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Jørgensen – Hayashi Catalyst Supported on Poly(ethylene glycol)s as Highly Efficient and Reusable Organocatalysts for Enamine-Catalyzed Asymmetric Michael Reaction

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Ai-Bao Xia, Can Zhang, Yan-Peng Zhang, Yan-Jun Guo, Xiao-Long Zhang, Zhao-Bo Li and Dan-Qian Xu*,a

A new kind of recyclable and reusable PEG-supported Jørgensen – Hayashi catalyst is synthesized for the first time and proven to be efficient for the enamine-catalyzed asymmetric Michael reaction with generally moderate to good diastereoselectivity and high to excellent enantioselectivity (up to 6 : 1 dr, 99% ee). The prepared PEG-supported catalyst can be recovered eight times and found to provide similar diastereoselectivity and enantioselectivity to unsupported functional catalyst.

Introduction

The use of organocatalysis as a new powerful tool for the asymmetric synthesis of pharmaceutical intermediates, biologically active compounds, and natural products has grown in recent years.[1] Various efficient organocatalysts, such as the S-proline and its derivatives, imidazolidine, and other chiral organocatalysts, have been used in organocatalytic methods.[2] However, high organocatalyst loadings (10 mol% to 30 mol%) are generally required in those transformations to afford ideal catalytic performance. Furthermore, homogeneous organocatalysts cannot be easily separated from reaction systems to further reuse them. Therefore, the development of catalyst immobilization may aid us in overcoming these problems, and it also holds great significance in both economic and environmental concerns.[3]

(S) - α, α - diarylprolinol silyl ethers, also known as Jørgensen–Hayashi catalysts, were proven to be promising organocatalysts,[4] and various different approaches for the immobilization of Jørgensen–Hayashi catalyst have been reported. Whereas the use of insoluble heterogeneous supports has gained widespread attention,[5] immobilization on soluble homogeneous polymers has scarcely been reported.[6] For example, Zeitler and co-workers have reported on a type of MeOPEG-supported Jørgensen–Hayashi catalyst through a stable 1,2,3-triazole linkage, and the immobilized catalyst provides unchanged reactivity and selectivity as compared with the homogeneous catalyst[6g]. In this article, we report the synthesis of unsupported functional Jørgensen–Hayashi catalyst **1** and its polyethylene glycol(PEG)-supported derivatives **2** through thiol–ene coupling for the first time (Figure 1)[5f, 5g, 7], as well as their application in enamine-catalyzed asymmetric Michael reaction[8].

Results and discussion

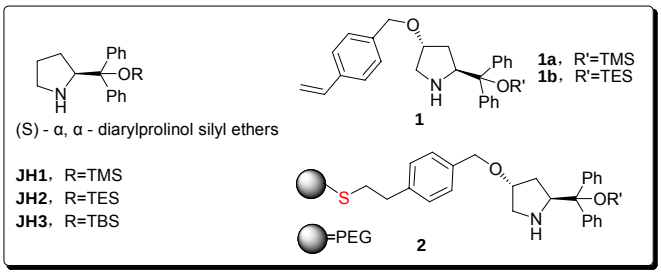
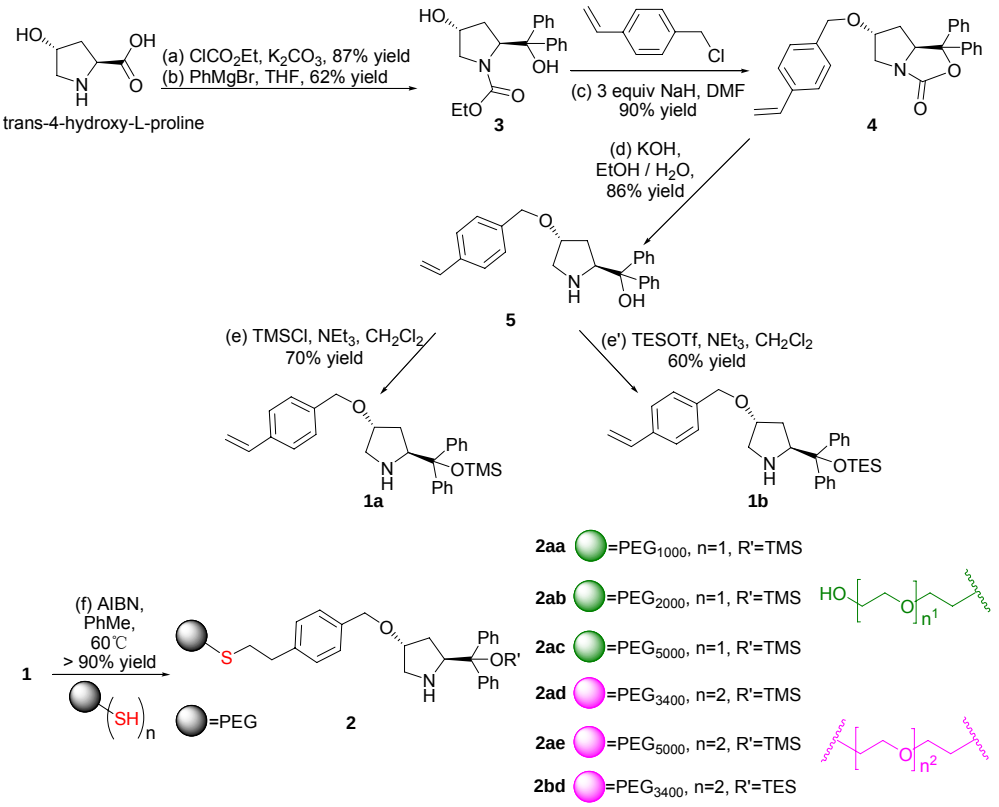


