Asymmetric cyclopropanation in protic media conducted by chiral bis(hydroxymethyl-dihydrooxazolyl)pyridine–ruthenium catalysts

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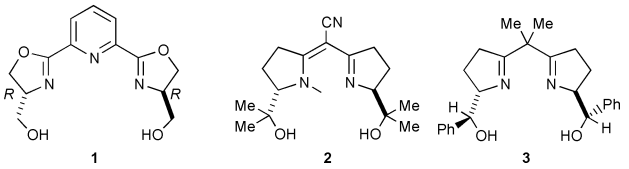
Received (in Liverpool, UK) 23rd October 2000, Accepted 20th November 2000
First published as an Advance Article on the web 14th December 2000

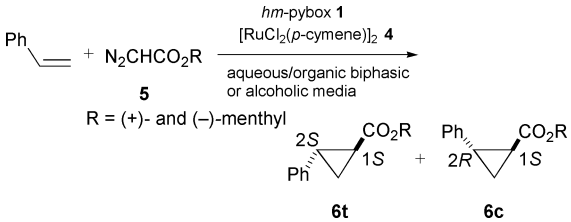
Cyclopropanation of styrene with diazoacetates, performed in aqueous/organic biphasic media or homogeneous alcoholic media in the combination of toluene by using chiral bis(hydroxymethyldihydrooxazolyl)pyridine–ruthenium catalyst, resulted in high enantiomeric excess up to 96–97% and *trans*:*cis* stereoselectivity to 97:3.

Enantioselective reactions of olefins and diazoacetates catalyzed by a variety of metal complexes to provide chiral cyclopropane materials have been well investigated.[1] We have reported ruthenium catalysts of chiral bis(dihydrooxazolyl)pyridine [pybox] for that purpose and their prominent feature of high *trans*-stereoselectivity with higher enantioselectivity.[2,3] Very recently, we reported a characteristic derivative of pybox, *hm*-pybox **1**, having two hydroxymethyl groups as the symmetric chiral stems of the oxazoline rings.[4] We observed that *hm*-pybox exhibits high solubility in water. One of the recent 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 bis(hydroxymethyldihydrooxazolyl)pyridine–ruthenium catalyst. In addition, however, we demonstrated the tolerance of the catalysis to protic media, such as alcoholic mixtures.

We surveyed previous research related to the catalytic cyclopropanation of olefins and diazoacetates but we could find no systems effective *in aqueous media or protic solvents.*[4] 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 **2**[6] or **3**[7]. It had also very recently been reported that although a small amount of water in the reaction solvent diminishes enatioselectivity of cyclopropanation with rhodium catalyst, the unfavorable effect of water was reduced by addition of an appropriate phosphite ligand.[8] Accordingly, we were intrigued to examine the catalysis with *hm*-pybox **1** and $[RuCl_2(p\text{-cymene})]_2$ **4**.



First, we tried an aqueous media for the cyclopropanation of styrene and (+)-menthyl diazoacetate **5a** with *hm*-pybox in the presence of co-solvent THF or toluene (Scheme 1). (+)-Menthyl ester was chosen on the basis of better matching to the (*R*,*R*)-absolute configuration of pybox, which ought to give higher enantioselectivity according to our previous work.[2b] The use of a single organic solvent resulted in lower yields and lower enantioselectivities (run 1 and 2 in Table 1). Surprisingly, addition of water to both media in runs 1 and 2 dramatically improved the enantioselectivities and slightly the yields (runs 4 and 5). This phenomenon can be simply accounted for by the increase of the solubility of the active catalyst Ru(*hm*-pybox)Cl_2(vacant or solvent) derived from *hm*-pybox **1** and pre-catalyst $[RuCl_2(p\text{-cymene})]_2$ **4**. 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. Into the two-phase system of water and organic solvent (initial ratio = 1:2), a solution of the diazoacetate **5** was slowly added under vigorous stirring to give the desired cyclopropanes **6** in moderate yields with higher enantioselectivity (88% for **6t**, runs 3 and 4). The



