Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2931–2935

TETRAHEDRON: *ASYMMETRY*

Heterogeneous asymmetric Diels–Alder reactions using a copper–chiral bis(oxazoline) complex immobilized on mesoporous silica†

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Received 9 October 2001; accepted 14 November 2001

Abstract—A chiral bis(oxazoline)–copper complex was immobilized onto mesoporous silica and the resulting heterogeneous catalyst was employed in asymmetric Diels–Alder reactions. Reactions using the catalyst exhibited good enantioselectivity of 78% enantiomeric excess and *endo*/*exo*-selectivity (17:1) better than the corresponding homogeneous reaction. The catalyst could be easily recovered and reused several times without significant loss of the remarkable reactivity, diastereoselectivity and enantioselectivity. © 2002 Published by Elsevier Science Ltd.

The Diels–Alder (DA) reaction is one of the most efficient carbon–carbon bond forming reactions affording cycloadducts equipped with a double bond and two newly formed C–C single bonds. Control of the *endo*/*exo*-diastereoselectivity as well as the enantioselectivity in the Diels–Alder reaction has been the focus of intense investigation and recent years have witnessed rapid development in the asymmetric DA reaction.[1] Among many approaches for asymmetric DA reactions, methods utilizing chiral catalysts have received much attention, and a number of Lewis acidic metal complexes employing chiral ligands have been developed. Recently, Evans[2] and Ghosh[3] have reported cationic copper(II)–bis(oxazoline) complexes as highly selective chiral Lewis acids for efficient asymmetric Diels–Alder reactions. However, often relatively large amounts of the chiral catalysts have been employed due to poor turnover, leaving room for the development of new, more practical asymmetric DA methodologies.

Towards the continuous large-scale production of chiral compounds, heterogenization of homogeneous catalysts has been extensively pursued.[4] Many homogeneous asymmetric catalysts were immobilized onto supports including organic polymers[5] and inorganic supports such as silicas and zeolites.[6] Recently, various mesoporous silicas[7] with pore sizes ranging from 2 to 10 nm have been successfully applied as supports for various chiral catalytic systems.[8,9] Herein we report on the heterogeneous asymmetric DA reaction utilizing novel chiral bis(oxazoline) catalysts immobilized on MCF (meso cellular foam).[7]

The overall procedure for the synthesis and immobilization of the bis(oxazoline) ligand onto MCF is shown in Scheme 1. A mixture of diethyl malonimidate and (1*R*,2*S*)-1-amino-2-indanol in dichloroethane was stirred for 2 days.[11] The resulting bis(oxazoline) derivative **1** (indabox) was coupled with *p*-(bromomethyl)phenyl pivalate or benzyl bromide to produce **2a** or **2b**, respectively. The pivalate esters of **2a** were removed to provide **3** upon treatment with lithium aluminum hydride.[10] Mesoporous Silica (MCF), composed of uniformly sized spherical cells that are interconnected by uniform windows, was prepared by the reported method.[12] The silica material exhibited surface area of 970 m^2 g^{-1}, total pore volume of 1.09 cm^3 g^{-1}, cell diameter of 8.61 nm, and window diameter of 3.5 nm. A chloropropyl linker was then grafted onto the MCF by treating with $(CH_3CH_2O)_3Si–CH_2CH_2CH_2Cl$

