Recoverable PEG-Supported Copper Catalyst for Highly Stereocontrolled Nitroaldol Condensation

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General. Anhydrous organic solvents were supplied by Fluka in Sureseal® bottles and used as received. EtOH was freshly distilled from Mg. All aldehydes were distilled before using. ¹H-NMR spectra were recorded on Varian 200 (200 MHz) or Varian 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuteriochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ¹³C-NMR spectra were recorded on a Varian 200 (50 MHz) or Varian 300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). Analytical high performance liquid chromatography (HPLC) was performed on a liquid chromatograph equipped with a variable wave-length UV detector (deuterium lamp 190-600 nm), using a Daicel Chiralcel™ AD, OJ and OD columns (0.46 cm I.D. x 25 cm) (Daicel Inc.). Chromatographic purification was done with 70-230 mesh aluminum oxide 90 mesh alumina or with 240-400 mesh silica gel. IR analysis were performed with a FT-IR spectrophotometer. IR spectra are expressed by wavenumber (cm⁻¹).

Synthesis of PEG-DAT2-Cu(OAc)₂ complex 5.

To a solution of PEG-DAT2 (120 mg, $\approx$ 0.02 mmol) **2** in anhydrous CH₂Cl₂ (5 mL) 4 mg of Cu(OAc)₂·4H₂O (0.02 mmol) were added and the blue solution was stirred at rt for 5h. Then the solution was concentrated and 10 mL of dry Et₂O were added with the concomitant precipitation of the copper complex. After 15 min stirring the supported complex was recovered by filtration, dried under vacuum (110 mg, yield $\approx$ 84%, pale green solid) and used in catalysis without further purification. IR (KBr): ν_{as} = 1570 cm⁻¹, ν_s = 1360 cm⁻¹.

Representative asymmetric Henry reaction with PEG-DAT2-Cu(OAc)₂.

Cu(OAc)₂ were suspended in 1 mL of anhydrous EtOH. Then, 0.2 mmol of the desired aldehyde were added, and after cooling to 0°C, 433 μ L MeNO₂ (8 mmol) were added. The clear mixture was stirred at 0°C for 40 h then the volatiles were removed under reduced pressure. The reaction products were recovered by stirring the green-yellow residue in 1.5 mL of anhydrous Et₂O that caused the precipitation of the complex. Washing of the catalyst was repeated three times with fresh Et₂O and the collected organic phases were evaporated under reduced pressure and the residue subjected to ¹H NMR and chiral HPLC analysis to determine reaction conversion (%) and ee (%) of **4**, respectively (see Table 1, SI).

Purification of the reaction crude was performed by flash chromatography (representative examples).

(S)-**4d** (*c*-Hex:EtOAc: 85:15), yield: 71%, [α]_D : -226.0 (*c* 1.7, CH₂Cl₂). (S)-**4e** (*c*-Hex:EtOAc: 80:20), yield: 75%, [α]_D : +18.0 (*c* 0.50, CH₂Cl₂); (S)-**4i** (*c*-Hex:EtOAc: 90:10), yield: 65% [α]_D : +10.8 (*c* 0.6, CH₂Cl₂).

Table 1 (SI).

4	convn (%) ^a	Column	Conditions	Retention times	ee (%)
(S)- 4a	96 (89)	OD	<i>n</i> -hex:IPA 90:10 flow 1.0 mL/min	<i>t</i> _S = 14.8 min <i>t</i> _R = 16.8 min	89
(S)- 4b	> 98 (85)	OD	<i>n</i> -hex:IPA 90:10 flow 1.0 mL/min	<i>t</i> _S = 15.8 min <i>t</i> _R = 18.2 min	88
(S)- 4c	85 (75)	AD	<i>n</i> -hex:IPA 98:2 flow 0.8 mL/min	<i>t</i> _S = 33.2 min <i>t</i> _R = 49.5 min	93
(S)- 4d	93 (71)	OD	<i>n</i> -hex:IPA 90:10 flow 0.7 mL/min	<i>t</i> _S = 28.0 min <i>t</i> _R = 30.1 min	90
(S)- 4e	95 (75)	OD	<i>n</i> -hex:IPA 80:20 flow 0.5 mL/min	<i>t</i> _S = 18.2 min <i>t</i> _R = 21.8 min	90
(S)- 4f	98 (89)	OD	<i>n</i> -hex:IPA 95:5 flow 0.5 mL/min	<i>t</i> _S = 19.1 min <i>t</i> _R = 22.8 min	92
(S)- 4g	92 (81)	OJ	<i>n</i> -hex:IPA 90:10 flow 0.5 mL/min	<i>t</i> _S = 22.5 min <i>t</i> _R = 25.3 min	84
(S)- 4h	> 98 (90)	AD	<i>n</i> -hex:IPA 97:3	<i>t</i> _S = 26.7 min	89