Scheme 1

Table 1 Asymmetric cyclopropanation of styrene and (+)-menthyl diazoacetate **5a** with chiral *hm*-pybox **1** and $[RuCl_2(p\text{-cymene})]_2$[a]

Run	Initial solvent (ml)	Solvent of **5a** (ml)	**6t** + **6c**[b] Yield %	Ratio	%Ee[c] **6t**	**6c**
1	THF (3)	THF (3)	39	83:17	8	30
2	Toluene (3)	Toluene (3)	38	89:11	8	28
3	THF (2) + H_2O (1)	THF (3)	46	95:5	78	45
4	Toluene (2) + H_2O (1)	Toluene (3)	56	96:4	88	51
5_{1st}[d]	Toluene (0.5) + H_2O (0.5)	Toluene (1.5)	57	97:3	94	76
5_{2nd}[e]		Toluene (1.5)	62	97:3	97	90

[a] Styrene (10 mmol), diazoacetate (2.0 mmol), pybox (0.14 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.05 mmol, 5 mol% of Ru), 40 °C. A solution of diazoacetate in 3.0 ml of the same solvent was slowly added by syringe for 6 h to the mixture of styrene and the catalyst in the initial solvent. [b] Isolated yield, ratios by ^1H NMR. [c] %Ee determined by the reported method, see ref 2. Absolute configuration: **6t** for all runs, (1*S*,2*S*); **6c** for run 1 and 2, (1*R*,2*S*); **6c** for runs 3 and 4, (1*S*,2*R*). [d] Half scale for run 1: diazoacetate (1.0 mmol), styrene (5.0 mmol), catalyst 5 mol%, for 4 h. [e] After ether extraction of the reaction mixture of the first run, styrene (5.0 mmol) and toluene (1.5 ml) were added followed by slow addition of **5a** in toluene.

DOI: 10.1039/b008516m

Table 2 Asymmetric cyclopropanation of styrene and (+)-menthyl diazoacetate **5a** with chiral *hm*-pybox **1** and $[RuCl_2(p\text{-cymene})]_2$ in the presence of alcohols[a]

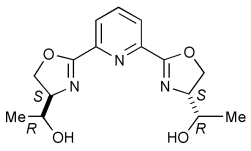
Run	Initial solvent (ml)	Solvent of **5a** (ml)	**6t** + **6c** Yield %	**6t** + **6c** Ratio	%Ee[b] **6t**	%Ee[b] **6c**
1	Toluene (1) + EtOH (1)	Toluene (3)	67	96:4	35	2
2	Toluene (1) + *t*-BuOH (1)	Toluene (3)	54	91:9	11	15
3	Toluene (1) + *i*-PrOH (1)	Toluene (3)	78	95:5	92	65
4[c]	Toluene (1) + *i*-PrOH (1)	Toluene (3)	52	97:3	96	88
5[d]	Toluene (1) + *i*-PrOH (1)	Toluene (3)	78	95:5	90	88
6	THF (1) + *i*-PrOH (1)	THF (3)	73	96:4	89	58
7	*i*-PrOH (2)	*i*-PrOH (3)	59	95:5	84	30

[a] The reaction scale and procedures were the same as those described in Table 1. [b] Absolute configuration: **6t** for all runs, (1*S*,2*S*); **6c** for run 2 and 6, (1*R*,2*S*); **6c** for runs 1,3,4,5 and 7, (1*S*,2*R*). [c] At 30 °C. The cyclopropanation did not proceed at 20 °C. [d] In place of (+)-menthyl diazoacetate, (−)-menthyl ester **5b** was used.

organic layer was extracted with degassed (or absolute) diethyl ether and concentrated to give the products. 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 (run 5). We are now further investigating the optimization and multi-time reuse of the catalyst.

