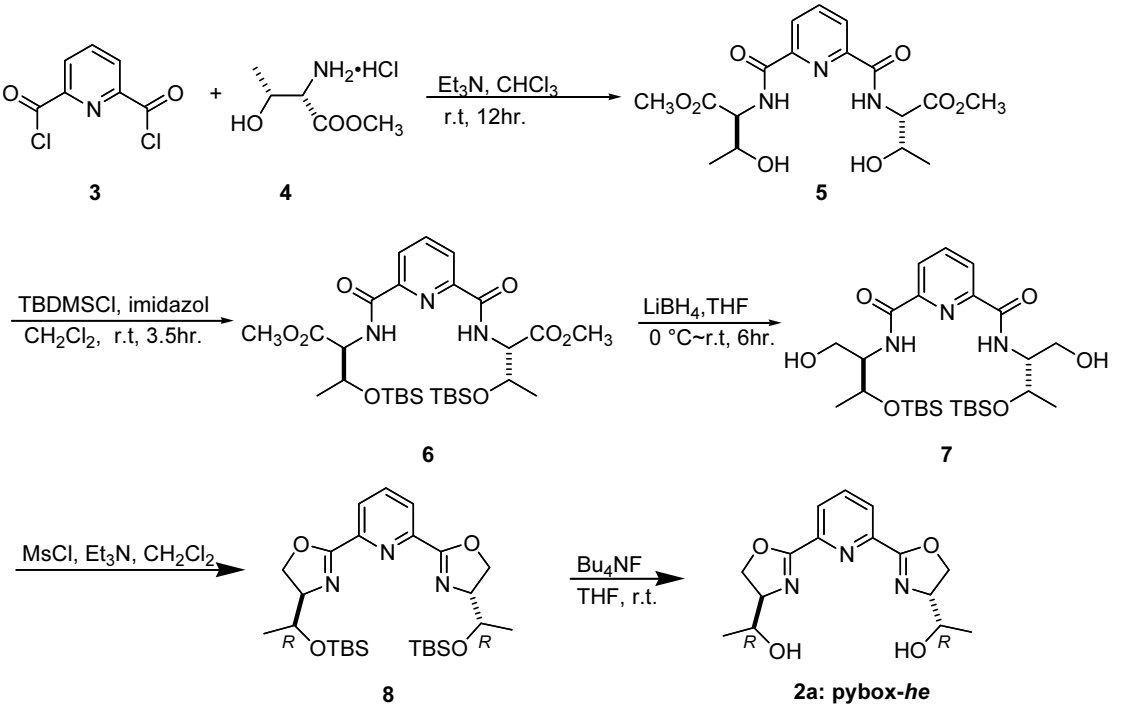
2.3. Catalytic asymmetric cyclopropanation of styrene with diazoesters

There were no systems effective in aqueous media or protic solvents related to the catalytic cyclopropanation of alkenes and diazoacetates.[8] However, we discovered that the existence of a free hydroxy group on chiral ligands does not interfere with the smooth running of cyclopropanation for copper catalyzed reactions, for example, in the case of bis(oxazoline) ligands.[9,10] It had also very recently been reported that although a small

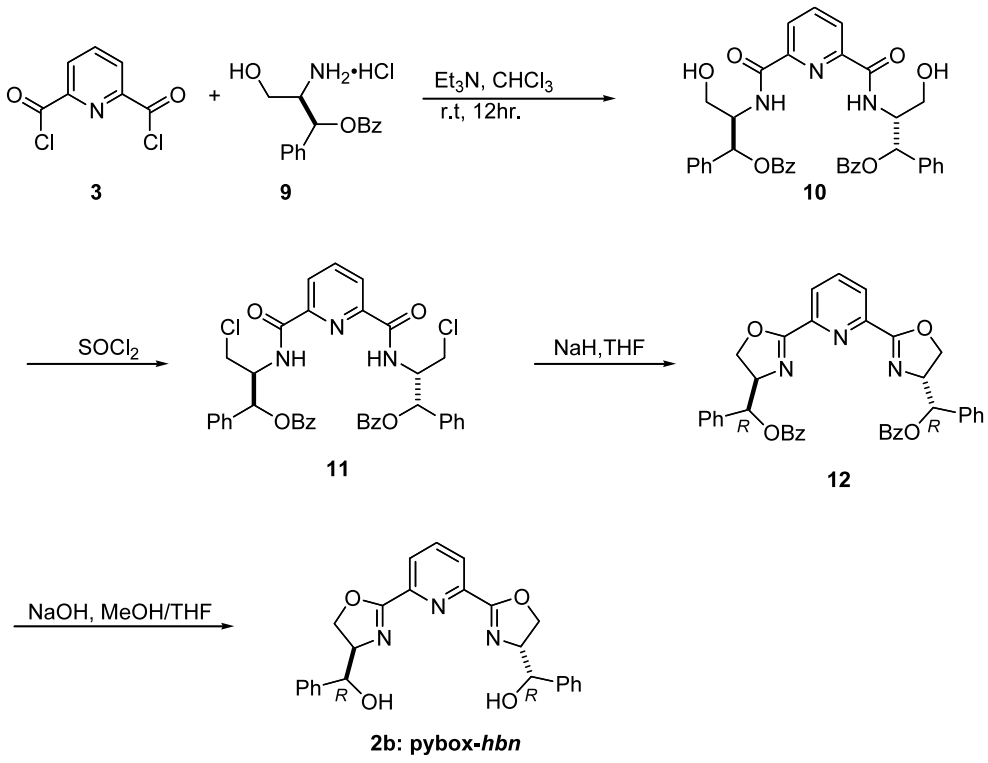


1a: R = H (pybox-*hm*)
1b: R = *t*-BuMe$_2$Si (pybox-*tbdmsom*)
2a: R = CH$_3$ (pybox-*he*)
2b: R = Ph (pybox-*hbn*)
2c: (pybox-*i-pr*)

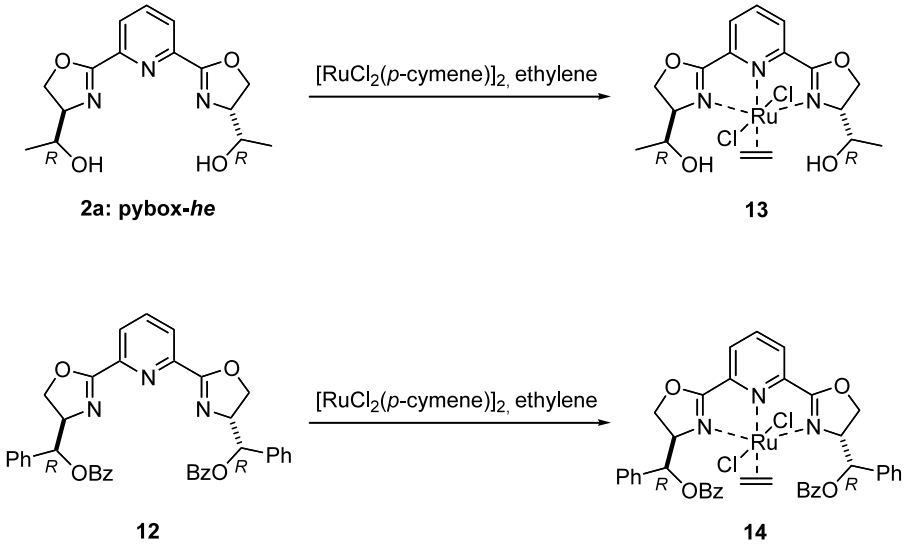
Figure 1. Pybox ligands.



