Supporting Information for:

Palladium-Catalyzed Synthesis of 4-Cyclohexylmorpholines from Reductive Coupling of Aryl Ethers and Lignin Model Compounds with Morpholines

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Experimental Section

Materials. Benzyl phenyl ether (>98%), morpholine (99%), cyclohexanol (>98.5%), ruthenium on carbon (Ru/C, 5 wt% Ru, reduced, nominally 50% water wet), phenethoxybenzene (98%), and *m*-xylene (>99%) were purchased from Aladdin. Phenol (99.5%), n-dodecane (99.5%), and cyclohexanone (99%) were achieved from TCI. Methylmorpholine (97%), 2,2-dimethylmorpholine (97%), (R)-3methylmorpholine (97%), and (S)-3-methylmorpholine (97%) were purchased from ARK. cis-2,6-Dimethylmorpholine (97%) was achieved from Alfa. Palladium on carbon (Pd/C, 10 wt% Pd, reduced, anhydrous), platinum on carbon (Pt/C, 10 wt% Pt, reduced, anhydrous), and palladium(II) 2,4-pentanedionate (34.7% Pd) were purchased from Innochem. Ethanol (99.9%) was obtained from Sinopharm. 2-Ethylmorpholine (97%) was purchased from Leyan. The compounds of 1b-11 were synthesized according to the literatures.^{1,2}

Instruments. Conversion and yields were determined by a gas chromatography (Agilent 7890B) with the FID detector and a HP-5 column ($30 \text{ m x } 320 \text{ }\mu\text{m } \text{ x } 0.25 \text{ }\mu\text{m}$). NMR data were recorded on a Bruker ARX 100 and Bruker ARX 400 spectrometers. High resolution transmission electron microscopy (HRTEM) was conducted on a Tecnai G2 F30 FETEM (FEI Corp.).

General procedures to conduct the reaction. The general procedure for the reaction of benzyl phenyl ether (1) with morpholine can be described as follows. In a 15 mL stainless steel reactor with a Teflon coating, the catalyst Pd/C (3 mol% Pd metal based on 1), aryl ether (1 mmol), morpholine (1.5 mmol), and *m*-xylene (3.5 mL) were combined and a magnetic stirring bar was added. The autoclave (15 mL) was purged three times with H₂ (1 MPa) and was then pressurized to the desired pressure with H₂. The autoclave was placed into an a constant-temperature air bath and heated to the desired temperature, and the reactions were stirred at 800 rpm for the desired reaction time. After the reaction, the products were analyzed quantitatively using *n*-dodecane as the internal standard by gas chromatography (GC) and gas chromatography coupled with mass spectroscopy (GC-MS).

General procedure for recycling experiment. To test the recyclability of Pd/C, the catalyst was separated from the reaction system by filtration, washed with ethanol for 4 times, and then dried under oven at 60 °C for 10 h. The sample was collected and

transferred into a ceramic boat, then moved to a tubular furnace for reduction under H_2/Ar atmosphere (containing 90% Ar) with a flow rate of 100 mL/min. The sample was heated with a heating rate of 10 °C min⁻¹ from room temperature to 250 °C and held at this temperature for 5 h. Afterwards, the tubular furnace was cooled down to room temperature. Finally, the catalyst was used in the next catalytic cycle.



Scheme S1. Activity of Ru/C for several control experiments.



Figure S1. (a) The original Pd/C, and (b) the recycled Pd/C after three cycles (6 h).



Scheme S2. Hydrogenation of toluene.

R1	$R_2 + R_3 + R_3 + R_4$	Pd/C H_2 R_1 N R_4 +	+	R_2
	1a-11 2a-2g n ₁ = 1 or 2	3a-3j	n ₂ = 0 or 1	n ₂ = 0 or 1
Entry	Substrates	Yield	of major Produ	icts ^b
1°	2f	(86.1)	(87.6)	(13.4)
2°	2g	(85.9)	(86.0)	(14.0)
3 ^d		n (>99.0)	(90.0)	(<u>9.2</u>)
4 ^d		1i (99.0)	(77.0)	(22.0)
5 ^d	John 1j	(84.7)	(67.0)	(17.6)
6 ^d		× (96.5)	(73.5)	(23.5)
7 ^e		(39.4)	(26.5)	(8.7)
8 ^e		(35.0)	(21.4)	((3.4)

Table S1. Pd-catalyzed reductive coupling of morpholine with benzyl aryl ethers.^a

^aReaction conditions: 1, 1.0 mmol; 2, 1.5 mmol; catalyst, 3 mol% metal based on 1; *m*-xylene, 3.5 mL; H₂ pressure, 1 MPa. The aromatic ether of entry 1 and 2 was benzyl phenyl ether. The amine used in entries 3-8 was morpholine. ^bThe yield were determined by GC using dodecane as a standard. ^cReaction temperature, 120 ^oC; reaction time,12 h. ^dCatalyst, 6 mol% metal based on 1, reaction temperature, 150 ^oC; H₂ pressure, 3 MPa; reaction time 12 h. ^cCatalyst, 9 mol% metal based on 1, reaction temperature, 170 ^oC; H₂ pressure, 3 MPa; reaction time, 24 h.