In this aqueous system, addition of phase-transfer reagents such as $(n\text{-Bu}_4N)(HSO_4)$ (10 mol% of **5a**) into the system of run 4 resulted in no improvement upon the reaction and the selectivities. 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 media, isopropyl alcohol resulted in the best enantioselectivities, up to 96% ee for *trans*-**6t** and 88% ee for *cis*-**6c** at 30 °C (Table 2, run 4). (−)-Menthyl diazoacetate **5b** showed a decrease of ee to 90% for *trans*-product (run 5), because of the unmatched steric pair toward *R*,*R*-absolute configuration of the ligand. Single use of isopropyl alcohol gave moderate ees (run 7). We have thus found that the choice of alcoholic solvents apparently influences the enantioselectivity. However, at present we cannot define the origin of the stereochemical outcomes for protic solvents.

We next intended stereochemical tuning of the hydroxymethyl group of **1** using *hydroxyethyl*-pybox **7** [*he*-pybox] synthesized from (−)-threonine (Scheme 2).† However, in aqueous biphasic media, toluene–H_2O, the enantioselectivities with ruthenium–**7** catalyst were not increased by using (−)-menthyl diazoacetate at 40 °C: 80% ee for *trans* and 50% ee for *cis*, in 96:4 *trans*:*cis* ratio (75% yield). In toluene–*i*-PrOH the enantioselectivities increased to 91% for *trans* and 78% ee for *cis*, in 94:6 *trans*:*cis* ratio (78% yield). In comparison, classic *ip*-pybox **8** with similar bulkiness to **7** was



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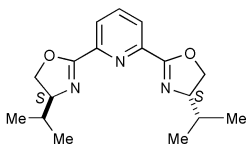

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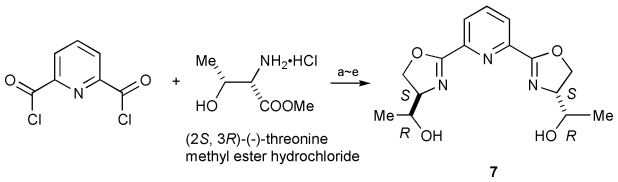
found in toluene–*i*-PrOH media to give 93% ee for *trans* and 90% ee for *cis*, in 97:3 *trans*:*cis* ratio (84% yield). *He*-pybox **7** thus proved to be inferior to *iso*-pybox **8**.

In conclusion, the hydroxymethyl derivative of pybox can provide excellent stereoselectivities for cyclopropanation of styrene, 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 favourable stereochemical environment around the active site for the cyclopropanation. Work is now under way to investgate the mechanism of reaction and on applications to other catalytic reactions performed in aqueous media.



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Scheme 2 *Reagents and conditions*: (a) Et_3N, $CHCl_3$, rt, 12 h, 92%. (b) TBDMSCl, imidazole, CH_2Cl_2, rt, 3.5 h, 98%. (c) $LiBH_4$, THF, 0 °C ~ rt, 6 h, 75%. (d) PPh_3, imidazole, CCl_4, CH_2Cl_2, rt, 4.5 h, 44%. (e) Bu_4NF (1.0 M in THF), rt, 3 h, 100%.

Footnotes and references

† Synthesis of *he*-pybox: the route is illustrated (Scheme 2) starting from (−)-threonine methyl ester·HCl and 2,6-pyridinecarboxylic acid chloride. **7**; white solid. mp 94–95 °C. δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.30 (d, *J* 6.4, 6 H), 2.70 (br d, 2 H), 3.77 (dq, 2 H), 4.29 (dt, 6 H), 4.59 (dd, 2 H), 7.91 (t, 1 H), 8.15 (d, 2 H). δ_C (75.5 MHz, $CDCl_3$, Me_4Si) 19.5, 70.1, 70.4, 73.2, 126.1, 137.7, 146.5, 163.6.

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