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Hitchhiker's Guide to Reductive Amination

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Abstract A comparative study of various widely used methods of reductive amination is reported. Specifically, such reducing agents as H₂, Pd/C, hydride reagents [NaBH₄, NaBH₃CN, NaBH(OAc)₃], and CO/Rh₂(OAc)₄ system were considered. For understanding the selectivity and activity of the reducing agents reviewed herein, different classes of starting materials were tested, including aliphatic and aromatic amines, as well as aliphatic and aromatic aldehydes and ketones. Most important advantages and drawbacks of the methods, such as selectivity of the target amine formation and toxicity of the reducing agents were considered from the viewpoint of green chemistry.

Key words reductive amination, selectivity, atom efficiency, borohydride, hydrogen, palladium, carbon monoxide

Introduction

Reductive amination is one of the most versatile and useful approaches for the preparation of amines in chemical and biological systems.^{1,2} The present work focuses on comparison of the most widespread and powerful reducing agents such as H_2/Pd , NaBH₄, NaBH₃CN, NaBH(OAc)₃,^{3–5} and CO/Rh^{6–8} system. Here we consider important chemical fea-



tures of these reducing agents both for laboratory practice and industry. The convenience of NaBH₄, NaBH(OAc)₃, and NaBH₃CN is in their physical solid state, these reagents are relatively easy to handle and very convenient for smallscale laboratory synthesis. In comparison to NaBH₄, less active NaBH(OAc)₃ and NaBH₃CN are known to be much more selective and tolerant to potentially reducible functional groups, which make the use of them very attractive for the late-stage modification of complex molecules. According to common belief given in the textbooks9 mild reagents NaBH₃CN and NaBH(OAc)₃ reduce rapidly iminium ions while carbonyl compounds are not affected (Scheme 1). However, possible releasing of boranes and hydrogen and sensitivity to moisture and air are shortcomings of NaBH(OAc)₃, NaBH₃CN, and NaBH₄. Moreover, sodium cyanoborohydride reductions require specialized disposal of highly toxic reaction by-products, for example, HCN.

The important value for chemical industry is the concept of atom economy¹⁰ and minimization of material and energy wastes. In an ideal chemical process, all atoms of the starting material are converted into the atoms of the target products. In this context, borohydrides are far from ideal reducing agents, while reductions with H₂ gas clearly fit atom economical principle. But, H₂ has another problem – low



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selectivity. System H₂, Pd/C can launch side reductions of other reducible functional groups and hydrogenolysis in addition to reductive amination. Besides, with regard to formation of wastes, it is necessary to consider the handling of not only the reaction itself but also the production of the reducing agents. In the case of H₂, steam methane reforming is used to produce it from natural gas, which requires two steps, high temperatures (750–800 °C), and separation of gas mixture. Borohydride-based reducing agents require even more labor-intensive manufacturing, which produces lots of wastes.

Carbon monoxide is a waste of metallurgy,^{11,12} so it has very low prime cost, although it requires separation of gas mixture and additional purification. The main advantage of CO/Rh system is lack of external hydrogen source, which provides unique selectivity for this approach. CO promoted by Rh-catalyst works both as a reducing agent and scavenger of the oxygen atom. In this case, the only by-product is carbon dioxide. Thus, after releasing of gases, almost no purification might be needed. The large drawback of carbon monoxide is toxicity and flammability of this agent. However, toxicity of CO is not as high as it is generally thought. Important physical and chemical characteristics of the reducing agents are set out in Table 1.

Results and Discussion

Although there are plenty of works in which reductions with chosen agents are reported,¹³⁻¹⁵ there is no unified reductive amination procedure for all types of carbonyl compounds and amines. Conditions such as solvent,¹⁶⁻²¹ temperature,^{22,23} and reaction time²⁴⁻²⁶ can vary. Besides, some additives are sometimes used in the processes: titanium isopropoxide and other Lewis acids for NaBH₄,^{27,28} AcOH, 3Å and 4Å molecular sieves for NaBH(OAc)₃,^{24,29,30} HCl and CF₃-CO₂H for NaBH₃CN,^{4,5,31} and AcOH for H₂/Pd.¹⁷ Thus, the first goal of this work is to investigate the applicability of equal conditions for reductive amination of different challenging substrates for every chosen reducing agent and identify the problems that will appear. Results are shown in Table 2. The second aim is to point out possible ways to optimize reaction conditions for those compounds, which would not be obtained in more than 60% yield (Table 3).