Copies of ¹H NMR and ¹³C NMR



¹H and ¹³C NMR spectra of compound 1b

¹H and ¹³C NMR spectra of compound 1c



¹H and ¹³C NMR spectra of compound 1d



¹H and ¹³C NMR spectra of compound 1e



¹H and ¹³C NMR spectra of compound 1f



¹H and ¹³C NMR spectra of compound 1g



¹H and ¹³C NMR spectra of compound 1h



¹H and ¹³C NMR spectra of compound 1i



¹H and ¹³C NMR spectra of compound 1j



¹H and ¹³C NMR spectra of compound 1k







¹H and ¹³C NMR spectra of compound 3b







¹H and ¹³C NMR spectra of compound 3d





¹H and ¹³C NMR spectra of compound 3e









HR-MS data

HR-MS for compound 3a



HRMS (ESI): Calcd for C₁₀H₂₀NO [M+H]⁺: 170.1545; Found: 170.1532.

Elemental Composition Report

Single Mass Analysis Tolerance = 500.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off

Monoisotopic Mass, Even Electron Ions 1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 10-10 H: 11-25 N: 1-1 O: 1-1 Na: 0-1 ZBX-1 89 (1.766) 1: TOF MS ES+ 1.88e+003 170.1532 100-% 171.1671 0-160 -1.5 50.0 Minimum: 500.0 10.0 Maximum: mDa PPM Mass Calc. Mass DBE Formula -1.3 -7.6 170.1532 170.1545 1.5 C10 H20 N O

HR-MS for compound 3b



HRMS (ESI): Calcd for $C_{11}H_{22}NO \ [M+H]^+$: 184.1701; Found: 184.1711.

Single Mas Tolerance = Element pre	ss Analysis 500.0 mDa / DE diction: Off	3E: min = -1	1.5, max =	50.0	
Monoisotopic 4 formula(e) e Elements Use C: 11-11 H ZBX-1-0803 12 1: TOF MS ES	Mass, Even Electro evaluated with 1 resu ed: 1: 12-25 N: 1-1 0 (2.352) +	n Ions ults within Iim O: 1-3 Na	nits (up to 50 a: 0-1) closest re	esults for each mass)
100				184.	.1711
			.*		185.1757
155.0) 160.0 165.0	170.0	175.0	180.0	185.0 190.0 195.0 200.0 205.0 210.0 215.0
Minimum: Maximum:		500.0	10.0	-1.5 50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
184.1711	184.1701	1.0	5.4	1.5	C11 H22 N O

HR-MS for compound 3c



HRMS (ESI): Calcd for C₁₂H₂₄NO [M+H]⁺: 198.1858; Found: 198.1841.



HR-MS for compound 3d



HRMS (ESI): Calcd for $C_{12}H_{24}NO \ [M+H]^+$: 198.1858; Found: 198.1841.

Single Mas Tolerance = Element pre	500.0 m	ysis Da / D Off	BE: min	= -1.5, max =	50.0						
Monoisotopic 4 formula(e) e Elements Use C: 12-12 H ZBX-3-0803 10 1: TOF MS ES	Mass, Ev evaluated ed: 1: 12-25 2 (2.006) +	ven Electro with 1 res N: 1-1	on lons sults withir O: 1-3	n limits (up to 50 Na: 0-1	D closest res	ults for each i	mass)				2 024±003
100			198.1	199.2003							2.0201000
0-1	170	180	190 2	00 210	220 23	0 240	250	260 27	0 280	290	300 m/z
Minimum: Maximum:			500.0	10.0	-1.5 50.0						
Mass	Calc.	Mass	mDa	PPM	DBE	Formula					
198.1841	198.18	58	-1.7	-8.6	1.5	C12 H24	N O				

HR-MS for compound 3e



HRMS (ESI): Calcd for $C_{12}H_{24}NO \ [M+H]^+$: 198.1858; Found: 198.1841.

Single Mas Tolerance = Element pre	s s Analysis 500.0 mDa / DE diction: Off	8E: min = -1	.5, max =	50.0	
Monoisotopic 4 formula(e) e Elements Use C: 12-12 H ZBX-4-0803 11 1: TOF MS ES	Mass, Even Electror evaluated with 1 resu ed: I: 12-25 N: 1-1 1 (2.179) +	n lons lts within lim O: 1-3 Na	nits (up to 50 a: 0-1	I closest res	sults for each mass)
100	198.1841				2.256+003
0-1	199.1951 199.1951 199.1951	بسرسرسر 260 280	300 320		րոփարարարարարարարարարարարարարարարարարարա
Minimum: Maximum:		500.0	10.0	-1.5 50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
198.1841	198.1858	-1.7	-8.6	1.5	C12 H24 N O

HR-MS for compound 3f1



(cis/trans = 1 : 17: 0.25)

HRMS (ESI): Calcd for $C_{11}H_{22}NO \ [M+H]^+$: 184.1701; Found: 184.1711.