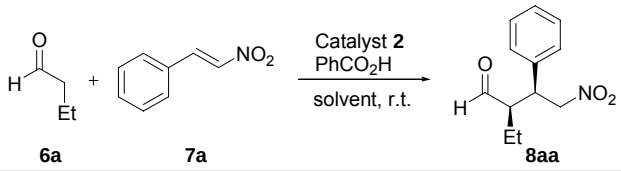
Figure 1. Catalysts used in this study

As described in Scheme 1, the unsupported functional Jørgensen–Hayashi catalyst **1** was accordingly synthesized and immobilized onto the thiol PEG. The PEG-supported Jørgensen–Hayashi catalysts **2** could be obtained in a very good overall yield (> 41% from **3**).[6g] According to the elemental analysis of nitrogen, the loading of functional Jørgensen–Hayashi catalyst **1a** on PEG-supported **2aa**, **2ab**, **2ac**, **2ad** and **2ae** was 0.65 mmol/g, 0.39 mmol/g, 0.17 mmol/g, 0.3 mmol/g and 0.19 mmol/g, respectively. And the loading of functional Jørgensen–Hayashi catalyst **1b** on PEG-supported **2bd** was 0.29 mmol/g.



Scheme 1. Synthesis of the Unsupported Functional Jørgensen–Hayashi Catalyst **1** and the PEG-Immobilized **2** from trans-4-Hydroxy-L-Proline

Table 1. Catalyst Screening and Reaction Optimization[a]



Entry	Cat	solvent	time (day)	C[b] (%)	Y[c] (%)	dr[d]	ee[e] (%)
1	**1a**	none	1	> 99	90	1.8:1	94
2	**1b**	none	1	95	88	1.9:1	92
3	**JH1**	none	1	95	89	2.6:1	94
4	**JH2**	none	1	92	89	2.6:1	89
5	**JH3**	none	1	88	85	2.6:1	88
6	**2aa**	none	7	< 5			
7	**2ab**	none	7	< 5			
8	**2ac**	none	7	15	10	1.1:1	99
9	**2ad**	none	7	64	60	3:1	98
10	**2ae**	none	7	41	37	2:1	99
11	**2ad**	PhMe	4	41	35	5:1	87
12	**2ad**	$(CH_2Cl)_2$	4	86	73	10:1	90
13	**2ad**	EtOH	4	> 99	87	2:1	86
14	**2ad**	MeOH	2	> 99	86	2.7:1	90
15	**2ad**	H_2O	2	> 99	85	1.5:1	87
16	**2ad**	$(CH_2Cl)_2$: H_2O (1:1)	2	> 99	55	1.5:1	90
17	**2ad**	$(CH_2Cl)_2$: H_2O (3:1)	2	> 99	87	5:1	97
18	**2ad**	$(CH_2Cl)_2$: H_2O (5:1)	2	67	31	4.6:1	92

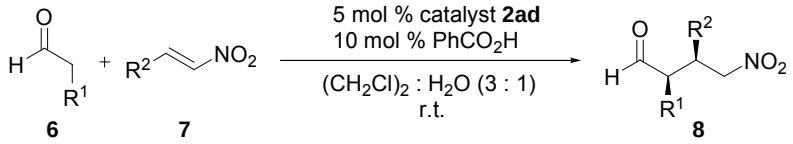
[a] Unless otherwise stated, the reaction was conducted by stirring in solvent (0.25 mL) using **6a** (0.5 mmol) and **7a** (0.1 mmol) with 5 mol% catalyst and 10 mol% $PhCO_2H$ at room temperature. [b] The conversion, determined by GC-MS. [c] Isolated yield of **8aa**. [d] The dr value of *syn*:*anti*, determined through HPLC analysis on a Chiralcel OD-H. [e] The ee value of the *syn* isomer, determined through HPLC analysis on a Chiralcel OD-H.

The unsupported functional Jørgensen–Hayashi catalysts **1**, regular Jørgensen-Hayashi catalysts **JH** and the PEG-supported Jørgensen–Hayashi catalysts **2** were then evaluated for the enamine-catalyzed asymmetric Michael reaction of butyraldehyde **6a** and trans-β-nitrostyrene **7a** without solvent at room temperature (Table 1, entries 1–10). Pleasingly, using catalysts **1a**, **1b**, **JH1**, **JH2** and **JH3**, Michael product **8aa** was obtained as the major product with significant similar diastereo- and enantiocontrol (Table 1, entries 1–5). Furthermore, among the tested PEG-supported Jørgensen–Hayashi catalysts (entries 6–10), **2ad** (entry 9), which exhibited slightly better diastereoselectivity and enantioselectiviy than the unsupported functional catalyst **1** (entry 1), was found to be the best catalyst among the supported catalysts for the reaction, providing **8aa** in 64% conversion, 3:1 dr with corresponding 98%, and 67% ee. Subsequent evaluation of solvent effects improved the yield to 87% when $(CH_2Cl)_2$:H_2O (3:1) was used as the solvent (entries 11–18).