Scheme 2. Synthesis of pybox-*he* ligand.



Scheme 3. Synthesis of pybox-*hbn*.



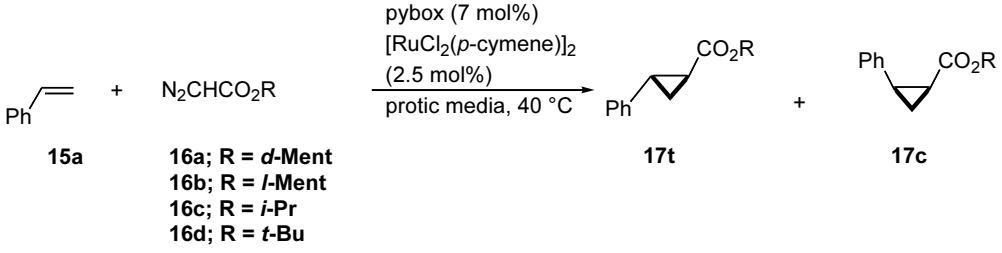
Scheme 4. Synthesis of Ru(pybox)(ethylene) complexes.

amount of water in the reaction solvent diminishes the enantioselectivity of cyclopropanation with rhodium catalysts, the unfavorable influence of water was reduced by addition of an appropriate phosphite ligand.[8] Accordingly, we were intrigued to examine the catalysis with pybox-*hm* **1a** and $[RuCl_2(p\text{-cymene})]_2$.[7] Firstly, we chose styrene as an terminal alkene and pybox-*hm* **1a** as a hydrophilic ligand to optimize the reaction conditions for intermolecular catalytic cyclopropanation in protic and biphasic media. The results are summarized in Table 1.[11] First, we tried aqueous media for the cyclopropanation of styrene and (*d*)-menthyl diazoacetate **16a** with pybox-*hm* **1a** in the presence of co-solvent THF or toluene (Scheme 5). The use of a single organic solvent resulted in lower yields and lower enantioselectivities (entries 1 and 2). Surprisingly, addition of water to both media in entries 1 and 2 dramatically improved the enantioselectivities and slightly the yields (entries 3 and 5). This phenomenon can be simply accounted for by the increase of the solubility of the active catalyst Ru(pybox-*hm*)Cl_2(vacant or solvent) derived from pybox-*hm* **1a** and pre-catalyst $[RuCl_2(p\text{-}$

Table 1. Catalytic asymmetric cyclopropanation of styrene and menthyl diazoeaters **16a–d** with chiral pybox-*hm* **1a** and $[RuCl_2(p\text{-cymene})]_2$ in the presence of water or alcohols[a]

Entry	Pybox	Diazoester	Initial solvent (mL)	Solvent of **16** (mL)	**17t**+**17c**[b]		% ee[c]	
					Yield (%)	Ratio	**17t**	**17c**
1	**1a**	**16a**	THF (3)	THF (3)	39	83:17	8	30
2	**1a**	**16a**	Toluene (3)	Toluene (3)	38	89:11	8	28
3	**1a**	**16a**	THF (2)+H_2O (1)	THF (3)	46	95:5	78	45
4	**1a**	**16b**	THF (2)+H_2O (1)	THF (3)	57	86:14	68	44
5	**1a**	**16a**	Toluene (2)+H_2O (1)	Toluene (3)	56	96:4	88	51
6[d]	**1a**	**16a**	Toluene (0.5)+H_2O (0.5)	Toluene (1.5)	57	97:3	94	76
7[d]	**1a**	**16c**	Toluene (0.5)+H_2O (0.5)	Toluene (1.5)	24	92:8	67	27
8[d]	**1a**	**16d**	Toluene (0.5)+H_2O (0.5)	Toluene (1.5)	30	92:8	57	26
9[d]	**2a**	**16b**	Toluene (0.5)+H_2O (0.5)	Toluene (1.5)	75	96:4	83	54
10[d]	**2a**	**16b**	Toluene (0.5)+H_2O (0.5)	Toluene (1.5)	35	95:5	89	60
11	**1a**	**16a**	Toluene (1)+EtOH (1)	Toluene (3)	67	96:4	35	2
12	**1a**	**16a**	Toluene (1)+*t*-BuOH (1)	Toluene (3)	54	91:9	11	15
13	**1a**	**16a**	Toluene (1)+*i*-PrOH (1)	Toluene (3)	78	95:5	92	65
14[f]	**1a**	**16a**	Toluene (1)+*i*-PrOH (1)	Toluene (3)	52	97:3	96	88
15	**1a**	**16b**	Toluene (1)+*i*-PrOH (1)	Toluene (3)	78	95:5	90	88
16	**1a**	**16a**	THF (1)+*i*-PrOH (1)	THF (3)	73	96:4	89	58
17	**1a**	**16a**	*i*-PrOH (2)	*i*-PrOH (3)	59	95:5	84	30
18	**1b**	**16a**	Toluene (2)	Toluene (3)	47	94:6	64	15
19	**1b**	**16a**	Toluene (1)+*i*-PrOH (1)	Toluene (3)	61	98:2	66	13
20	**2a**	**16b**	Toluene (1)+*i*-PrOH (1)	Toluene (3)	78	94:6	91	78
21	**2a**[e]	**16b**	Toluene (1)+*i*-PrOH (1)	Toluene (3)	65	97:3	91	71

[a] Styrene (10 mmol), diazoacetate (2.0 mmol), pybox (0.14 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.05 mmol), 40°C. A solution of diazoacetate in 1.5–3.0 mL of the same solvent was slowly added by syringe for 6–8 h to the mixture of styrene and the catalyst in the initial solvent.
[b] Isolated yield, ratios by ^1H NMR.
[c] % ee determined by reported method, see Ref. 7a. Absolute configuration: **17t** for entries 1–8 and 11–19, (1*S*,2*S*); for entries 9, 10, 20 and 21, (1*R*,2*R*); **17c** for entries 3–8, 11 and 13–19, (1*S*,2*R*); for entries 1, 2, 9, 10, 12, 20 and 21, (1*R*,2*S*).
[d] Half scale for entry 1: styrene (5 mmol), diazoacetate (1.0 mmol), catalyst 5 mol%, for 4 h.
[e] Ethylene complex was used.
[f] 30°C. The cyclopropanation did not proceed at 20°C.



Scheme 5. Catalytic asymmetric cyclopropanation of styrene with *d*-menthyl diazoacetate.

cymene)]$_2$. When the catalytic asymmetric cyclopropanation was carried out in toluene/water biphasic media, the product gave a enantioselectivity of 94% (entry 6). Into the two-phase system of water and organic solvent (initial ratio = 1:2), a solution of the diazoacetate **16a** was slowly added under vigorous stirring to give the desired cyclopropanes **17** in moderate yields with higher enantioselectivity (88% for **17t**, entries 3 and 5). The organic layer was extracted with degassed (or absolute) diethyl ether and concentrated to give the products. In this aqueous system, addition of phase-transfer reagents such as (n-Bu_4N)(HSO_4) (10 mol% of **16a**) into the system of entry 5 resulted in no improvement in the reaction and the selectivities. The influence of substituents on the diazoesters was also examined. Sterically hindered diazoesters gave higher stereoselectivities in toluene/water phase. (*d*)-Menthyl ester was better matching to the (*R*,*R*)-absolute configuration of pybox, which ought to give higher enantioselectivity according to our previous work (entries 3 and 6–8).[7b] The use of pybox-*he* **2a** and Ru(pybox-*he*)(ethylene) complex **13** gave moderate enantioselectivities (entries 9–10).