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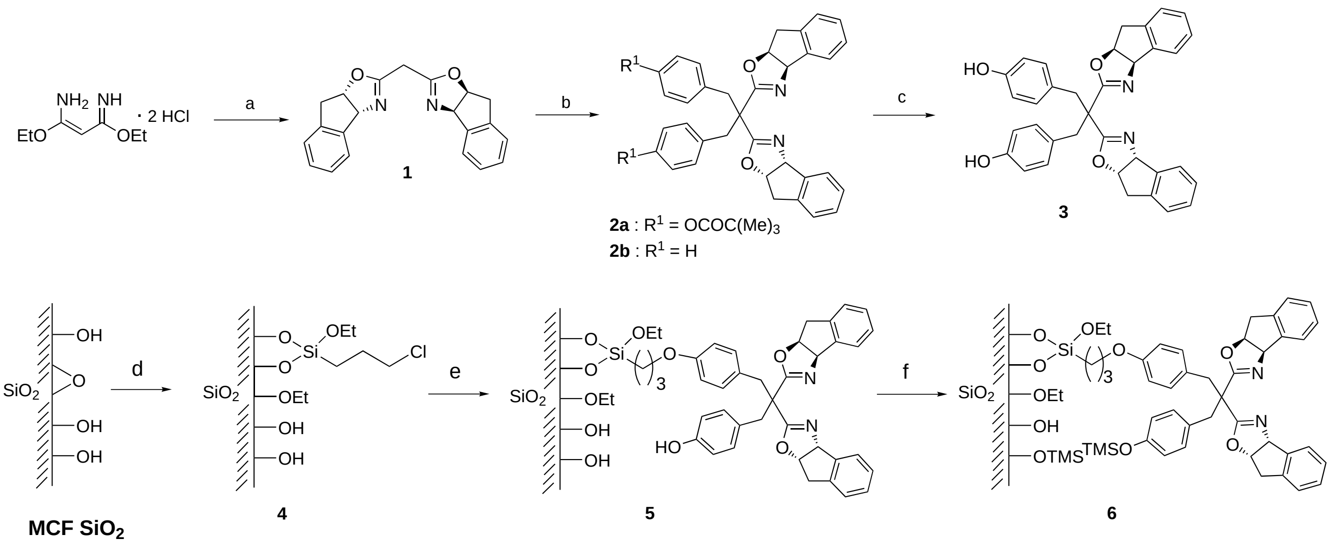
† Part of this manuscript was reported at the National Meeting of the 221st American Chemical Society, San Diego, USA, Org-602, April 4, 2001.

0957-4166/01/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0957-4166(01)00529-8

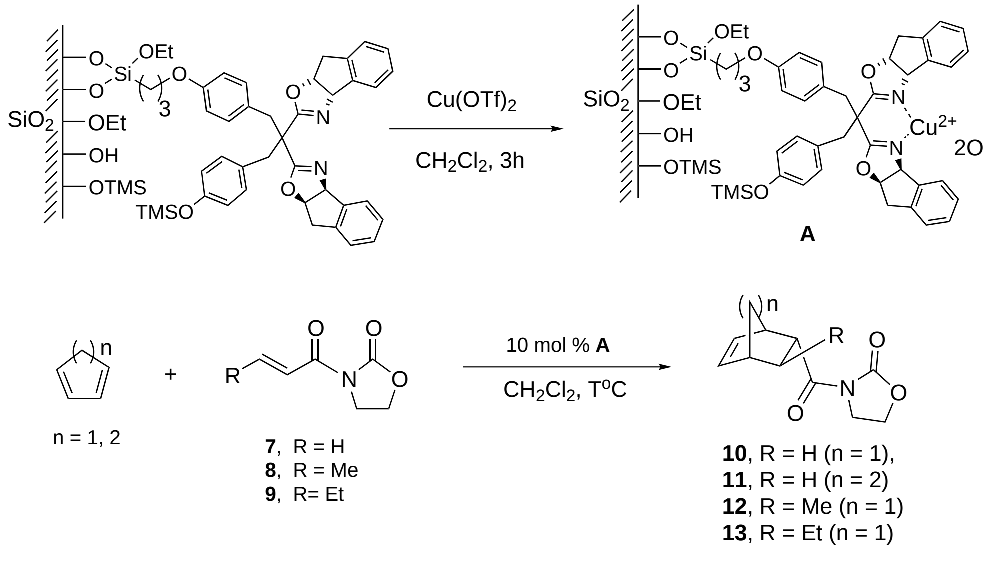


Scheme 1. Preparation of mesoporous-silica grafted catalysts **5** and **6**. *Reagents and conditions*: (a) (1*S*,2*R*)-1-amino-2-indanol, dichloroethane, 2 days, 70%; (b) *p*-(bromomethyl)phenyl pivalate or benzyl bromide, LiHMDS, THF, −78°C, 3 h, 77 and 82%, respectively; (c) $LiAlH_4$, THF, 6 h, quant.; (d) chloropropyltriethoxysilane, toluene, reflux, 12 h; (e) **3**, toluene, reflux, 12 h; (f) HMDS, reflux, 12 h.