After obtaining the optimized reaction conditions, a series of experiments were performed to investigate the substrate scope for the enamine-catalyzed asymmetric Michael reaction of aldehydes **6** and *trans*-β-nitrostyrenes **7**. As summarized in Table 2, different combinations of **6** and **7** were allowed to react smoothly in the presence of 5 mol% of the supported catalyst **2ad** to afford the expected adducts **8** in moderate to excellent yields (40% to 95%), moderate to good diastereoselectivities (1:1 to 6:1 dr) and high to excellent enantioselectivities (*syn* isomer, 85% to 99% ee). Variations in the aldehydes **6** (Table 2, entries 1–6) as well as in the nitroolefins **7a**–**7g** (Table 2, entries 7–13) are well tolerated. Aldehyde **6f** with more sterically demanding moiety in the β-position also yielded the addition product **8fa** with high enantioselectivity (85% ee) (Table 2, entry 6). In addition, also the nitrodiene **7h** with aldehyde **6a** was also successfully converted to the conjugate addition product in good yield and excellent enantioselectivity (Table 2, entry 14). These results demonstrate that the PEG-supported Jørgensen–Hayashi catalyst **2ad** is a highly efficient catalyst.

Next, the recyclability and stability of the PEG-supported catalyst **2ad** was examined. The recycling experiment was performed at the premise of recovering the PEG-supported catalyst by using acid-based extraction method. After the Michael reaction, the recovered PEG-supported catalyst was extracted from the aqueous phase, dried, and then directly subjected to the next run. As shown in Table 3, the PEG-supported catalyst **2ad** can be reused for at least eight times without losing the enantioselectivity (94 to 99% ee) and diastereoselectivity (dr 4:1 to 5:1). After the seventh run, due to the hydrolysis of the silyl ether, we could observe a significant decrease in catalytic activity, although diastereoselectivity and enantioselectivity maintained. But after simply treating the deactivation PEG-supported catalyst **2ad** with $ClSi(CH_3)_3$ in CH_2Cl_2, the catalytic activity of the **2ad** can be recovered effectively(Table 3, entry 9). [5d, 5i] The **JH1** was also tested in the recycling experiment, in the fourth run with the recovered catalyst, quite low yield (only 14%) with constant level of diastereo- and enantioselectivity was observed (Table 3, entry 4). And when the PEG-supported catalyst **2bd** with more robust TES was used, it can be reused for eight times without losing the enantioselectivity (99% ee) and diastereoselectivity (dr 9:1 to 10:1). .

Table 2. Scope of the enamine-catalyzed asymmetric Michael reaction[a]

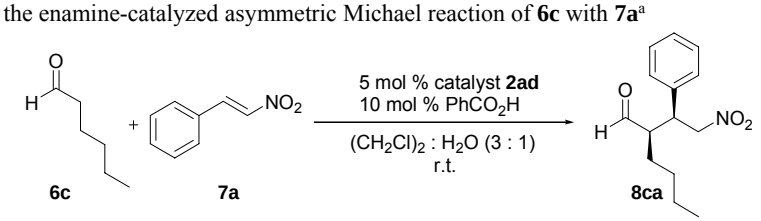


6 7 8

Entry	R^1 / **6**	R^2 / **7**	**8** / yield[b] (%)	dr[c] (*syn*:*anti*)	ee[d] (%)
1	Et / **6a**	C_6H_5 / **7a**	**8aa** / 87	5:1	97
2	Pr / **6b**	C_6H_5 / **7a**	**8ba** / 90	5:1	87
3	Butly / **6c**	C_6H_5 / **7a**	**8ca** / 93	4:1	91
4	Pentyl / **6d**	C_6H_5 / **7a**	**8da** / 70	4:1	99
5[e]	Hexyl / **6e**	C_6H_5 / **7a**	**8ea** / 92	5:1	96
6	*i*-Pr / **6f**	C_6H_5 / **7a**	**8fa** / 40	1:1	85
7[e]	Et / **6a**	4-CH_3-C_6H_4 / **7b**	**8ab** / 85	6:1	98
8	Et / **6a**	4-Br-C_6H_4 / **7c**	**8ac** / 91	1:1	92
9[e]	Et / **6a**	3-Br-C_6H_4 / **7d**	**8ad** / 86	3:1	99
10[e]	Et / **6a**	2-Br-C_6H_4 / **7e**	**8ae** / 88	3:1	99
11	Et / **6a**	2-Thienyl / **7f**	**8af** / 75	2:1	98
12	Butly / **6c**	4-Br-C_6H_4 / **7c**	**8cc** / 95	5:1	99
13	Butly / **6c**	4-Cl-C_6H_4 / **7g**	**8cg** / 57	3:1	99
14	Et / **6a**	4-Br-C_6H_4CH=CH / **7h**	**8ah** / 68	2:1	89

[a] Unless otherwise stated, the reaction was conducted by stirring in 0.25 mL solvent using **6** (0.5 mmol) and **7** (0.1 mmol) with 5 mol% catalyst **2ad** and 10 mol% $PhCO_2H$ at room temperature for 2 days. In the case of racemic samples, 50 mol% DL-proline were used in DMF. [b] Isolated yield. [c] Determined by chiral-phase HPLC. [d] The ee value of the syn isomer, determined by chiral-phase HPLC. [e] The ee value of the syn isomer was determined by chiral HPLC analysis after conversion of the aldehyde into the corresponding alcohol by reduction with $NaBH_4$.