On the other hand, when alcohols such as ethanol, isopropyl alcohol, and *tert*-butyl alcohol in place of water were adopted to provide a homogeneous protic

medium, isopropyl alcohol resulted in the best enantioselectivities, up to 96% ee for *trans*-**17t** and 88% ee for *cis*-**17c** at 30°C (entries 11–13 and 14). (*l*)-Menthyl diazoacetate **16b** showed a decrease of ee to 90% for the *trans*-product (entry 15), because of the unmatched steric pair toward (*R*,*R*)-absolute configuration of the ligand. Use of pure isopropyl alcohol gave moderate ees (entry 17). We have thus found that the choice of alcohol solvents apparently influences the enantioselectivity. Although at present we cannot define clearly the origin of the stereochemical outcomes for protic solvents, we believe that weak interactions between the solvent and chiral ligands such as hydrogen bonding is the most important factor in protic and biphasic solvent systems. With pybox-*he* **2a** synthesized from (L)-threonine, the enantioselectivities with the ruthenium catalyst were found to be moderate by using (*l*)-menthyl diazoacetate **16b** at 40°C: 83% ee for *trans* and 54% ee for *cis*, in 96:4 *trans*: *cis* ratio (entry 9). In toluene/*i*-PrOH the enantioselectivities increased to 91% for *trans* and 78% ee for *cis*, in 94:6 *trans*:*cis* ratio. (entry 20). In comparison, classic pybox-*ipr* **2c** with similar bulkiness to **2a** was found in toluene/*i*-PrOH media to give 93% ee for *trans* and 90% ee for *cis*, in 97:3 *trans*/*cis* ratio (84% yield). Pybox-*he* **2a** thus proved to be inferior to pybox-*ipr* **2c**. Furthermore, pybox-*tbdmsom* **1b** which was reported by us as an excellent chiral ligand for 1,3-dipolar cycloaddition reactions gave 64–66% ee for *trans* (entries 18 and 19).[12]

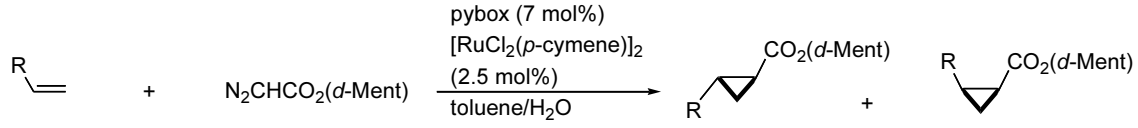
2.4. Catalytic asymmetric cyclopropanation of vinyl ethers with diazoester

Next, we applied our protic conditions to various more electron rich terminal alkenes such as vinyl ethers to afford functionalized chiral cyclopropane rings. The results are summarized in Table 2. For all of the substrates, the cyclopropanation reactions were carried out smoothly in biphasic media with high stereoselectivities to give β-functionalized chiral cyclopropane compounds (entries 1–7). In the case of *tert*-butyl vinyl ether, the reactivity and *trans*/*cis* ratio was found to be low (entry 8). Electron deficient alkenes such as vinyl acetate could not reacted with the diazoester under same reaction condition because of electronic reasons (entry 9).

2.5. Intramolecular version

We examined briefly an intramolecular version for catalytic asymmetric cyclopropanation using *trans*-cinnamyl diazoester **26** in the presence of Ru(II)(pybox)

Table 2. Catalytic asymmetric cyclopropanation of various electron rich terminal alkenes and *d*-menthyl diazoeaters **16a** with chiral pybox-*hm* **1a** and $[RuCl_2(p\text{-cymene})]_2$ in the presence of water[a]



15a: R = C_6H_5 **16a** ***trans*** ***cis***
15b: R = *p*-$CH_3C_6H_4$
15c: R = *p*-$CH_3OC_6H_4$
15d: R = *p*-ClC_6H_4
15e: R = *o*-ClC_6H_4
15f: R = OC_4H_9
15g: R = $OCH_2CH(CH_3)_2$
15h: R = $OC(CH_3)_3$
15i: R = $OCOCH_3$
17–25

Entry	Alkene	Time (h)	*trans*+*cis*[b]		% ee[c] *trans*
			Yield (%)	Ratio	
1	**15a**	18	**17** (62)	98:2	97
2	**15b**	22	**18** (82)	97:3	96
3	**15c**	19	**19** (70)	96:4	92
4	**15d**	22	**20** (55)	97:3	94
5	**15e**	23	**21** (58)	99:1	94
6	**15f**	29	**22** (56)	94:6	97
7	**15g**	23	**23** (57)	95:5	94
8	**15h**	18	**24** (24)	74:26	90[d]
9	**15i**	33	ND[e]	–	–

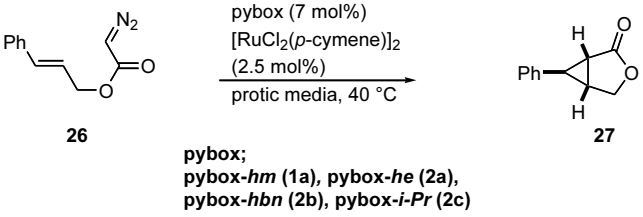
[a] Alkene (5 mmol), diazoacetate (1.0 mmol), pybox-*hm* **1a** (0.07 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), 40°C. A solution of diazoacetate in 1.5 mL of the same solvent was slowly added by syringe for 9 h to the mixture of alkene and the catalyst in the initial solvent.
[b] Isolated yield, ratios by ^1H NMR.
[c] % ee determined by chiral GC. Absolute configuration: for all products **17**–**24**, (1*S*,2*S*).
[d] 82 % ee for *cis* isomer.
[e] The cyclopropanation did not proceed.

catalyst in a single organic and biphasic media. The solvent effects are summarized in Table 3. To our surprise, the reactivities of pybox catalysts were different from the intermolecular versions. Ru(pybox-*hm*)Cl_2 catalyst gave relatively low enantioselectivity for *trans* (entries 1–3). Interestingly, Ru(pybox-*he*)Cl_2 catalyst gave an enantioselectivity of 52% for the corresponding cyclopropane ring fused lactone (entry 6). Bulky substituents of the hydroxy groups on the oxazoline rings in pybox ligand seems to be increase the enantioselectivity for intramolecular cyclopropanation reactions (entries 10–12) (Scheme 6).

Table 3. Catalytic asymmetric intramolecular cyclopropanation reaction of trans cinnamyl diazoester **26** in protic media[a]

Entry	Pybox	Solvent	Yield (%)[b]	% ee[c] *trans*
1	**1a**	CH_2Cl_2	72	5
2	**1a**	Toluene	68	10
3	**1a**	Toluene+H_2O	77	13
4	**2a**	CH_2Cl_2	82	16
5	**2a**	Toluene	63	39
6	**2a**	Toluene+H_2O	70	52
7	**2b**	CH_2Cl_2	51	–
8	**2b**	Toluene	30	25
9	**2b**	Toluene+H_2O	9	–
10	**12**	CH_2Cl_2	63	68
11	**12**	Toluene	86	77
12	**12**	Toluene+H_2O	33	48

[a] **25** (0.3 mmol), catalyst 5 mol%, 40°C. A solution of **26** in 1.5 mL of toluene was slowly added by syringe for 6 h to the catalyst in the solvent.
[b] Isolated yield.
[c] % ee determined by reported method, see Ref. 7a. Absolute configuration: for entries 1–3, 8 and 10–12, (1*R*,5*S*). for entries 4–6, (1*S*,5*R*).