in refluxing toluene. Reaction of **3** with chloropropyl-derivatized MCF **4** yielded the indabox-grafted silica **5**. In order to protect the remaining free SiOH groups on the walls of mesoporous silica, **5** was treated in refluxing hexamethyldisiloxane (HMDS) for 12 h and the resulting **6** was vacuum-dried (<0.01 torr) at 130°C for 12 h. The resulting bis(oxazoline)-ligand grafted, TMS-capped MCF **6** exhibited surface area of 542 m^2 g^{-1}, total pore volume of 0.65 cm^3 g^{-1}, cell diameter of 7.48 nm, and window diameter of 3.6 nm. The grafted amount of chiral ligand was 0.24–0.17 mmol g^{-1} of silica support.

The DA reactions were carried out using cyclopentadiene or cyclohexadiene as the diene and 3-(2-propenoyl)-2-oxazolidinone **7**, 3-(2(*E*)-butenoyl)-2-oxazolidinone **8**, or 3-((2*E*)-pentenoyl)-2-oxazolidinone **9** as the dienophile in CH_2Cl_2 for 24 h using 10 mol% of the silica-grafted chiral ligand, which was premixed for 3 h with varying amounts of $Cu(OTf)_2$ as shown in Scheme 2. The results are summarized in Tables 1 and 2.

First, a control reaction between cyclopentadiene and the acryloyl derivative **7** employing the parent homogeneous catalyst **2b** (11 mol%) and $Cu(OTf)_2$ (10 mol%) was carried out at −78°C to provide a 96% yield of a mixture of *endo*- and *exo*-adducts in a 9:1 ratio, with the *endo*-diastereomer having 88% e.e. by chiral HPLC analysis (entry 1). When the DA reaction of the same substrates employing heterogenized chiral ligand **6** (10



Scheme 2. Diels–Alder reaction catalyzed by silica-indabox **A**.

Table 1. Asymmetric Diels–Alder reaction between cyclopentadiene and **7** using 10 mol% of **6**

Entry	Amounts of $Cu(OTf)_2$ (mol%)	*T* (°C)	Yield (%)[e]	*endo*/*exo*[f]	*endo* (% e.e.)[f]
1[a]	10	−78	96	9:1	88
2[b]	6	0	99	10:1	15
3[b]	6	0	99	8:1	39
4[c]	10	0	99	9:1	11
5[b]	10	−50	99	9:1	50
6[b]	10	−70	97	12:1	65
7[b]	30	−70	97	11:1	65
8	–	−70	22	10:1	–
9	10	−78	**99**	**13:1**	**75**
10[d]	10	−78	**99**	**17:1**	**78**

[a] Reaction was carried out in solution phase.

[b] Washing conditions are detailed in the text.

[c] Washed with acetone twice.

[d] Reaction using catalyst **5**.

[e] Yield was determined through ^{1}H NMR (300 MHz) analysis based on remaining starting material. ^{1}H NMR yields were almost identical to the isolated yields.

[f] Enantio- and *endo*/*exo*-selectivities were determined through HPLC analysis using Chiralcel OD column (1 mL/min, 10% iPrOH in hexane) and ^{1}H NMR (300 MHz).