Table 3. Recycling of **2ad** for the enamine-catalyzed asymmetric Michael reaction of **6c** with **7a**[a]



6c **7a** **8ca**

recycle	method	yield of **8ca**[b] (%)	dr[c] (*syn*:*anti*)	ee[c] (%)(syn)
	A	79	5:1	96
	B	60	4:1	99
	C	82	9:1	99
1	A	79	5:1	96
	B	58	4:1	99
	C	80	9:1	99
2	A	78	4:1	99
	B	58	4:1	99
	C	79	9:1	99
3	A	67	5:1	99
	B	59	5:1	99
	C	78	9:1	99
4	A	71	5:1	98
	B	14	5:1	99
	C	76	9:1	99
5	A	69	4:1	94
	C	76	10:1	99
6	A	65	5:1	95
	C	76	10:1	99
7	A	55(71)[d]	5:1 (5:1)[d]	97 (97)[d]
	C	75	10:1	99
8	A	46(71)[e]	5:1 (5:1)[e]	97 (97)[e]
	C	75	9:1	99
9[f]	A	69	5:1	95

[a] Method A: unless otherwise stated, the reaction was conducted by stirring in 5 mL solvent using **6c** (2.4 mmol) and **7a** (2 mmol) with 5 mol% catalyst **2ad** and 10 mol% $PhCO_2H$ at room temperature in 2 days. Method B: **JH1** was used as the catalyst. Method C: **2bd** was used as the catalyst. [b] Isolated yield of **8ca**. [c] Determined through HPLC analysis on a Chiralcel OD-H. [d] Reaction time = 3 days. [e] Reaction time = 5 days. [f] Using the reactivated catalyst **2ad**.

Conclusions

In summary, a novel recyclable, and reusable PEG-supported Jørgensen–Hayashi catalyst is synthesized for the first time. The catalyst is proven to be efficient catalyst for the enamine-catalyzed asymmetric Michael reaction of a wide range of aldehydes with both nitroolefins and nitrodiene. Moderate to excellent yield (40% to 95%), moderate to good diastereoselectivities (1:1 to 6:1 dr), and high to excellent enantioselectivities (87% to 99% ee) are achieved using only 5 mol% PEG-supported catalyst loading. The prepared PEG-supported catalyst can be recovered eight times and found to provide similar diastereoselectivity and enantioselectivity to unsupported functional catalyst. Further study on the wide application of this efficient strategy for the synthesis of potentially valuable chiral molecules is under investigation in our laboratory.

Experimental

General information

The ^1H NMR and ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane. GC−MS experiments were performed on a GC system with a mass selective detector. HRMS data were measured on a LC/TOF-MS with ESI source or GC/TOF-MS with EI source. Elemental analyses of N, C, and H, and IR spectra were performed for catalysts **2aa**, **2ab**, **2ac**, **2ad, 2ae** and **2bd**. Column chromatography and flash chromatography experiments were performed on silica gel (200-300 mesh) eluting with ethyl ether and petroleum ether. TLC experiments were carried out on glass-backed silica plates. In each case, enantiomeric ratio was determined on a chiral column in comparison with authentic racemates by chiral HPLC. Compound **3** was synthesized according to the reference 6g.

Conventional procedure for the synthesis of PEG-supported Jørgensen–Hayashi catalysts 2

Synthesis of compound 4

Sodium hydride (1.69 g, 0.044 mmol, 4.4 equiv., 60 (ω%)) was

added in a N_2-filled round-bottom flask containing 30 mL dried DMF at room temperature with stirring for 10 min. Then, the solution of **3** (3.41 g, 0.01 mmol, 1 equiv.) in 9 mL of dried DMF was added in 30 min at 0 °C. After an hour, 1-(chloromethyl)-4-vinylbenzene (1.67 g, 0.011 mmol, 1.1 equiv.) was added slowly using a septum. The resulting reaction mixture was allowed to react with stirring at ambient temperature. Subsequently, the reaction was quenched with diethyl ether (10 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with diethyl ether several times. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 8/1 to 5/1) to afford the product **4**, yield: 18.5 g, 90 %; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58−7.56 (m, 2H), 7.45−7.42 (m, 2H), 7.41−7.37 (m, 6H), 7.35−7.27 (m, 4H), 6.76−6.72 (q, *J* = 11.0, 17.5 Hz, 1H), 5.81−5.78 (m, 1H), 5.31−5.28 (m, 1H), 4.90−4.93 (q, *J* = 5.0, 11.5 Hz, 1H), 4.48 (s, 2H), 4.18 (t, *J* = 5.5 Hz, 1H), 4.08−4.05 (q, *J* = 5.5, 12.5 Hz, 1H), 3.38−3.35 (m, 1H), 1.96−1.92 (q, *J* = 5.0, 13.5 Hz, 1H), 1.25−1.19 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.4, 143.0, 140.2, 137.4, 137.2, 136.4 (×2), 128.7 (×2), 128.5 (×2), 128.0 (×2), 127.8, 126.4 (×2), 126.1 (×2), 125.5 (×2), 114.2, 85.8, 78.4, 71.1, 67.5, 53.8, 36.2 ppm; GC−MS: m/z 411.2 (100), 165.1, 91.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{26}NO_3$ 412.1913; Found 412.1922.

Synthesis of compound 5

A N_2-filled three-necked round-bottom flask was charged with **4** (4.11 g, 0.01 mmol) in 25 mL ethanol. Potassium hydroxide (1.12 g, 0.02 mmol, 2 equiv.) in water (4.6 mL) was added in a drop-wise manner. After being stirred for 30 h at 45 °C, the reaction was diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 8/1 to 4/1) to afford the product **5**, yield: 16.6 g, 86 %; white solid, mp: 70.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (*d*, J = 7.0 Hz, 2H), 7.53 (t, *J* = 1.0 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.36−7.30 (m, 6H), 7.24−7.19 (m, 2H), 6.79−6.73 (q, *J* = 10.5, 17.5 Hz, 1H), 5.78 (d, *J* = 17.5 Hz, 1H), 5.28 (d, *J* = 11.0 Hz, 1H), 4.63−4.60 (q, *J* = 6.5, 9.5 Hz, 1H), 4.49−4.44 (m, 2H), 4.09−4.07 (m, 1H), 3.20−3.16 (m, 2H), 1.86−1.80 (m, 1H), 1.74−1.70 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.8, 145.0, 138.0, 137.1, 136.6, 128.3 (×2), 128.0 (×2), 127.8 (×2), 126.6, 126.4, 126.3 (×2), 126.0 (×2), 125.5 (×2), 113.9, 79.5, 76.9, 70.6, 63.5, 52.6, 33.0 ppm; (ESI+) m/z 386.28; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}NO_2$ 386.2115; Found 386.2119.