Scheme 6. Catalytic asymmetric intramolecular cyclopropanation reaction in protic media.

2.6. On the re-use of the water phase containing active catalyst

When the catalyst was dissolved in the protic or biphasic media, the protic phase was immediately colorlized to dark purple while toluene phase was almost colorless. It could easily be seen from the dark-violet coloring of the bottom phase that most of the catalyst was dissolved in the aqueous phase. As the reaction proceeded, the toluene phase was slightly colorlized to pale red. This phenomenon suggested the ruthenium complex or the intermediate was slightly soluble in the organic phase during the reaction even though the catalyst was soluble in the water phase. As the active species remained in the aqueous phase, the second run was carried out by addition of styrene and diazoacetate to give a similar result (entry 2 in Table 4). We repeated the same reaction using the same water phase. During the fourth cycle, the yield and selectivitiy were dramatically decreased. These results suggested that some active intermediate such as a ruthenium carbenoid was extracted into the organic phase or the catalyst was destroyed by dissolved oxygen. We are now investigating further the optimization and recycling of the catalyst.

Table 4. Re-use of the water phase for catalytic asymmetric cyclopropanation reaction[a]

Run	Time (h)	*trans*+*cis*[b]		% ee[c] *trans*
		Yield (%)	Ratio	
1	18	62	98:2	97
2	22	55	98:2	97
3	42	33	96:4	89
4	72	13	83:17	42

[a] Styrene (5 mmol), diazoacetate (1.0 mmol), pybox-*hm* **1a** (0.07 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), 40°C. A solution of diazoacetate in 1.5 mL of the same solvent was slowly added by syringe for 9 h to the mixture of styrene and the catalyst in toluene. Then the organic phase was removed and the water phase was used for next cycles.
[b] Isolated yield, ratios by ^1H NMR.
[c] The ee was determined by chiral GC.

3. Conclusion

One of the recent social demands for organic synthesis and catalysis, with environmental concerns in mind, has been for the reactions to be carried out in non-halogenated solvents or in aqueous and protic media.[5] We therefore had expectations of developing a new process in aqueous media for asymmetric catalytic cyclopropanation using our water-soluble Ru(pybox-*hm*) catalyst. The hydroxymethyl derivative of pybox can provide excellent stereoselectivities for cyclopropanations of electron rich terminal alkenes, compared to the hydroxyethyl or isopropyl derivatives, in moderate yields in aqueous and protic media. We hypothesize that appropriate solvation of water or alcohols around the hydroxy group causes a more favorable chiral environment around the active site for the cyclopropanation. Work is now under way on applications to other catalytic reactions performed in aqueous media.

4. Experimental

4.1. General

All reactions were carried out under a nitrogen atmosphere. Common solvents were purified before use. THF (anhydrous), Et_2O (anhydrous), toluene and CH_2Cl_2 (anhydrous) are commercially available from

Kanto Chemical Co. Ltd., and were used without further purification. All reagents were reagent grade and purified when necessary. Reactions were monitored by TLC using 250 μm Merck (Art. 5715) precoated silica gel. Flash column chromatography was performed over Merck (Art. 7734) silica gel. Melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 spectrometer. ^{1}H NMR chemical shifts are reported as δ values(ppm) relative to internal tetramethylsilane and splitting patterns are designated as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants are given in Hz. IR spectra were recorded with JASCO FT/IR-230 spectrometer and are reported in reciprocal centimeter (cm^{-1}). Elemental analyses were performed with Yanagimoto MT-3 CHN corder. Optical rotations were measured on JASCO DIP-140 polarimeter at the sodium D line (1 mL sample cell).

Chiral ligands, **pybox-*hm* 1a** were synthesized according to the literature. Starting styrene derivatives are commercially available. The absolute stereochemistry of cyclopropanation product **17t**, **17c**, **18**–**25** and **27** was determined by chiral GPLC.

4.2. Synthesis of pybox ligands

4.2.1. Synthesis of pybox-*he* 2a

4.2.1.1. Bis-amide ester 5. L-Threonine methyl ester hydrochloride **4** (5.00 g, 29.5 mmol) was placed in a 200 mL, three necked round bottomed flask equipped with a magnetic stirring bar, nitrogen inlet tube and 100 mL addition funnel. The flask was degassed with vacuum pump, and flushed with nitrogen gas. The flask was charged with 45 mL of chloroform. The solution was stirred and cooled to 0°C. Triethylamine (10.0 mL, 72.1 mmol) was added dropwise to the solution. After stirring for 5 min, 2,6-pyrizine dicarboxylic acid chloride **3** (3.00 g, 14.7 mmol) in chloroform (20 mL) was added dropwise to the solution. When the adding was finished, the reaction mixture was stirred at rt for 12 h. Then $CHCl_3$ was removed on rotary evaporator. Purification by silica gel chromatography (AcOEt/MeOH = 20:1) gave 4.88 g (12.3 mmol, yield 91.8%) of amide ester **5** as a white solid. Mp 127–128°C. IR (NaCl); 3384, 2977, 1745, 1673, 1531, 1439, 1356, 1273, 1175, 1135, 1084, 1018 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.31 (d, J = 6.4 Hz, 6H), 3.27 (brs, 2H), 3.80 (s, 6H), 4.51 (ddq, J = 6.4, 6.2, 2.6 Hz, 2H), 4.77 (dd, J = 9.0, 2.7 Hz, 2H), 8.01 (d, J = 7.9 Hz, 2H), 8.78 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 20.4, 52.9, 68.4, 125.4, 139.2, 148.4, 164.1, 171.6. Anal. calcd for $C_{17}H_{23}N_3O_8 \cdot 0.5H_2O$: C, 50.24; H, 5.95; N, 10.34. Found: C, 50.17; H, 6.13; N, 10.24%.

4.2.1.2. Bis-amide ester 6. 2,6-Bis[(1′-(*S*)-carbomethoxy-2′-(*R*)-hydroxy)propyl carbamoyl]pyridine **5** (4.85 g, 12.2 mmol) and imidazole (4.16 g, 85.4 mmol) were placed in a 300 mL, round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet tube. The flask was degassed with vacuum pump, and flushed with nitrogen gas. The flask was charged with 100 mL of dichloromethane and stirred at rt for 5 min. Then *tert*-butyldimethylsilylchloride (4.60 g, 30.5 mmol) was added in one portion. After the reaction mixture was stirred at rt for 3.5 h, the solution was evaporated under reduce pressure. Purification by silica gel chromatography (AcOEt/*n*-Hex = 1:2) gave 7.50 g (12.0 mmol, yield 97.5%) of bis-amide ester **6** as a colorless oil. IR (NaCl); 3418, 2929, 2856, 1746, 1682, 1568, 1519, 1471, 1445, 1377, 1361, 1321, 1257, 1210, 1173, 1093 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.06 (s, 6H), 0.08 (s, 6H), 0.91 (s, 18H), 1.25 (d, J = 6.3 Hz, 6H), 3.76 (s, 6H), 4.51 (ddq, J = 6.3, 6.3, 3.0 Hz, 2H), 4.83 (dd, J = 9.1, 3.0 Hz, 2H), 8.04 (t, J = 8.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.36 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75.0 MHz, $CDCl_3$); δ −5.0, −4.4, 18.0, 20.6, 52.4, 58.5, 69.1, 125.7, 138.9, 149.0, 164.1, 170.5. Anal. calcd for $C_{29}H_{51}N_3O_8Si_2$: C, 55.65; H, 8.21; N, 6.71. Found: C, 55.53; H, 8.23; N, 6.57.