Reductive Amination with H₂/Pd

In the case of reduction with H_2/Pd , several factors made it impossible to obtain most of the target amines in good yields. First, there is a side reduction of starting carbonyl compounds. Second, reduction of potentially reducible functional groups, for example, NO₂ and Cl, proceeded.



^a Extraction causes additional wastes of organic solvents.

^b Sigma-Aldrich, Safety Data Sheet.

^c Reducing agent does not react with water.

^d NaBH₄, NaBH(OAc)₃, and NaBH₃CN are decomposed in contact with large amounts of H₂O.

 $^{\circ}$ LD50 (Oral-Rat) = 162 mg/kg. Sigma-Aldrich, Material Safety Data Sheet, Mutagenic activity of emitted product B₂H₆.

^f LD50 (Oral-Rat) = 2000.0 mg/kg. Sigma-Aldrich, Safety Data Sheet.

^g Toxic compound, but no available LD50 data. Sigma-Aldrich, Safety Data Sheet.

^h LC50 (Inhalation-Rat) = 3760 ppm/h. Treatment continued for 14 h. Linde Gas North America LLC, Material Safety Data Sheet.

ⁱ The price of the reagent/catalyst per mol product in case of 100% yield. For details, see Supporting Information.

Third, hydrogenolysis of compounds with Bn and Cbz groups occurred under H_2 , Pd/C system. Thus, aromatic aldehydes might be a problem for reductive amination process using H_2/Pd .

Though H_2 , Pd/C showed the worst efficiency and selectivity for selected substrates even at room temperature and low pressure, it is notable that the reaction between 3phenylpropanal and anisidine proceeded better (61%) than with other reducing agents. Similar result was obtained for 4-methoxybenzaldehyde and piperidine (64%). Other compounds were prepared in 0–11% yields (Table 2). To prevent the problem of reduction of starting material, we decided first to mix carbonyl compounds, amines, and Pd/C without H₂ for possible formation of Schiff base. Addition of H₂ after preparation of imine should cause its reduction. Besides we decreased the process temperature down to room temperature to reduce probability of other side reactions. After this optimization, we obtained products **2**, **3**, and **8** in 40–48% yields (Table 3). However, NO₂ group was reduced again in the reaction of 3-nitrobenzaldehyde with aniline. Besides, the yields of products **6** and **10** decreased under mild conditions. Selectivity of reductive amination with H₂ could be improved through use of poisoned Pd/CaCO₃³² catalyst or other more selective catalysts,^{33,34} but our aim was to carry out reductive amination by means of the simplest, commercially available reagents.



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Table 2 (continued)



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^a Amine (1.2 equiv), carbonyl compound (1 equiv), Rh₂(OAc)₄ (0.7 mol%), THF, 120 °C, 22 h, 50 atm. ^b Amine (1 equiv), carbonyl compound (1.2 equiv), and MeOH were refluxed for 2 h. Then 2 equiv of NaBH₄ were added and the reaction mixture was stirred at r.t. overnight. After that it was refluxed for 2 h.

^c Amine (1 equiv), carbonyl compound (1 equiv), NaBH(OAc)₃ (1.4 equiv), and DCE were stirred at r.t. for 18 h under argon. ^d Amine (1 equiv), AcOH (1 equiv), and MeOH were stirred. Then, carbonyl compound (1 equiv) and NaBH₃CN (2 equiv) in MeOH (1 mL) were added and the reaction mixture was stirred for 24 h.

^e Amine (1 equiv), carbonyl compound (1 equiv), 10% Pd/C (5 mol%), EtOH, 40 °C, 24 h, 5 atm H₂.

^f The range of yields is pointed out for several experiments.