			flow 0.8 mL/min	$t_R = 28.2$ min	
(S)- 4i	88 (65)	AD	<i>n</i> -hex:IPA 90:10 flow 1.0 mL/min	$t_S = 16.1$ min $t_R = 20.2$ min	83

^a Isolated yields in brackets.

Representative asymmetric Henry reaction with PEG-DAT2-Cu(OAc)₂ complex (5), recovering of the catalyst.

All the reactions were carried out as described for the representative Henry reaction. After dryness, the complex was reused in consecutive runs by the addition of fresh reagents. Reaction conversion (%) and ees (%) of **4b** are listed in Table 2 SI.

Table 2 (SI).

run	convn (%) ^a	ee (%) ^b
1	97	87
2	90	84
3	95	85
4	84	84
5	75	84

^a Determined by ¹H-NMR on the reaction crude. ^b Determined by chiral HPLC (OD).

Recovering/purification/reusing of PEG-DAT2-Cu(OAc)₂ in consecutive asymmetric Henry reactions with different aldehydes.

All the reactions were carried out as described for the representative Henry reaction. No evidence of contamination by previously employed substrates were observed in the experiments by NMR analysis of each reaction crudes (Figure 1, SI).

Figure 1 (SI)

Compound **4a**

Compound **4a**

Compound **4f**

Compound **4f**

Compound **4g**

Compound **4g**

Compound **4h**

Compound 4h

3,5-dimethoxybenzoic acid
Pulse Sequence: zgpg30
Solvent: CDCl3
Ambient temperature
QNP1H-200 90min1200"

Relax. delay 1.000 sec
Pulse 32.0 degrees
Acq. time 1.458 sec
Width 12500.0 Hz
13032 repetitions
OBSERVE C13 50.2637558 MHz
DECUPLE H1 189.8760755 MHz
Power 30 dB
CONTINUOUSLY ON
WALTZ16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 073 hr, 24 min, 8 sec

Compound 4i

Compound **4i**

OD 90:10 0.7 o-NO2 racemo

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Injection Date : 11/04/2007 12.30.00
Sample Name : 856-NO2 Location : -
Acq. Operator : riccardo
Acq. Instrument : HPLC Nuovo Inj Volume : Manually
Acq. Method : C:\MSDCHEM\2\METHODS\EASMAN.M
Last changed : 11/04/2007 12.10.20 by riccardo
(modified after loading)
Analysis Method : C:\MSDCHEM\1\METHODS\DEF_LC.M
Last changed : 13/04/2007 0.07.58
(modified after loading)

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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=220.4 Ref=450.80 (HPLC_H-1\O-NITR-1.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.012	MF	1.3716	3392.15405	41.21991	7.6359
2	30.185	FM	1.9404	4.10317e4	352.42648	92.3641

Totals : 4.44239e4 393.64639

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=214,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.833	MM	0.6652	341.22321	8.54985	5.6301
2	16.839	MM	0.8882	5719.44189	107.32034	94.3699

Totals : 6060.66510 115.87019

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.862	MM	0.7414	6009.51758	135.09457	6.1710
2	18.116	MM	1.0294	9.13741e4	1479.45313	93.8290

Totals : 9.73836e4 1614.54770

Compound 3c

Data File C:\HPCHEM\1\DATA\HENRYA-1\RS07T4-1.D Sample Name: rs07t4
rs07t1 98/2 0.7