4.2.1.3. Bis-amide alcohol 7. Lithium borohydride (0.61 g, 25.6 mmol) was placed in a 200 mL, three necked round bottomed flask equipped with a magnetic stirring bar, nitrogen inlet tube and 100 mL dropwise funnel. The flask was degassed with vacuum pump, and flushed with nitrogen gas. The flask was charged with 40 mL of dry tetrahydrofuran and cooled to 0°C. 8.00 g (12.8 mmol) of bis-amide ester **6** in tetrahydrofuran (35 mL) was added dropwise over 20 min. After the reaction mixture was stirred at 0°C–rt for 6 h, 3 mL of water was added the reaction mixture and extracted with dichloromethane (100 mL×3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated by rotary evaporator. The crude was purified by column chromatography (AcOEt/*n*-Hex = 2:1) to yield 5.45 g (9.56 mmol, yield 74.8%) of bis-amide alcohol **7** as a colorless oil. IR (NaCl); 3408, 3055, 2929, 2844, 2857, 2360, 1667, 1593, 1570, 1524, 1471, 1444, 1376, 1361, 1258, 1216, 1171, 1098, 1005 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.05 (s, 6H), 0.08 (s, 6H), 0.94 (s, 18H), 1.22 (d, J = 6.2 Hz, 6H), 3.16 (brs, 2H), 5.83 (dd, J = 4.9, 4.6 Hz, 4H), 4.02 (ddt, J = 8.6, 4.6, 2.2 Hz, 2H), 4.29 (dq, J = 6.2, 2.2 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H), 8.03 (t, J = 7.9 Hz, 1H), 8.35 (d, J = 7.9 Hz, 2H). ^{13}C NMR (75.0 MHz, $CDCl_3$); δ −4.8, −4.3, 18.0, 20.8, 57.4, 63.2, 67.9, 125.5, 139.1, 149.0, 164.5.

4.2.1.4. Pybox-*he* 2a. Bis-amide alcohol **7** (2.00 g, 3.50 mmol), imidazol (1.67 g, 24.5 mmol) and triphenyl phosphine (2.01 g, 7.7 mmol) were placed in a 50 mL, round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet tube. The flask was degassed with vacuum pump, and flushed with nitrogen gas. The flask was charged with 15 mL of dry dichloromethane and stirred at rt for 5 min. And then 4 mL of carbontetrachloride was added at one portion. After the reaction mixture was stirred at rt for 4.5 h, the solvent was removed under reduce pressure. Then the residue was washed with *n*-hexane (10 mL×3) and the solution was concentrated and to yield 0.83 g (1.55 mmol, yield 44.3%) of **8** as a pale yellow oil which was used in a next step without further purification.

Compound **8** (0.80 g, 1.50 mmol) was placed in a 100 mL, round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet tube. The flask was degassed with vacuum pump, and flushed with nitrogen gas. The flask was charged with 18 mL of tetrahydrofuran and stirred at rt for 5 min. Then 4.2 mL (4.2 mmol) of tetrabutylammoniumfluoride (DCM, THF solution) was added slowly. After the mixture was stirred at rt for 3 h, the solvent was removed on rotary evaporator. Purification by silica gel chromatography (AcOEt/MeOH = 20:1). And then obtained solid was washed small amount of water and to yield 0.46 g (1.50 mmol, yield 100%) of pybox-*he* **2a** as a white solid. Mp 94–95°C. IR (NaCl); 3390, 2926, 1661, 1575, 1532, 1456, 1532, 1319, 1247, 1174, 1145, 1104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 1.30 (d, J = 6.4 Hz, 6H), 2.70 (brs, 2H), 3.77 (dq, J = 6.4, 3.5 Hz, 2H), 4.29 (ddd, J = 13.7, 12.2, 3.5 Hz, 4H), 4.59 (dd, J = 13.7, 12.2 Hz, 2H), 7.91 (t, J = 7.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 2H). ^{13}C NMR (75.0 MHz, $CDCl_3$); δ 19.5, 70.1, 70.4, 73.2, 126.1, 137.7, 146.5, 163.6. Anal. calcd for $C_{15}H_{19}N_3O_4$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.48; H, 6.48; N, 13.00%.

4.2.2. Synthesis of pybox-hydroxy benzyl

4.2.2.1. Bis-amide alcohol 10. Triethylamine (4.5 mL, 35.1 mmol) was added dropwise to a solution of 2,6-pyridinedicarboxylic acid (1.63 g, 8.00 mmol) in dichloromethane (20 mL) at 0°C. The mixture was then added to suspension of amino ester (4.34 g, 16.0 mmol) in dichloromethane (50 mL) at 0°C and stirred for 3 h. After warming to room temperature the reaction medium was concentrated. Purification of the residue by silica gel chromatography (AcOEt/*n*-Hex = 3:1) gave the bis-amide alcohol (4.19 g, 6.2 mmol, yield 77.8%) as a white solid. Mp 109–111°C. IR; 3358, 3064, 2926, 2854, 1705, 1669, 1532, 1449, 1271, 1113, 1075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 9.00 (d, J = 9.5 Hz, 2H), 8.02 (d, J = 7.7 Hz, 2H), 7.87–7.38 (m, 20H), 7.26 (d, J = 7.7 Hz, 1H), 6.76 (d, J = 10.1 Hz, 2H), 4.80 (ddddd, J = 12.1, 10.1, 6.8, 3.5, 2.6 Hz, 2H), 3.94 (dd, J = 12.1, 2.6 Hz, 2H), 3.65 (dd, J = 12.1, 3.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 168.0, 163.80, 147.66, 138.86, 136.47, 133.35, 129.41, 129.03, 128.86, 128.37, 127.79, 124.34, 75.78, 62.35, 57.01. Anal. calcd for $C_{39}H_{35}N_3O_8$: C, 69.53; H, 5.24; N, 6.24. Found: C, 69.36; H, 5.46; N, 6.21%.

4.2.2.2. Bis-amide chloride 11. To a suspension of **10** (4.19 g, 6.22 mmol) in benzene (30 mL) was added thionylchloride (5 mL, 66.7 mmol). The resulting mixture was kept at reflux for 3 h. The solvent and excess of thionylchloride were removed under reduced pressure. The residue was washed with dichloromethane (20 mL×3) and concentrated. Purification of the residue by silica gel chromatography (AcOEt/*n*-Hex = 2:1) gave **11** (3.50 g, 5.1 mmol, yield 76.0%) as a white solid. Mp 88–90°C. IR; 3361, 1683, 1522, 1448, 1268, 1110, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 8.81 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 7.9 Hz, 2H), 8.08 (dd, J = 8.2, 1.1 Hz, 4H), 7.91 (t, J = 7.9 Hz, 1H), 7.61–7.33 (m, 16H), 6.43 (d, J = 9.0 Hz, 2H), 4.97 (dddd, J = 11.7, 9.0, 4.8, 3.8 Hz, 2H), 3.88 (dd, J = 11.7, 3.8 Hz, 2H), 3.47 (dd, J = 11.7, 4.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 159.61, 156.88, 141.07, 131.90, 129.15, 126.34, 122.85, 122.52, 122.22, 122.00, 121.44, 118.00, 69.68, 68.85, 48.51, 37.36. Anal. calcd for $C_{39}H_{33}Cl_2N_3O_6$: C, 65.92; H, 4.68; N, 6.00. Found: C, 66.12; H, 4.81; N, 5.91%.