Synthesis of compound 1

Fresh triethylamine (1.31 g, 0.013 mmol, 1.3 equiv.) was added slowly to a solution of **5** (3.85 g, 0.01 mmol, 1 equiv.) in anhydrous dichloromethane (30 mL) under N_2-atmosphere. After being stirred for 10 min, fresh chlorotrimethylsilane (1.19 g, 0.011 mmol, 1.1 equiv.) or TESOTf (2.91 g, 0.011 mmol, 1.1 equiv.) was added in a drop-wise manner at 0 °C. The reaction was allowed proceed with stirring at ambient temperature for a further 3 days. Subsequently, the mixture was poured into ice water followed by extraction with dichloromethane. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl ether 5/1 to 3/1) to afford the product **1**. **1a**, yield: 3.2 g, 70 %; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52−7.50 (m, 2H), 7.41−7.38 (m, 4H), 7.32−7.24 (m, 8H), 6.77−6.71 (q, *J* = 11.0, 18.0 Hz, 1H), 5.77 (d, *J* = 18.0 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.42 (t, *J* = 5.5 Hz, 3H), 3.84−3.83 (m, 1H), 3.05−3.03 (m, 1H), 2.88−2.85 (m, 1H), 1.78−1.75 (m, 2H), 0.06 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 145.3, 138.1, 137.0, 136.6, 128.5 (×2), 127.9 (×2), 127.7 (×2), 127.6 (×2), 127.5 (×2), 127.0, 126.9, 126.3 (×2), 113.8, 82.8, 79.0, 70.6, 63.8, 52.8, 34.3, 2.2 (×3) ppm; (ESI+) m/z 458.21; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{36}NO_2Si$ 458.2516; Found 458.2515. **1b**, yield: 3.0 g, 60 %; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64−7.63 (m, 2H), 7.51−7.47 (m, 4H), 7.41−7.36 (m, 8H), 6.87−6.81 (q, *J* = 11.0, 17.5 Hz, 1H), 5.87 (d, *J* = 18.0 Hz, 1H), 5.36 (d, *J* = 11 Hz, 1H), 4.54−4.46 (m, 3H), 3.85 (m, 1H), 3.15−2.98 (m, 1H), 2.85−2.82 (m, 1H), 1.95−1.78 (m, 2H), 1.10−0.94 (m, 9H), 0.70−0.63 (m, 2H), 0.51−0.46 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.5, 145.2, 138.2, 136.9, 136.6, 128.8 (×2), 128.0 (×2), 127.8 (×2), 127.6 (×2), 127.2 (×2), 127.0, 126.9, 126.2 (×2), 113.7, 82.6, 79.3, 70.6, 63.9, 52.9, 34.5, 7.2 (×3), 6.5 (×3) ppm; (ESI+) m/z 500.27; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{42}NO_2Si$ 500.2985; Found 500.2983.

Synthesis of PEG-supported Jørgensen − Hayashi catalysts 2

A mixture of **1** (0.038 g, 0.082 mmol, 1.1 equiv.), PEG-SH (0.075 mmol, 1 equiv.), AIBN (0.012 g, 0.075 mmol, 1 equiv.) in toluene (1.5 mL) was stirred at 60 °C for 1d, then the reaction mixture was precipitated with diethyl ether, filtered, and dried under vacuum. In the case of SH-PEG-SH, **1** (0.072 g, 0.157 mmol, 2.1 equiv.) and AIBN (0.024 g, 0.15 mmol, 2 equiv.) were used. Anal. Calcd. for **2aa** Found: C, 58.40; H, 8.41; N, 0.91. IR (KBr): γ_{max}/cm^{-1} 3731, 2924, 1105, 951, 757. Anal. Calcd. for **2ab** Found: C, 56.80; H, 8.51; N, 0.55. IR (KBr): γ_{max}/cm^{-1} 3731, 2869, 1108, 950, 707. Anal. Calcd. for **2ac** Found: C, 54.80; H, 9.10; N, 0.24. IR (KBr): γ_{max}/cm^{-1} 3731, 3504, 1110, 955, 759. Anal. Calcd. for **2ad** Found: C, 54.80; H, 8.32; N, 0.42. IR (KBr): γ_{max}/cm^{-1} 3429, 2885, 1112, 956, 760. Anal. Calcd. for **2ae** Found: C, 54.70; H, 8.40; N, 0.27. IR (KBr): γ_{max}/cm^{-1} 3430, 2876, 1109, 953, 732. Anal. Calcd. for **2bd** Found: C, 54.81; H, 8.33; N, 0.41. IR (KBr): γ_{max}/cm^{-1} 3443, 2874, 1112, 951, 706.

Conventional procedure for the asymmetric Michael reaction catalyzed by 2d

Solvent (0.25 mL) was added to a mixture of aldehydes **6** (0.5 mmol) with nitroolefins or nitrodiene **7** (0.1 mmol) in the presence of 5 mol% catalyst **2ad** and 10 mol% $PhCO_2H$ at room temperature with vigorous stirring. After 2 days, the reaction mixture was extracted with DCM, washed with water, dried, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl ether/petroleum ether = 1:3 as eluent) to yield the faintly yellow liquid products **8**. Enantiomeric ratio was determined by HPLC analysis on a chiral column.

