

Hitchhiker's guide to reductive amination

A comparative study of various widely used methods of reductive amination

Evgeniya Podyacheva^a

Oleg I. Afanasyev^a

Alexey A. Tsygankov^a

Maria Makarova^{a,b}

Denis Chusov^{*a,c,d}

^a Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, Vavilova 28, Moscow 119991, Russian Federation

^b Dmitry Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, Moscow 125047, Russian Federation

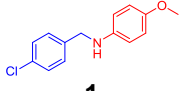
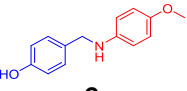
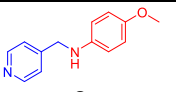
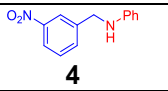
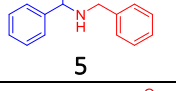

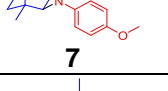
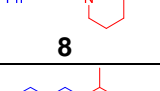

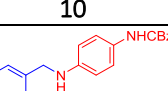
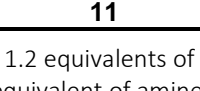
^c Peoples' Friendship University of Russia, 6 Miklukho-Maklaya Street, Moscow 117198, Russian Federation

^d Moscow Institute of Physics and Technology, 9 Institutskiy per., Dolgoprudny, Moscow Region, 141700, Russian Federation

DOI: [10.1055/s-0037-1611788](https://doi.org/10.1055/s-0037-1611788)

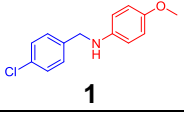
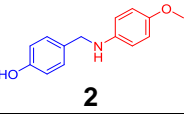
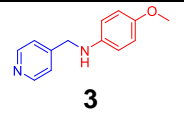
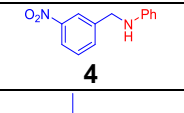
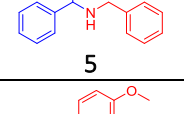
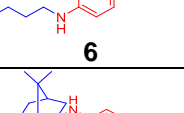
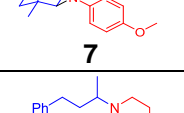
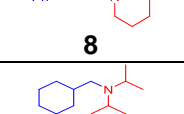
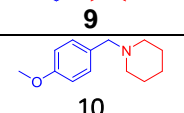
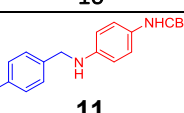
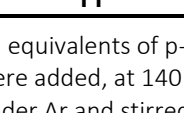
Featured at: <https://www.organic-chemistry.org/synthesis/C1N/amines/reductiveamination.shtm>

Table 1 Reductive amination using unified procedure for every reducing agent

	$\text{R}^1-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^2 + \text{R}^3-\overset{\text{H}}{\text{N}}-\text{R}^4 \xrightarrow[\text{solvent}]{\text{reducing agent}} \text{R}^1-\overset{\text{R}^3}{\underset{\text{R}^2}{\text{N}}}-\text{R}^4$				
Product	Rh/CO ^a	NaBH ₄ ^b	NaBH(OAc) ₃ ^c	NaBH ₃ CN ^d	H ₂ /Pd ^e
 1	94%	94%	99%	93%	0%
 2	84%	96%	93%	82%	0%
 3	89%	92%	83%	92%	11%
 4	86%	10%	75%	>99%	0%
 5	85%	32%	58-74% ^f	23%	0%
 6	21-25% ^f	27%	52-66% ^f	33%	61%
 7	8%	0%	0%	0%	0%
 8	>99%	0%	13%	6%	0%
 9	18%	<1%	29%	0%	0%
 10	98%	14%	84%	57%	64%
 11	60%	40%	60%	87-92% ^f	0%

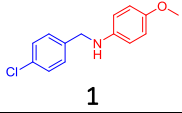
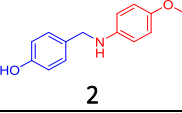
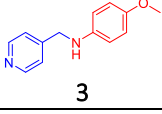
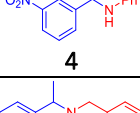
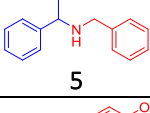
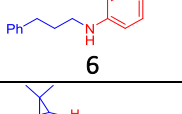
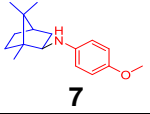
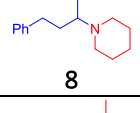
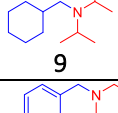
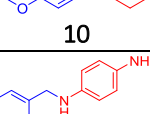
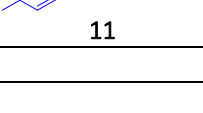
^a 1.2 equivalents of amine, 1 equivalent of carbonyl compound, 0.7 mol % Rh₂(OAc)₄, THF, 120 °C, 22 h, 50 atm. ^b 1 equivalent of amine, 1.2 equivalents of carbonyl compound, MeOH were refluxed for 2 h. Then 2 equivalents of NaBH₄ were added and reaction mixture was stirred at RT overnight. After that it was refluxed for 2 h. ^c 1 equivalent of amine, 1 equivalent of carbonyl compound, 1.4 equivalents NaBH(OAc)₃, DCE were stirred at RT for 18 h under Ar. ^d 1 equivalent of amine, 1 equivalent of AcOH, MeOH were stirred. Then 1 equivalents of carbonyl compound and 2 equivalents NaBH₃CN in 1 ml of methanol were added. Reaction mixture was stirred for 24 h. ^e 1 equivalent of amine, 1 equivalent of carbonyl compound, 5% (10% Pd/C), EtOH, 40 °C, 24 h, 5 atm H₂. ^f The range of yields is pointed out for several experiments.