Injection Date : 16/04/2007 11.10.48 Location : -
Sample Name : rs07t4
Acq. Operator : riccardo
Acq. Instrument : HPLC Nuovo Inj Volume : Manually
Acq. Method : C:\HPCHEM\1\METHODS\RIK.M
Last changed : 16/04/2007 11.09.04 by riccardo
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\DEF_LC.M
Last changed : 16/04/2007 10.14.59
(modified after loading)

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=215,4 Ref=450,80 (HENRYA-1\RS22_O-1.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.699	MM	0.8872	31.69621	1.00788	9.2940
2	49.467	SV	1.0337	876.37872	11.40748	86.6640
Totals :				1010.07194	12.41550	

Data File C:\HPCHEM\1\DATA\HPLC_H-1\RSO-NI-1.D Sample Name: rs2nitro4
CD 93.5/6.5 0.8

Injection Date : 17/04/2007 16.54.42 Location : -
Sample Name : rs2nitro4
Acq. Operator : riccardo
Acq. Instrument : HPLC Vecchio Inj Volume : Manually
Acq. Method : C:\HPCHEM\1\METHODS\RIK.M
Last changed : 17/04/2007 16.38.55 by riccardo
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\DEF_LC.M
Last changed : 18/04/2007 0.55.12
(modified after loading)

Compound 4d

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=450,80 (HPLC_H-1\RSO-NI-2.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.570	VV	1.0533	3022.77930	33.99657	5.2938
2	37.033	VB	1.5621	5.40778e4	408.90488	94.7062
Totals :				5.71006e4	442.90144	

OD 80:20 0.5 p-Cl racemo

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Injection Date	: 11/04/2007 11.01.03	Location	: -
Sample Name	: RSp-Cl		
Acq. Operator	: riccardo		
Acq. Instrument	: HPLC Nuovo	Inj Volume	: Manually
Acq. Method	: C:\HPCHEM\2\METHODS\EASWAR.M		
Last changed	: 11/04/2007 10.31.37 by marco b		
	(modified after loading)		
Analysis Method	: C:\HPCHEM\1\METHODS\DEF_LC.M		
Last changed	: 12/04/2007 23.49.01		
	(modified after loading)		

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Compound 4e

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=450,80 (HPLC_H-1\F-CLOR-3.D)
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.874	NM	0.8567	2502.65796	48.68826	5.0840
2	21.091	NM	1.0429	4.67236e4	746.72302	94.9160

Totals : 4.92263e4 795.41129

Signal 2: DAD1 A, Sig=214,4 Ref=450,80 (HPLC_H-1\F-CLRA-1.D)

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.123	MM	0.6922	859.77039	20.70215	3.9040
2	21.864	MM	1.0217	2.11631e4	345.23538	96.0960

Totals : 2.20228e4 365.93753

Results obtained with enhanced integrator!

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=214,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.511	MM	0.5354	164.98131	5.13547	8.6445
2	25.324	MM	0.7090	1743.54004	40.98508	91.3555

Totals : 1908.52135 46.12055

Results obtained with enhanced integrator!

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=208,4 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.682	MM	0.4688	4532.63525	118.37311	5.5313
2	28.201	MM	1.1592	7.74123e4	1112.98816	94.4687

Totals : 8.19449e4 1231.36127

Results obtained with enhanced integrator!

rs100 90.10 1.0

Injection Date : 16/04/2007 13.30.26
 Sample Name : rs100 Location : -
 Acq. Operator : riccardo
 Acq. Instrument : HPLC Nuovo Inj Volume : Manually
 Acq. Method : C:\HPCHEM\2\METHODS\RIK.M
 Last changed : 16/04/2007 13.24.09 by riccardo
 (modified after loading)
 Analysis Method : C:\HPCHEM\1\METHODS\DEF_LC.M
 Last changed : 10/04/2007 1.05.52
 (modified after loading)

Compound 4i

Area Percent Report

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 A, Sig=214.4 Ref=450.00 (HPLC_H-1\RS35DI-1.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.087	BB	0.7100	6776.36279	122.99148	91.2905
2	20.254	BB	1.0237	646.49561	10.52504	8.7095

Totals : 7422.85840 133.51652