(2R,3R)-2-ethyl-4-nitro-3-phenylbutanal (8aa).[5a] yield: 19.2 mg, 87 %; 97 % ee; 5:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (95:5) as the eluent, Flow: 1.0 mL/min;

UV = 224 nm; t^{syn}_{minor} = 37.573 min, t^{syn}_{major} = 32.482 min; t^{anti}_{minor} = 58.752 min, t^{anti}_{major} = 34.854 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 2.5 Hz, 1H), 7.36−7.34 (m, 2H), 7.31−7.28 (m, 1H), 7.19−7.17 (m, 2H), 4.74−4.61 (m, 2H), 3.84−3.77 (m, 1H), 2.71−2.66 (m, 1H), 1.55−1.46 (m, 2H), 0.82 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.1, 136.8, 129.1 (×2), 128.1, 128.0 (×2), 78.5, 53.4, 42.8, 20.4, 10.7 ppm; GC−MS: m/z 145.1, 117.1, 104.1, 91.1 (100), 77.1.

(R)-2-((R)-2-nitro-1-phenylethyl)pentanal (8ba).[5a] yield: 21.2 mg, 90 %; 87 % ee; 5:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (90:10) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{minor} = 22.518 min, t^{syn}_{major} = 24.932 min; t^{anti}_{minor} = 20.212 min, t^{anti}_{major} = 34.877 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 3.0 Hz, 1H), 7.38−7.34 (m, 2H), 7.33−7.30 (m, 1H), 7.20−7.18 (m, 2H), 4.74−4.64 (m, 2H), 3.81−3.77 (m, 1H), 2.74−2.70 (m, 1H), 1.51−1.47 (m, 1H), 1.39−1.32 (m, 2H), 1.22−1.18 (m, 1H), 0.82 (t, *J* = 7.0Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 136.9, 129.1 (×2), 128.2, 128.0 (×2), 78.4, 53.9, 43.3, 29.5, 19.8, 13.9 ppm; GC−MS: m/z 145.2 (100), 117.2, 104.2, 91.2, 77.2.

(R)-2-((R)-2-nitro-1-phenylethyl)hexanal (8ca).[5a] yield: 21.16 mg, 93 %; 91 % ee; 4:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (90:10) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{minor} = 17.039 min, t^{syn}_{major} = 20.918 min; t^{anti}_{minor} = 18.612 min, t^{anti}_{major} = 29.811 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 3.0 Hz, 1H), 7.37−7.34 (m, 2H), 7.32−7.29 (m, 1H), 7.20−7.18 (m, 2H), 4.74−4.63 (m, 2H), 3.81−3.77 (m, 1H), 2.73−2.69 (m, 1H), 1.51− 1.47 (m, 1H), 1.43−1.40 (m, 1H), 1.28−1.19 (m, 2H), 1.18−1.13 (m, 2H), 0.79 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.3, 136.9, 129.1 (×2), 128.1, 128.0 (×2), 78.4, 53.9, 43.2, 28.5, 27.0, 22.5, 13.6 ppm; GC−MS: m/z 145.2 (100), 117.2, 105.2, 104.2, 91.2.

(R)-2-((R)-2-nitro-1-phenylethyl)heptanal (8da).[5a] yield: 18.41 mg, 70 %; 99 % ee; 4:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (90:10) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{major} = 19.745 min; t^{anti}_{minor} = 26.491 min, t^{anti}_{major} = 17.652 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.69 (d, *J* = 2.5 Hz, 1H), 7.36−7.33 (m, 2H), 7.31−7.28 (m, 1H), 7.19−7.18 (m, 2H), 4.74−4.63 (m, 2H), 3.82−3.77 (m, 1H), 2.72−2.70 (m, 1H), 1.49−1.47 (m, 1H), 1.39−1.38 (m, 1H), 1.28−1.11 (m, 6H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 136.8, 129.0 (×2), 128.0 (×3), 78.4, 53.8, 43.1,31.5, 27.2, 26.0, 22.1, 13.7 ppm; GC−MS: m/z 117.1 (100), 115.1, 104.1, 77.1, 91.1.

(R)-2-((R)-2-nitro-1-phenylethyl)octanal (8ea).[8f] yield: 25.48 mg, 96 %; 11% ee; 5:1 dr; yellow liquid; The product was converted to the corresponding alcohol with $NaBH_4$ and enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/i-PrOH (95:5) as the eluent, Flow: 1.0 mL/min; UV = 208 nm; t^{syn}_{minor} = 12.866 min, t^{syn}_{major} = 11.493 min; t^{anti}_{minor} = 16.479 min, t^{anti}_{major} = 14.199 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.67 (d, *J* = 2.5 Hz, 1H), 7.34−7.31 (m, 2H), 7.28−7.25 (m, 1H), 7.18−7.17(m, 2H), 4.72−4.61 (m, 2H), 3.81−3.76 (m, 1H), 2.72−2.67 (m, 1H), 1.48−1.10 (m, 10H), 0.81 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.3, 136.9, 129.1 (×2), 128.0 (×3), 78.4, 53.9, 43.2, 31.4, 28.5, 27.3, 26.4, 22.4, 14.0 ppm; GC−MS: m/z 145.1 (100), 105.1, 104.1, 91.1, 78.1.