Table 2. Asymmetric Diels–Alder reaction between cyclopentadiene (cPt) or cyclohexadiene (cHx) and various dienephiles **7**–**9** at 0°C in the presence of 10 mol% **6** and 10 mol% $Cu(OTf)_2$

Entry	Diene	Dienophile	Yield (%)[d]	*endo*/*exo*[e]	*endo* (% e.e.)[e]
1[a]	cPt	**8**	95	3:1	85
2	cPt	**8**	99	4:1 (4:1)[f]	72 (72)[f]
3[a]	cPt	**9**	95	3:1	82
4	cPt	**9**	99	4:1 (4:1)[f]	65 (60)[f]
5[a,b]	cHx	**7**	95	>99:1	61
6[c]	cHx	**7**	53	>99:1	53

[a] Reactions carried out in solution phase.

[b] Reaction was run for 3 days.

[c] Reaction was run for 7 days.

[d] Yield was determined through ^{1}H NMR (300 MHz) analysis based on remaining starting material.

[e] HPLC Conditions for determination of isomeric ratios (**12**: Chiralcel OD-H column, 1 mL/min, 2% reagent ethanol in hexanes; **13**: 0.9% iPrOH in hexanes through Chiralcel AD column; **11**: after conversion to the corresponding iodolactone, temp. 160°C 1.5 mL/min through Cyclodex-β (J & W)).

[f] Numbers in parentheses are the results obtained from repetition experiments using the recycled chiral ligand.

mol%) and 6 mol% of $Cu(OTf)_2$ was carried out at 0°C, the cycloadducts were obtained in almost quantitative yield (99%) with *endo*-selectivity of 10/1, however the *endo*-isomer exhibited only 15% e.e. (entry 2). We reasoned that even with 0.6 equiv. of $Cu(OTf)_2$ to the chiral ligand, some uncomplexed copper reagent might still remain in the mixture, lowering the enantioselectivity of the reaction. In order to remove free copper species from the reaction mixture, the Cu-complexed silica was washed with CH_2Cl_2 before the reaction and a noticeable improvement in the enantioselectivity (39% e.e.) was observed under otherwise identical reaction conditions (entry 3). However, when the silica was washed with acetone instead of dichloromethane to ensure complete removal of free $Cu(OTf)_2$, the enantioselectivity of the reaction dropped precipitously (11% e.e.), though the yield of the reaction and the *endo*/*exo*-selectivity remained unchanged (entry 4).[13] To examine the temperature effect, the reaction was carried out at −50°C using the catalyst prepared from 10 mol% of $Cu(OTf)_2$ and silica followed by washing with dichloromethane. The enantioselectivity of the reaction increased, giving 50% e.e. with a similar level of *endo*-selectivity (entry 5). The enantioselectivity and *endo*-selectivity were further improved (65% e.e. and 12/1, respectively) when the temperature was lowered to −70°C (entry 6). In an attempt to ensure complete removal of uncomplexed copper species from the silica surface, the silica **6** was treated with 30 mol% of $Cu(OTf)_2$ and washed with dichloromethane (three times), stirred with 10 equiv. of 3-acryloyloxazolidin-2-one in dichloromethane for 10 h at room temperature and finally washed with dichloromethane (three times). Even after this extensive washing, the DA reaction proceeded with the same enantioselectivity (65% e.e.) and in almost quantitative yield (99%) (entry 7). This indicates that the free copper species might not be responsible for the reduction in the enantioselectivity at the lower temperature. Indeed, 20 and 2% yields of the *endo*- and *exo*-products, respectively, were obtained

Table 3. Recycling DA reaction between cyclopentadiene and **7** at −78°C [14]

	Method	1st (*endo*/*exo*)	2nd (*endo*/*exo*)	3rd (*endo*/*exo*)	4th (*endo*/*exo*)	5th (*endo*/*exo*)
Catalyst **5**	A	75 (15:1)	71 (13:1)	69 (12:1)	63 (13:1)	–
	B	78 (17:1)	72 (15:1)[a]	73 (16:1)	70 (14:1)	72 (15:1)[b]
Catalyst **6**	A	67 (13:1)	75 (13:1)	48 (14:1)	56 (13:1)[b]	52 (13:1)

[a] The reaction was run at −73°C.