4.2.2.3. Pybox 12. Sodium hydride (0.29 g, 12.8 mmol) was added to a solution of dichlorodiamide (3.50 g, 5.1 mmol) in tetrahydrofuran (40 mL) at 0°C and stirred at 0°C–rt for 5 h. The solvent was removed and purification by silica gel chromatography (AcOEt/*n*-Hex = 2:1) gave pybox **12** (2.64 g, 4.15 mmol, yield 81.4%) as a white solid. Mp 220–222°C IR;1724, 1647, 1582, 1452, 1279, 1127 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 8.26 (d, J = 7.9 Hz, 2H), 8.08 (dd, J = 7.1, 1.3 Hz, 4H), 7.88 (t, J = 7.9 Hz, 1H), 7.56–7.25 (m, 16H), 6.14 (d, J = 6.2 Hz, 2H), 4.97 (ddd, J = 10.1, 8.1, 6.2 Hz, 2H), 4.50 (dd, J = 10.1, 9.0 Hz, 2H), 4.36 (dd, J = 9.0, 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 166.86, 164.13, 148.34, 139.13, 136.41, 133.58, 130.10, 129.78, 129.46, 129.24, 128.68, 127.67, 125.25, 76.92, 76.11, 55.75, 44.61. Anal. calcd for $C_{39}H_{31}N_3O_6$: C, 73.46; H, 4.90; N, 6.59. Found: C, 73.55; H, 4.94; N, 6.63%.

4.2.2.4. Pybox-*hbn* 2b. To 10% NaOH (20 mL) was added **12** (2.64 g, 4.15 mmol) in methanol/tetrahydrofuran (15 mL/1 mL) in one portion. After stirring 20 min at rt, the solvent was evaporated under reduced pressure. Purification of the residue by silica gel chromatography (AcOEt only) gave pybox-*hbn* (**2b**) (1.78 g, 4.14 mmol, yield 99.8%) as a white solid. Mp 85–87°C. IR; 3336, 1732, 1650, 1580, 1246, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 8.28 (d, J = 7.9 Hz, 2H), 7.93 (t, J = 7.9 Hz, 4H), 7.44–7.26 (m, 10H), 4.66–4.57 (m, 4H), 4.36 (dd, J = 9.5, 8.6 Hz, 2H), 4.22 (dd, J = 8.6, 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.99, 146.74, 139.83, 137.81, 129.00, 128.78, 127.32, 126.61, 77.85, 73.73, 70.40. Anal. calcd for $C_{25}H_{23}N_3O_4 \cdot 0.67H_2O$: C, 73.46; H, 4.90; N, 6.59. Found: C, 73.55; H, 4.94; N, 6.63%.

4.3. Synthesis of Ru(pybox-*he*)(ethylene) 13

A solution of pybox-*he* **2a** (90mg, 29.5mmol) and $[RuCl_2(p\text{-cymene})]_2$ (90.3 mg, 14.8 mmol) in dichloromethane (2 mL) was stirred at room temperature under ethylene atmosphere (1 atm) for 24 h. After solvent was removed under reduced pressure, purification of the residue by silica gel chromatography at 0°C with acetone gave **13** (138.3 mg, 26.6 mmol, yield 90%) as dark red solid. Mp 103–105°C. IR; 3388, 2972, 1699, 1569, 1492, 1402, 1251, 1209, 1104, 1001 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 8.00 (s, 3H), 5.70–5.10 (m, 2H), 4.92 (dd, J = 9.2, 2.4 Hz, 2H), 4.89 (dd, J = 9.2, 3.3 Hz, 2H), 4.24 (ddd, J = 8.4, 3.3, 2.4 Hz, 2H), 3.88 (dq, J = 6.4, 2.4 Hz, 2H), 3.60–3.57 (m, 2H), 1.23 (d, J = 6.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 166.02, 146.60, 134.25, 124.28, 76.51, 75.33, 70.80, 69.16, 18.95. Anal. calcd for $C_{15}H_{26}Cl_2N_3O_4Ru$: C, 40.40; H, 4.59; N, 8.31. Found: C, 40.29; H, 4.69; N, 8.24%.

4.4. Synthesis of 14

A solution of **12** (100 mg, 15.7 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (49.1 mg, 7.85 mmol) in dichloromethane (2 mL) was stirred at rt under an ethylene atmosphere (1 atm) for 24 h. After solvent was removed under reduced pressure, purification of the residue by silica gel chromatography at 0°C with acetone gave ethylene complex **14** (122.8 mg, 14.4 mmol, yield 92.0%) as dark red solid. Mp 210–212°C. IR; 3060, 2358, 1724, 1585, 1492, 1450, 1401, 1313, 1068, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 8.20–8.18 (m, 4H), 7.79 (t, $J=8.43$ Hz, 1H), 7.68–7.21 (m, 18H), 6.58 (d, $J=2.0$ Hz, 2H), 5.95–5.92 (m, 2H), 5.20 (dd, $J=9.2$, 9.0 Hz, 2H), 5.04 (ddd, $J=9.1$, 9.0, 2.0 Hz, 2H), 4.87 (t, $J=8.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 166.77, 164.20, 134.21, 133.78, 133.46, 130.10. Anal. calcd for $C_{42}H_{38}Cl_2N_3O_6Ru$: C, 69.53; H, 5.24; N, 6.24. Found: C, 69.36; H, 5.46; N, 6.21%.

4.5. Catalytic asymmetric cyclopropanation of styrene in biphasic media[7b]

Entry 6 in Table 1: To a solution of pybox-*hm* **1a** and $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.05 mmol) in toluene (0.5 mL) were stirred at rt under a nitrogen atmosphere. After 30 min stirring water (0.5 mL) and styrene (0.57 mL, 5.00 mmol) were added to the mixture and stirring at rt for 30 min. To the mixture was added a solution of L-menthyldiazoacetate (224.3 mg, 1.00 mmol) in toluene (1.5 mL) through a microsyringe pump over 4 h at 40°C. After the mixture had been stirred for an additional 17 h, the organic layer was extracted with diethylether (5 mL×4), dried over Na_2SO_4. Purification by silica gel chromatography (AcOEt/*n*-Hex = 1:20) gave a oily mixture **17t** and **17c** (234.3 mg, 0.78 mmol, yield 57.0%, *trans*/*cis* ratio 97:3, *trans* 94% ee, *cis* 76% ee).

Entry 20 in Table 1: Pybox-*he* **2a** (42.7 mg, 0.14 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 0.05 mmol) in toluene (1 mL) were stirred at rt under a nitrogen atmosphere. After 30 min stirring isopropanol (1 mL) and styrene (1.14 mL, 10.0 mmol) were added to the mixture and stirred at rt for 30 min. To the mixture was added a solution of L-menthyldiazoacetate (448.6 mg, 1.00 mmol) in toluene (3 mL) through a microsyringe pump over 8 h at 40°C. After the mixture had been stirred for an additional 17 h, the organic layer was extracted with diethylether (5 mL×4), dried over Na_2SO_4. Purification by silica gel chromatography (AcOEt/*n*-Hex = 1:20) gave a oily mixture **17t** and **17c** (466.0 mg, 1.55 mmol, yield 78.0%, *trans*/*cis* ratio 94:6, *trans* 91% ee, *cis* 78% ee).