(2R,3R)-2-isopropyl-4-nitro-3-phenylbutanal (8fa).[5a] yield: 9.40 mg, 40 %; 85 %; 47 % ee; 1:1 dr; white solid, mp: 114.4 °C; The enantiomeric excess was determined by HPLC on Daicel Chiralpak IC-H with hexane/i-PrOH (95:5) as the eluent, Flow: 1.0 mL/min; UV = 212nm; t^{syn}_{minor} = 29.745 min, t^{syn}_{major} = 33.878 min; t^{anti}_{minor} = 14.439 min, t^{anti}_{major} = 19.159 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.91(d, *J* = 2.0 Hz, 1H), 7.36−7.33 (m, 2H), 7.30−7.27 (m, 1H), 7.21−7.20 (m, 2H), 4.70−4.55 (m, 1H), 3.94−3.89 (m, 1H), 2.80−2.77 (m, 1H), 1.73−1.69 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.4, 137.2, 129.1 (×2), 128.0 (×3), 79.0, 58.7, 42.0, 27.9, 21.6, 16.9 ppm; GC−MS: m/z 145.2 (100), 104.2, 117.2, 131.2, 91.2.

(2R,3R)-2-ethyl-4-nitro-3-p-tolylbutanal (8ab).[8h] yield: 19.98 mg, 98 %; 43 % ee; 6:1 dr; yellow liquid; The product was converted to the corresponding alcohol with $NaBH_4$ and enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (97:3) as the eluent, Flow: 1.0 mL/min; UV = 212 nm; t^{syn}_{minor} = 59.725 min, t^{syn}_{major} = 63.937 min; t^{anti}_{minor} = 47.476 min, t^{anti}_{major} = 51.595 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 3.0 Hz, 1H), 7.16−7.13 (m, 2H), 7.08−7.06 (m, 2H), 4.72−4.59 (m, 2H), 3.77−3.76 (m, 1H), 2.67−2.65 (m, 1H), 2.33 (s, 3H), 1.53−1.50 (m, 2H), 0.84 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.3, 137.9, 133.7, 129.8 (×2), 127.9 (×2), 78.7, 55.1, 42.4, 21.0, 20.4, 10.7 ppm; GC−MS: m/z 159.2, 143.2, 118.2 (100), 117.2, 91.2.

(2R,3R)-3-(4-bromophenyl)-2-ethyl-4-nitrobutanal (8ac).[8e] yield: 27.21 mg, 92 %; 75 % ee; 1:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak IC-H with hexane/i-PrOH (95:5) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{minor}= 41.210 min, t^{syn}_{major} =44.663 min; t^{anti}_{minor} = 36.397 min, t^{anti}_{major} = 26.531 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 2.5 Hz, 1H), 7.49−7.47 (m, 2H), 7.08−7.07 (m, 2H), 4.74−4.57 (m, 2H), 3.80−3.75 (m, 1H), 2.69−2.64 (m, 1H), 1.57−1.45 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.8, 136.0, 132.4 (×2), 129.8 (×2), 122.2, 78.3, 54.7, 42.2, 20.4, 10.6 ppm; GC−MS: m/z 223.0, 115.1 (100), 103.1, 91.1, 77.1.

(2R,3R)-3-(3-bromophenyl)-2-ethyl-4-nitrobutanal (8ad). yield: 25.71 mg, 86 %; 99 % ee; 99:1 dr; yellow liquid; The product was converted to the corresponding alcohol with $NaBH_4$ and enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (97:3) as the eluent, Flow: 0.6 mL/min; UV = 228 nm; t^{syn}_{major} =80.238 min; t^{anti}_{minor} = 58.952 min, t^{anti}_{major} = 62.618 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.70 (d, *J* = 2.5 Hz, 1H), 7.44−7.41 (m, 1H), 7.36−7.35 (m, 1H), 7.24−7.18 (m, 1H), 7.14−7.13 (m, 1H), 4.74−4.59 (m, 2H), 3.82−3.75 (m, 1H), 2.70−2.65 (m, 1H), 1.57−1.46 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.7, 139.4, 131.4, 131.1, 130.7, 126.7, 123.1, 78.1, 54.7, 42.2, 20.4, 10.6 ppm; GC−MS: m/z 169.0, 115.1 (100), 103.1, 91.1, 77.1. HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{14}BrNO_3$ 299.0157; Found 299.0163.

(2R,3R)-3-(2-bromophenyl)-2-ethyl-4-nitrobutanal (8ae).[8e] yield: 26.31 mg, 88 %; 99 % ee; 3:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (90:10) as the eluent, Flow: 1.0 mL/min; UV = 232 nm; t^{syn}_{major} = 29.997 min; t^{anti}_{minor} = 41.356 min, t^{anti}_{major} = 28.786 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.73 (d, *J* = 2.0 Hz, 1H), 7.61−7.60 (m, 1H), 7.33−7.30 (m, 1H), 7.22−7.18 (m, 1H), 7.17−7.13 (m, 1H), 4.87−4.67 (m, 2H), 4.38−4.37 (m, 1H), 2.93 (s, 1H), 1.66−1.57

(m, 1H), 1.56−1.47 (m, 1H), 0.67 (t, J = 15.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.9, 136.3, 133.9, 129.5 (×2), 128.1 (×2), 77.4, 54.4, 41.3, 19.6, 11.6 ppm; GC−MS: m/z 184.1 (100), 169.1, 115.1, 104.2, 77.2.