[b] Additional Cu(OTf)$_2$ (1 equiv.) was added at this run.

when a DA reaction was carried out using the ligand-grafted silica **6** *without copper reagent* at −70°C for 24 h (entry 8). This result clearly indicates that the TMS-capped silica **6** exerts some catalytic activity in the Diels–Alder reaction even at −70°C. When the temperature was lowered to −78°C, the highest enantioselectivity was observed (75% e.e., entry 9). It is of particular note that increased *endo*/*exo*-selectivity (13/1) compared to that obtained in the homogenous reaction was observed using the immobilized catalyst. In the reaction using catalyst **5**, which is not protected with the TMS group (entry 10), the enantio- and *endo*/*exo*-selectivity were higher than those obtained with catalyst **6** (78% e.e. and 17/1, respectively). All of the reactions examined in Table 1 employing the immobilized catalyst **5** and **6** afforded almost quantitative yields (>97%) indicating excellent catalyst reactivity.

To examine the scope of the reaction employing the catalyst **6**, we carried out DA reactions using various dienes and dienophiles, the results are summarized in Table 2. When a reaction employing cyclopentadiene and the dienophile **8** in the presence of the homogenous catalyst **2b** was carried out at 0°C, the DA cycloadducts were obtained with 3/1 *endo*-selectivity and the *endo*-isomer **12** was obtained with 85% e.e. (entry 1). When the same reactions were carried out using 10 mol% each of heterogenized ligand **6** and Cu(OTf)$_2$, a 4:1 mixture of *endo*- and *exo*-products was obtained with 72% e.e. for **12** (entry 2). A homogeneous DA reaction between cyclopentadiene and dienophile **9** employing **2b** gave the *endo*-isomer **13** with 82% e.e. and *endo*-selectivity of 3:1 (entry 3). In heterogeneous reactions employing **6**, the e.e. of **13** was 65% and *endo*-selectivity was 4:1 (entry 4). In a preliminary attempt to test the recyclability of the catalyst from the reactions of entries 2 and 4, almost the same diastereo- and enantioselectivities were observed (numbers in parentheses in entries 2 and 4). When a homogenous reaction employing cyclohexadiene and the dienophile **7** was carried out at 0°C, the DA cycloadducts were obtained with *endo*-selectivity of >99/1 and the *endo* isomer **11** had 61% e.e. (entry 5). With heterogenized ligand **6**, the *endo*-product (with 53% e.e.) and *endo*/*exo*-selectivity of >99:1 were observed (entry 6). Both reactions of cyclohexadiene proceeded very slowly. The fact that there are 8–17% differences in the e.e. between homogenous and heterogeneous reactions indicates that some reactions are catalyzed by sources other than the immobilized catalyst prepared from **6**.

Encouraged by the results from the preliminary recycling experiments (entries 2 and 4, Table 2), we further examined the recycling capability of the catalysts **5** and **6**.[14] Reactions were carried out with the catalyst prepared from adding 30 mol% of Cu(OTf)$_2$ to 10 mol% of **5** or **6** followed by washing extensively with dichloromethane. According to different ways of washing the catalyst, two different protocols have been employed. In method A, after mixing the silica ligand and Cu(OTf)$_2$ in dichloromethane, the mixture was stirred for 3 h, washed with dichloromethane and dried before use. In method B, after stirring the silica ligand with Cu(OTf)$_2$, the mixture was diluted with a large amount of dichloromethane and stirred for another 0.5 h, filtered and dried before use. After 24 h reaction, the mixture was filtered and the solid residue was washed with hexane twice. The recycling experiments were carried out using new batches of diene and dienophile and the results are summarized in Table 3. When TMS-capped ligand **6** was utilized using method A, almost consistent *endo*/*exo*-selectivity was observed and the e.e. of the *endo*-product peaked at the second run (75%) and gradually decreased. When the ligand **5** was examined under the same method (A), the enantioselectivies were similar initially and stayed above 60% e.e. up to the 4th recycle. When method B was employed for catalyst **5**, much more consistent enantioselectivities (over 70% e.e.s) were observed. Further study will be required to clarify the reason why catalyst **5** gives better results than catalyst **6**.