Entry 21 in Table 1: Ru(pybox-*he*)(ethylene) (25.2 mg, 0.05 mmol) in toluene (0.5 mL) was stirred at rt under a nitrogen atmosphere. After 30 min stirring isopropanol (0.5 mL) and styrene (0.57 mL, 5.00 mmol) were added to the mixture and stirred at rt for 30 min. To the mixture was added a solution of L-menthyldiazoacetate (224.3 mg, 1.00 mmol) in toluene (1.5 mL) through a micro syringe pump over 4 h at 30°C. After the mixture had been stirred for an additional 17 h, the organic layer was extracted with diethylether (5 mL×4), dried over sodium carbonate. Purification by silica gel chromatography (AcOEt/*n*-Hex = 1:20) gave a oily mixture L-menthyl-2-phenyl cyclopropane carboxylic acid (195.3 mg, 0.65 mmol, Yield 65.0%, *trans*/*cis* ratio 97:3, *trans* 91% ee, *cis* 71% ee).

Entry 6 in Table 3: To a solution of Ru(pybox-*he*)(ethylene) (7.8 mg, 0.015 mmol, 5 mol%) in toluene (1 mL)/H_2O (1 mL) was added dropwise a solution of *trans*-cinnamyl diazoacetate (60.7 mg, 0.3 mmol) in toluene (1.5 mL) at 40°C for 6 h under an argon atmosphere. After adding diazoacetate, stirred for 1 h. The reaction mixture was concentrated and purified by silica gel chromatography (AcOEt/*n*-Hex = 1:5) gave **27** (26.1 mg, 0.21 mmol, yield 70%, 52% ee) as a white solid. The enantiomeric purity was measured by GLC (SPERCO, 30 m).

4.5.1. 2-Phenyl-cyclopropanecarboxylic acid *d*-menthyl ester(*trans*) 17. All of the reaction procedure in Table 2 was same as entry 6 in Table 1. 96% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column temperature 200°C, injector and detector temperature 230°C, detection FID, $tR = 25.8$ (*cis*), 26.0 (*cis*), 29.4 (*trans*, major), 31.7 (*trans*, minor) min. $[\alpha]_D = +227.0$ (*c* 1.00, CH_2Cl_2, 23.9°C). White solid (mp = 61.5–62.5°C). IR (neat): 3031, 2953, 2868, 1721, 1604, 1497, 1457, 1404, 1330, 1266, 1183, 1082, 1032, 982, 937, 847, 755, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.77 (d, $J=6.9$, 3H), 0.80–1.14 (m, 9H), 1.28 (ddd, $J=8.4$, 6.4, 4.5, 1H), 1.33–1.54 (m, 2H), 1.58 (ddd, $J=9.1$, 5.2, 4.5, 1H), 1.64–1.73 (m, 2H), 1.83–1.93 (m, 2H), 1.98–2.05 (m, 1H), 2.52 (ddd, $J=9.1$, 6.4, 4.2, 1H), 4.72 (ddd, $J=10.8$, 10.8, 4.4, 1H), 7.10 (d, $J=7.14$, 2H), 7.20 (t, $J=7.42$, 1H), 7.29 (dd, $J=7.42$, 7.14, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.4, 17.1, 20.9, 22.1, 23.5, 24.4, 26.0, 26.3, 31.5, 34.3, 41.1, 47.2, 74.5, 126.3, 126.5, 128.5, 140.4, 173.0.

4.5.2. 2-*p*-Tolyl-cyclopropanecarboxylic acid *d*-menthyl ester(*trans*) 18. 96% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column temperature 200°C, injector and detector temperature 230°C, detection FID, $tR = 31.2$ (*cis*), 31.9 (*cis*), 40.7 (*trans*, major), 43.9 (*trans*, minor) min. $[\alpha]_D = +221.9$ (*c* 1.00, CH_2Cl_2, 24.3°C). White solid (mp = 53.5–54.5°C). IR (neat): 2952, 2866, 1721, 1516, 1454, 1398, 1329, 1266, 1181, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.75–1.13 (m, 12H), 1.25 (ddd, $J=8.4$, 6.2, 4.4, 1H), 1.33–1.58 (m, 3H), 1.63–1.73 (m, 2H), 1.82–1.93 (m, 2H), 1.98–2.05 (m, 1H), 2.32 (s, 3H), 2.48 (ddd, $J=9.3$, 6.2, 4.0, 1H), 4.71 (ddd, $J=10.9$, 10.9, 4.5, 1H), 7.00 (d, $J=8.0$, 2H), 7.10 (d, $J=8.0$, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.4, 17.0, 20.9, 21.1, 22.1, 23.5, 24.3, 25.7, 26.3, 31.5, 34.4, 41.1, 47.2, 74.4, 126.2, 129.2, 136.1, 137.3, 173.1. Anal. calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.23; H, 9.57%.

4.5.3. 2-(4-Methoxyphenyl)-cyclopropanecarboxylic acid *d*-menthylester ester(*trans*) 19. 93% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column

temperature 220°C, injector and detector temperature 250°C, detection FID, tR = 34.8 (*cis*), 35.5 (*cis*), 46.6 (*trans*, major), 49.9 (*trans*, minor) min. $[\alpha]_D$ = +236.2 (*c* 1.00, CH_2Cl_2, 24.2°C). Colorless oil. IR (neat): 2951, 2868, 1719, 1612, 1515, 1454, 1399, 1252, 1182, 1103, 1036, 981, 939, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.76–1.13 (m, 12H), 1.22 (ddd, J = 8.5, 6.5, 4.5, 1H), 1.33–1.56 (m, 3H), 1.63–1.72 (m, 2H), 1.78–1.93 (m, 2H), 1.97–2.04 (m, 1H), 2.48 (ddd, J = 9.2, 6.5, 4.1, 1H), 3.79 (s, 3H), 4.71 (td, J = 10.8, 10.8, 4.4, 1H), 6.83 (d, J = 8.8, 2H), 7.03 (d, J = 8.8, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.5, 16.8, 20.9, 22.1, 23.6, 24.1, 25.4, 26.3, 31.5, 34.4, 41.1, 47.2, 55.4, 74.4, 114.0, 127.5, 132.3, 158.4, 173.1. Anal. calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.44; H, 8.99%.

4.5.4. 2-(4-Chlorophenyl)-cyclopropanecarboxylic acid *d*-menthylester ester(*trans*) 20. 93% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column temperature 200°C, injector and detector temperature 230°C, detection FID, tR = 55.9 (*cis*), 56.7 (*cis*), 72.1 (*trans*, major), 78.1 (*trans*, minor) min. $[\alpha]_D$ = +211.6 (*c* 1.00, CH_2Cl_2, 24.6°C). White solid (mp = 97.0–98.0°C). IR (KBr): 2952, 2868, 1716, 1491, 1453, 1405, 1326, 1192, 1094, 1039, 1004, 983, 937, 817, 740 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.75–1.13 (m, 12H), 1.24 (ddd, J = 8.4, 6.4, 4.5, 1H), 1.33–1.54 (m, 2H), 1.58 (ddd, J = 9.1, 5.3, 4.5, 1H), 1.64–1.73 (m, 2H), 1.82–1.92 (m, 2H), 1.97–2.04 (m, 1H), 2.48 (ddd, J = 9.1, 6.4, 4.2, 1H), 4.71 (ddd, J = 10.8, 10.8, 4.4, 1H), 7.02 (d, J = 8.2, 2H), 7.25 (d, J = 8.2, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.5, 17.0, 20.9, 22.1, 23.6, 24.5, 25.3, 26.4, 31.5, 34.3, 41.1, 47.2, 74.7, 127.7, 128.7, 132.2, 138.9, 172.7. Anal. calcd for $C_{20}H_{27}ClO_2$: C, 71.73; H, 8.13. Found: C, 71.55; H, 8.05%.