(2R,3S)-2-ethyl-4-nitro-3-(thiophen-2-yl)butanal (8af).[8g] yield: 17.03 mg, 98 %; 70 % ee; 2:1 dr; yellow liquid; The product was converted to the corresponding alcohol with $NaBH_4$ and enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (98:2) as the eluent, Flow: 0.5 mL/min; UV = 228nm; t^{syn}_{minor} = 123.112 min, t^{syn}_{major} = 129.573 min; t^{anti}_{minor} = 113.667 min, t^{anti}_{major} = 105.861 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.717(d, J = 2.0 Hz, 1H), 7.25−7.23 (m, 1H), 6.96−6.94 (m, 1H), 6.91−6.90 (m, 1H), 4.75−4.62 (m, 2H), 4.20−4.14 (m, 1H), 2.72−2.67 (m, 1H), 1.69−1.61 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5, 139.5, 127.2, 127.1, 125.3, 78.9, 55.8, 38.4, 20.3, 10.9 ppm; GC−MS: m/z 180.1, 151.1, 110.1 (100), 137.1, 97.1.

(R)-2-((R)-1-(4-bromophenyl)-2-nitroethyl)hexanal (8cc). yield: 31.07 mg, 95 %; 99 % ee; 5:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/i-PrOH (95:5) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{minor} = 16.159 min, t^{syn}_{major} = 13.972 min; t^{anti}_{major} = 19.652 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.68 (d, J = 7.0 Hz, 1H), 7.49−7.47 (m, 2H), 7.08−7.07 (m, 2H), 4.72−4.59 (m, 2H), 3.79−3.74 (m, 1H), 2.71−2.66 (m, 1H), 1.48−1.37 (m, 2H), 1.26−1.14 (m, 4H), 0.79 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8, 136.0, 132.2 (×2), 129.7 (×2), 122.1, 78.1, 53.6, 42.5, 28.4, 27.0, 22.5, 13.6 ppm; GC−MS: m/z 184.0, 115.1 (100), 103.1, 91.1, 77.1. HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{17}BrO$ 280.0463 $[M - HNO_2]^+$; Found 280.0473.

(R)-2-((R)-1-(4-chlorophenyl)-2-nitroethyl)hexanal (8cg). yield: 16.13 mg, 57 %; 99 % ee; 3:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with hexane/i-PrOH (97:3) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{minor} = 30.762 min, t^{anti}_{major} = 32.548 min; t^{anti}_{major} = 37.866 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.70 (d, J = 5.0 Hz, 1H), 7.35−7.32 (m, 2H), 7.15−7.12 (m, 2H), 4.73−4.60 (m, 2H), 3.80−3.75 (m, 1H), 2.71−2.67 (m, 1H), 1.49−1.40 (m, 2H), 1.25−1.16 (m, 4H), 0.81 (t, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8, 135.4, 131.1, 129.4 (×2), 129.4 (×2), 78.2, 53.7, 42.5, 28.4, 27.1, 22.5, 13.6 ppm; GC−MS: m/z 179.0, 138.0 (100), 115.1, 103.1, 77.1. HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{17}ClO$ 236.0968 $[M - HNO_2]^+$; Found 236.0979.

(2R,3S,E)-5-(4-bromophenyl)-2-ethyl-3-(nitromethyl)pent-4-enal (8ah). yield: 22.10 mg, 68 %; 90 % ee; 2:1 dr; yellow liquid; The enantiomeric excess was determined by HPLC on Daicel Chiralpak IC-H with hexane/i-PrOH (95:5) as the eluent, Flow: 1.0 mL/min; UV = 228 nm; t^{syn}_{minor} = 37.184 min, t^{syn}_{major} = 41.757 min; t^{anti}_{minor} = 31.478 min, t^{anti}_{major} = 25.638 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.69 (d, J = 2.0 Hz, 1H), 7.43−7.41 (m, 2H), 7.20−7.18 (m, 2H), 6.48−6.45 (m, 1H), 6.00−5.59 (q, J = 9.5, 16.0 Hz, 1H), 4.58−4.46 (m, 2H), 3.56−3.31 (m, 1H), 2.51−2.47 (m, 1H), 1.79−1.66 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.6, 134.8, 133.8, 131.7 (×2), 128.0 (×2), 124.6, 122.0, 77.6, 54.2, 40.9, 20.0, 11.1 ppm; GC−MS: m/z 171.1, 129.1 (100), 141.1, 115.1, 77.1. HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{16}BrNO_3$ 325.0314; Found 325.0302.

Recycling of catalyst 2ad or 2bd

After 2 days, 50 mL ethyl ether and 20mL (0.1 (ω %)) aqueous NaOH solution were added in the reaction solution. Then the layers were separated and the aqueous phase was extracted by CH_2Cl_2 (25 mL×3), simply dried over anhydrous Na_2SO_4 and then subjected to the next run directly. And the PEG supported catalysts can be easily recovered in quantitative yields for each run.

Reactivating of the deactivation catalyst 2ad

Fresh triethylamine (1.3 eq) was added slowly to a solution of the recovered deactivation PEG-supported catalyst **2ad** (1 equiv.) in anhydrous DCM (10 mL) under N_2-atmosphere. After being stirred for 10 min, fresh chlorotrimethylsilane (2 equiv.) was added in a drop-wise manner at 0 °C. The reaction was allowed proceed with stirring at ambient temperature for a further 3 days. Subsequently, the mixture was poured into ice water followed by extraction with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and dissolved in toluene. The mixture was further precipitated with diethyl ether, filtered, and dried under vacuum to obtain the reactivated catalyst **2ad**.

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Notes and references

[a] *Catalytic Hydrogenation Research Centre, State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou, 310014, China; E-mail: chrc@zjut.edu.cn.*

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