To address the possible cause of the observed gradual decrease in enantioselectivity upon repeated use of the ligand, we examined the copper quantity after repetition experiment using **5** through EPMA (electron probe microanalyser) analysis and the results are listed in Table 4. From the data, it was obvious that the copper content decreased considerably after each run and this might have caused the slight reduction of enantioselectivity. In Table 3, after additional Cu(OTf)$_2$ was added, the reaction enantioselectivity rebounded a little.

Table 4. Leaching experiment with method B through EPMA

	1st	2nd	3rd
Si:Cu	89.6:10.4	91.9:8.1	94.2:5.8

Conclusions

In summary, we have prepared a new heterogeneous catalyst system containing a chiral bis(oxazoline) ligand immobilized onto MCF. The immobilized catalyst exhibited good enantioselectivity of up to 78% e.e. and high *endo*/*exo*-selectivity of 17:1 in the reaction between cyclopentadiene and the dienophile **7**. When cyclohexadiene and other dienophiles were examined with the heterogeneous catalyst system, the enantioselectivities were found to be 8–17% lower than the corresponding homogeneous reaction enantioselectivies. The catalyst was easily recovered and reused several times without losing its high reactivity and enantioselectivity.

Acknowledgements

We would like to thank the Brain Korea 21 Program supported by the Ministry of Education for the financial support. B.M.K. acknowledges the support from the KOSEF through the Center for Molecular Catalysis at Seoul National University.

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10. Physical data of **3**: ^{1}H NMR 3.07–2.91 (m, 6H), 3.40–3.31 (m, 4H), 5.33 (t, $J=7.1$ Hz, 2H), 5.48 (d, $J=8.7$ Hz, 2H), 6.31 (d, $J=8.3$ Hz, 4H), 6.62 (d, $J=8.3$ Hz, 4H), 7.39–7.28 (m, 8H); ^{13}C NMR 38.6, 40.0, 50.0, 80.0, 85.1, 115.9, 126.3, 126.6, 127.1, 128.6, 129.8, 132.3, 141.3, 142.4, 157.7, 169.7; $[\alpha]_D^{26} = 133$ (c 1, MeOH); LCMS m/z 543.5; HRMS (FAB+) m/z 543.2301 (calcd for $C_{35}H_{30}N_2O_4$ +H^+ 543.2284).
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13. Presumably binding of acetone to copper might have altered the reaction transition state geometry.
14. **Typical experimental procedures**:

    Method A: Indabox-immobilized silica (40 mg, 0.23 mmol g^{-1}) was mixed with Cu(OTf)$_2$ (2–3 equiv. to the ligand) in CH_2Cl_2 (1 mL). The mixture was stirred for 3 h and the solid residue was washed with CH_2Cl_2 (5 mL) and dried under reduced pressure. Then the silica-copper complex was charged with CH_2Cl_2 (0.7 mL) and a dienophile. At the specified temperature cyclopentadiene (10 equiv.) was added. After the dienophile disappeared completely according to TLC analysis, the silica copper complex was washed with CH_2Cl_2 (5 mL) and dried under reduced pressure.

    Method B: Indabox-immobilized silica (40 mg, 0.23 mmol/g) was mixed with Cu(OTf)$_2$ (2–3 equiv. to the ligand) in CH_2Cl_2 (1 mL). The mixture was stirred for 3 h and then charged with additional CH_2Cl_2 (10 mL) and stirred for 30 min. The solid residue was filtered and dried under reduced pressure. Then the silica copper complex was charged with CH_2Cl_2 (0.7 mL) and a dienophile. At the specified temperature cyclopentadiene (10 equiv.) was added. After the dienophile disappeared according to TLC, the silica copper complex was washed with hexane (10 mL) and dried under reduced pressure.