4.5.5. 2-(2-Chlorophenyl)-cyclopropanecarboxylic acid *d*-menthylesterester 21. 93% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column temperature 200°C, injector and detector temperature 230°C, detection FID, tR = 46.9 (*cis*), 49.3 (*cis*), 65.9 (*trans*, major), 67.7 (*trans*, minor) min. $[\alpha]_D$ = +126.0 (*c* 1.00, CH_2Cl_2, 24.4°C). Colorless oil. IR (neat): 3065, 2952, 2867, 1721, 1446, 1400, 1326, 1268, 1183, 1091, 1046, 984, 944, 849, 753, 680 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.77–1.14 (m, 12H), 1.32–1.76 (m, 7H), 1.93–2.06 (m, 2H), 2.71 (ddd, J = 8.9, 6.8, 4.3, 1H), 4.71 (ddd, J = 10.8, 10.8, 4.4, 1H), 7.02–7.07 (m, 1H), 7.14–7.22 (m, 2H), 7.34–7.40 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.8, 16.4, 20.9, 22.1, 23.3, 23.4, 24.6, 26.2, 31.5, 34.4, 41.1, 47.3, 74.6, 126.8, 127.5, 128.0, 129.4, 136.0, 137.6, 173.0. Anal. calcd for $C_{20}H_{27}ClO_2$: C, 71.73; H, 8.13. Found: C, 71.77; H, 8.07%.

4.5.6. 2-Butoxy-cyclopropanecarboxylic acid *d*-menthylester ester(*trans*) 22. 95% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column temperature 145°C, injector and detector temperature 175°C, detection FID, tR = 44.7 (*trans*, major), 46.4 (*trans*, minor), 65.8 (*cis*), 67.9 (*cis*) min. $[\alpha]_D$ = +85.3 (*c* 1.00, CH_2Cl_2, 21.3°C). Colorless oil. IR (neat): 2952, 2870, 1721, 1451, 1379, 1323, 1258, 1220, 1171, 1100, 1035, 947, 870 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.76 (d, J = 6.9, 3H), 0.80–1.12 (m, 12H), 1.17–1.30 (m, 2H), 1.31–1.59 (m, 6H), 1.62–1.75 (m, 3H), 1.82–1.99 (m, 2H), 3.49–3.54 (m, 2H), 3.56 (ddd, J = 6.6, 4.5, 2.1, 1H), 4.66 (ddd, J = 10.8, 10.8, 4.4, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 15.5, 16.6, 19.3, 20.8, 21.5, 22.1, 23.7, 26.6, 31.46, 31.48, 34.3, 41.1, 47.2, 60.7, 71.1, 74.3, 172.3. Anal. calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.92; H, 10.69%.

4.5.7. 2-Isobutoxy-cyclopropanecarboxylic acid *d*-menthylester ester(*trans*) 23. 94% ee determined by GLC (GL Sciences TC-WAX (30 M×0.25 mm): column temperature 145°C, injector and detector temperature 175°C, detection FID, tR = 31.5 (*trans*, major), 33.0 (*trans*, minor), 48.8 (*cis*), 49.8 (*cis*) min. $[\alpha]_D$ = +81.6 (*c* 1.00, CH_2Cl_2, 22.0°C). Colorless oil. IR (neat): 2954, 2871, 1721, 1451, 1380, 1324, 1259, 1219, 1171, 1098, 1049, 964, 870 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.78 (d, J = 6.9, 3H), 0.83–1.12 (m, 15H), 1.18–1.28 (m, 2H), 1.33–1.54 (m, 2H), 1.63–1.75 (m, 3H), 1.78–2.00 (m, 3H), 3.26 (dd, J = 9.3, 6.7, 1H), 3.30 (dd, J = 9.3, 6.7, 1H) or 3.26 (dd, J = 11.7, 6.7, 1H), 3.30 (dd, J = 11.7, 6.7, 1H), 3.56 (ddd, J = 4.3, 4.3, 2.1, 1H), 4.66 (ddd, J = 10.8, 10.8, 4.4, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.6, 16.6, 19.3, 19.4, 20.8, 21.6, 22.1, 23.7, 26.6, 28.2, 31.5, 34.4, 41.1, 47.2, 60.9, 74.3, 78.2, 172.3. Anal. calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.95; H, 10.80%.

4.5.8. *t*-Butoxy-cyclopropanecarboxylic acid *d*-menthylester ester(*trans*) 24. 91% ee determined by GLC (Chiraldex B-DA (30 M×0.25 mm): column temperature 170°C, injector and detector temperature 200°C, detection FID, tR = 20.3 (*trans*, minor), 23.2 (*trans*, major) min. $[\alpha]_D$ = +84.5 (*c* 1.00, CH_2Cl_2, 23.0°C). Colorless oil. IR (neat): 2958, 2870, 1718, 1448, 1390, 1327, 1259, 1156, 1098, 1035, 951, 919, 856 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.75 (d, J = 7.2, 3H), 0.78–1.06 (m, 9H), 1.13 (ddd, J = 9.4, 5.4, 4.5, 1H), 1.21–1.27 (m, 10H), 1.32–1.54 (m, 2H), 1.63–1.71 (m, 3H), 1.85–2.00 (m, 2H), 3.52 (ddd, J = 7.0, 4.5, 2.3, 1H), 4.66 (ddd, J = 10.9, 10.9, 4.3, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 16.2, 20.9, 22.1, 23.0, 23.3, 26.2, 28.0, 31.5, 34.3, 41.1, 47.1, 54.6, 74.3, 75.7, 172.5. Anal. calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.13; H, 10.68%.

4.5.9. *t*-Butoxy-cyclopropanecarboxylic acid *d*-menthylester ester 24-*cis*. 81% ee determined by GLC (Chiraldex B-DA (30 M×0.25 mm): column temperature 170°C, injector and detector temperature 200°C, detection FID, tR = 26.4 (*cis*, minor), 28.3 (*cis*, major) min. $[\alpha]_D$ = +87.0 (*c* 1.00, CH_2Cl_2, 24.5°C). White solid (mp = 65.0–66.0°C). IR (neat): 2956, 2930, 2865, 1725, 1454, 1390, 1264, 1232, 1191, 1158, 1106, 981, 945, 826, 760 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.74 (d, J = 6.9, 3H), 0.78–1.11 (m, 10H), 1.23 (s, 3H), 1.30–1.53 (m, 3H), 1.59–1.70 (m, 3H), 1.92–2.10 (m, 2H), 3.54 (ddd, J = 6.9, 6.9, 4.9, 1H), 4.69 (ddd, J = 10.8, 10.8, 4.4, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.7, 16.2, 21.0, 21.6, 22.1, 23.3, 25.8, 27.9, 31.5, 34.4, 41.2, 47.1, 52.9, 74.3, 75.2, 170.2.

4.5.10. Intramolecular cyclopropanation of *trans*-cinnamyl diazoester[7b] (Table 3, entry 6). To a solution of Ru(pybox-*he*)(ethylene) complex (7.8 mg, 5 mol%) in toluene (1.0 mL)/H_2O (1.0 mL) was added dropwise to a solution of *trans*-cinnamyl daizoacetate (60.7 mg, 0.3 mmol) in toluene (1.5 mL) at 40°C for 6 h under an argon atmosphere. After addition of diazoacetate, the stirring was continued for another 1 h. The reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 5:1) to give bicyclo[3.1.0]hexane **27** (26.1 mg) in 70% yield as white solid. 52% ee determined by GLC (SPERCO β-DEX-225, 30 m×0.25 mm): column temperature 170°C, injector and detector temperature 200°C, detection FID, tR = 67.5 (*cis*, minor), 69.9 (*cis*, major) min.

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