Single Mas Tolerance = Element pred	s Analysis 500.0 mDa / D diction: Off	BE: min = -1	l.5, max = 5	50.0	
Monoisotopic 4 formula(e) e Elements Use C: 11-11 H ZBX-5-0803 92 1: TOF MS ES+	Mass, Even Electro valuated with 1 res d: : 12-25 N: 1-1 (1.817)	on lons ults within lim O: 1-3 Na	iits (up to 50 a: 0-1	closest resu	lits for each mass)
		184.1711 185.17 185.17 180 185 19	57 11-1 - 195 - 200	205 210	21.100.000 215 220 225 230 235 240 245 250 255 260 265 270
Minimum: Maximum:		500.0	10.0	-1.5 50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
184.1711	184.1701	1.0	5.4	1.5	C11 H22 N O

HR-MS for compound 3f₂



(cis/trans = 1:12.2)

HRMS (ESI): Calcd for $C_{11}H_{22}NO \ [M+H]^+$: 184.1701; Found: 184.1711.

Single Ma Tolerance Element pr	ass Analysis = 500.0 mDa / E rediction: Off)BE: min = -	1.5, max = {	50.0	
Monoisotop 4 formula(e Elements U C: 11- <mark>1</mark> 1	ic Mass, Even Electr) evaluated with 1 res sed: H: 12-25 N: 1-1	on lons sults within lir O: 1-3 N	nits (up to 50 a: 0-1	closest res	ults for each mass)
ZBX-6-0803 9 1: TOF MS E	92 (1.817) :S+				0.450.000
100		184.1711			2.156+00.
%		185.1	757 1 		······································
155 ·	160 165 170 175	180 185 19	90 195 200	205 210	215 220 225 230 235 240 245 250 255 260 265 270
Maximum:		500.0	10.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
184.1711	184.1701	1.0	5.4	1.5	C11 H22 N O

HR-MS for compound 3g



(cis/trans = 2.7:1)

HRMS (ESI): Calcd for $C_{11}H_{22}NO \ [M+H]^+$: 184.1701; Found: 184.1711.

Single Mas Tolerance = Element pred	s Analysis 500.0 mDa / DB diction: Off	E: min = -1	.5, max = 5	50.0	
Monoisotopic 1 formula(e) e Elements Use C: 11-11 H ZBX-2 17 (0.36 1: TOF MS ES-	Mass, Even Electror valuated with 1 resu d: : 11-25 N: 1-1 5)	n Ions Its within Iim O: 1-1 Na	its (up to 50 a: 0-1	closest resu	ults for each mass)
100 184 	L1711				0.3287002
- - 0	185.1807 185.200 200 220 240	260 280	300 320	340 360 3	ngangangangangangangangangangangangangan
Minimum: Maximum:		500.0	10.0	-1.5 50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
184.1711	184.1701	1.0	5.4	1.5	C11 H22 N O

HR-MS for compound 3h



(cis/trans = 1.1 : 1)

HRMS (ESI): Calcd for C₁₁H₂₂NO₂ [M+H]⁺: 200.1651; Found: 200.1670

Elemental Composition Report

Single Mass Analysis Tolerance = 500.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off

Monoisotopic Mass, Even Electron Ions 9 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 11-11 H: 11-25 N: 1-2 O: 2-4 Na: 0-1

ZBX-3 18 (0.382) 1: TOF MS ES+



HR-MS for compound 3i



(cis/trans = 3.5 : 0.2 : 1 : 0.6)

HRMS (ESI): Calcd for $C_{12}H_{24}NO \ [M+H]^+$: 198.1858; Found: 198.1841.

Single Ma Tolerance = Element pr	Single Mass Analysis Folerance = 500.0 mDa / DBE: min = -1.5, max = 50.0 Element prediction: Off								
Monoisotopi 1 formula(e) Elements Us C: 12-12 ZBX-4 19 (0.3 1: TOF MS E	ic Mass, Even Electror evaluated with 1 resu sed: H: 11-25 N: 1-1 ³⁹⁹⁾ S+	n Ions lits within Iim O: 1-1 Na	its (up to 50 a: 0-1	closest resu	ults for each mass)				
100 - - - - - - -	198.1841				1.53e+003				
0	180 200 220 240	260 280	300 320	340 360	ngnagangangangangangangangangangangangan				
Minimum: Maximum:		500.0	10.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	Formula				
198.1841	198.1858	-1.7	-8.6	1.5	C12 H24 N O				

HR-MS for compound 3j



(cis/trans = 1 : 0.7 : 2.1 : 0.5)

HRMS (ESI): Calcd for C₁₂H₂₄NO [M+H]⁺: 198.1858; Found: 198.1841.



Reference:

- (1) W. B. Wu and J. M. Huang, J. Org. Chem., 2014, 79, 10189-10195.
- (2) A. S. Singh, S. S. Shendage and J. M. Nagarkar, *Tetrahedron Lett.*, 2014, 55, 7243-7246.