Table 2 Optimization of reductive amination

$R^1-C(=O)-R^2 + R^3-NH-R^4 \xrightarrow[\text{solvent}]{\text{reducing agent}} R^1-CH_2-NH-R^4$		yields were more than 60% in table 1			
Product	Rh/CO ^{a,b,c}	NaBH ₄ + Ti(Oi-Pr) ₄ ^d or TiCl ₄ ^e	NaBH(OAc) ₃ + AcOH ^f or Ti(Oi-Pr) ₄ ^d	NaBH ₃ CN + Ti(Oi-Pr) ₄ ^d	H ₂ /Pd ⁱ
 1	✓	✓	✓	✓	0% ⁱ
 2	✓	✓	✓	✓	48% ⁱ
 3	✓	✓	✓	✓	41% ⁱ
 4	✓	77% ^d	✓	✓	0% ⁱ
 5	✓	>99% ^d	69% ^f	65% ^d	0% ⁱ
 6	40% ^a	>99% ^d	✓	>99% ^d	✓
 7	69% ^b	0% ^d	0% ^f 0% ^d	0% ^d	0% ⁱ
 8	✓	8% ^e	54% ^g	71% ^d	40% ⁱ
 9	63% ^c	16% ^e	60-71% ^h	27% ^d	17% ⁱ
 10	✓	30% ^d	✓	79% ^d	✓
 11	✓	40%	✓	✓	4% ⁱ

^a 2 equivalents of p-anisidine were added, 160 °C for 22 h in toluene; ^b 160 °C for 48 h in THF; ^c 5 equivalents of (*i*-Pr)₂NH were added, at 140 °C for 2 h in THF; ^d carbonyl compound, amine and Ti(Oi-Pr)₄ were placed into dry Schlenk glassware under Ar and stirred in dry THF for 3 h. Then THF was evaporated under reduced pressure and the corresponding reducing agent NaBH₄, NaBH(OAc)₃ or NaBH₃CN was added with the same solvent as in unified procedure for that. Time and temperature of reduction were used the same as in unified procedure for every reducing agent; ^e Under these conditions instead of 2 equivalents of Ti(Oi-Pr)₄ 0.5 equivalent of TiCl₄ were used in comparison to ^d; ^f 1 equivalent of AcOH was added to amine, carbonyl compound and NaBH(OAc)₃. Reaction time was 22 h; ^g preparation of this substrate was conducted the same as according to unified procedure but during 48 h; ^h preparation of this substrate was conducted at room temperature for 8 h using 10 mmol of reagents and 14 mmol of NaBH(OAc)₃; ⁱ carbonyl compound, amine and 1% of (10% Pd/C) were premixed and stirred overnight. Then H₂ (3 atm) was charged and reaction mixture was stirred for 24 h

Table 3 Reaction mass efficiency

$\text{R}^1\text{C}(=\text{O})\text{R}^2 + \text{R}^3\text{N}(\text{H})\text{R}^4 + \text{reducing agent} + \text{solvent} \longrightarrow \text{R}^1\text{C}(\text{R}^2)\text{N}(\text{R}^3)\text{R}^4 + \text{by-products}$						
	Product	Rh/CO	NaBH ₄	NaBH(OAc) ₃	NaBH ₃ CN	H ₂ /Pd
	 1	77%	63%	44%	51%	0%
	 2	75%	64%	39%	44%	42% ^b
	 3	67%	62%	34%	47%	34% ^b
	 4	67%	21% ^a	34%	55%	0%
	 5	72%	24% ^a	23%	15% ^a	0%
RME, %	 6	19%	26% ^a	23%	25%	39%
	 7	65%	0%	0%	0%	0%
	 8	76%	0%	12% ^a	17% ^a	34%
	 9	75%	9%	33%	29%	38%
	 10	47%	0%	13% ^a	6% ^a	3% ^b
	 11	61%	30%	31%	55%	0%
	Average RME	64%	27%	25%	31%	17%
	Generalized RME*	14.3%	0.55%	4.11%	0.99%	0.78%

^a Procedure with Ti(Oi-Pr)₄
^b 1% (10% Pd/C), 5 atm H₂, RT

* Solvents are taken into account in the calculation