Table 3 Optimization of Reductive Amination



Product	Rh/CO ^{a,b,c}	$NaBH_4 + Ti(Oi-Pr)_4^d \text{ or } TiCl_4^e$	NaBH(OAc) ₃ + AcOH ^f or Ti(O <i>i</i> -Pr) ₄ ^d	$NaBH_3CN + Ti(Oi-Pr)_4^d$	H_2/Pd^9
	1	*	*	*	0% ^g
HO 2	1	4	4	1	48% ^g
A A A A A A A A A A A A A A A A A A A	1	*	4	*	41% ^g
O ₂ N H Ph	1	77% ^d	4	1	0%a

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Table 3 (continued)

Product	Rh/CO ^{a,b,c}	NaBH ₄ + Ti(O <i>i</i> -Pr) ₄ ^d or TiCl ₄ ^e	NaBH(OAc) ₃ + AcOH ^f or Ti(O <i>i</i> -Pr) ₄ ^d	NaBH ₃ CN + Ti(O <i>i</i> -Pr) ₄ ^d	H_2/Pd^9
	4	>99% ^d	69% ^f	65% ^d	0%ª
Ph N H 6	40%ª	>99% ^d	4	>99%d	1
The second secon	69% ^b	0% ^d	0% ^f 0% ^d	0% ^d	0%ª
Ph N	4	8% ^e	54% ^h	71% ^d	40% ^g
	63% ^c	16% ^e	60–71% ⁱ	27% ^d	17% ^g
	1	30% ^d	4	79% ^d	1
NHCBz H 11	4	40%	4	4	4% ^g

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^a Two equiv of *p*-anisidine were added. Reaction conditions: 160 °C for 22 h in toluene.

^b Reaction conditions: 160 °C for 48 h in THF.

^c Five equiv of *i*-Pr₂NH were added. Reaction conditions: 140 °C for 2 h in THF.

^d Carbonyl compound, amine, and Ti(Oi-Pr)₄ and anhydrous THF were placed in a dry Schlenk glassware under argon and stirred 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 the unified procedure. Same time and temperature for reduction were used as in the unified procedure for every reducing agent.

e Under these conditions instead of 2 equiv of Ti(Oi-Pr)4, 0.5 equiv of TiCl4 was used in comparison to the procedure given in footnote d.

^f One equiv of AcOH was added to amine, carbonyl compound, and NaBH(OAc)₃. Reaction time: 22 h.

⁹ Carbonyl compound, amine, and 1% of (10% Pd/C) were premixed and stirred overnight. Then, H_2 (3 atm) was charged and the reaction mixture was stirred for 24 h.

^h Preparation of this substrate was conducted according to the unified procedure but over 48 h.

¹ Preparation of this substrate was conducted at r.t. for 8 h using 10 mmol of reagents and 14 mmol of NaBH(OAc)₃.

Reductive Amination with NaBH₄

NaBH₄ allows to afford high efficiency (93–96%) of reductive amination between aromatic aldehydes with electron-withdrawing or electron-donating groups. However, the main drawback of reductive amination using NaBH₄ is side reduction of starting carbonyl compounds. It was confirmed by several of our experiments (Table 2). According to literature data, combination of NaBH₄ and Ti(O*i*-Pr)₄²⁷ or TiCl₄²⁸ allows to improve the efficiency of reductive amination, thanks to preliminary formation of a Schiff base that is subsequently reduced. Promoting ability of Ti(O*i*-Pr)₄ was confirmed by good to excellent yields (77-99%) of **4**, **5**, and **6** (Table 3). TiCl₄ appeared to be more active in cases of **8** and **9**. The yields of **8** and **9** with TiCl₄ appeared to be 8–16\%, whereas Ti(O*i*-Pr)₄ was totally powerless in these cases.

Interestingly, low efficiency of the reaction between 4methoxybenzaldehyde and piperidine (30%) even after addition of $Ti(Oi-Pr)_4$ points out to difficulties in reductive amination of secondary amines with aldehydes and ketones. According to literature data, reductive amination products between secondary amines and aldehydes or keF

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tones with NaBH₄ can be obtained in good yields using more complicated methods. Process should be conducted in the presence of silica gel-supported sulfuric acid,³⁵ silicasupported boron sulfonic acid,³⁶ or silica chloride.³⁷ Efficiency of the reaction can be improved also by using 2,2,2trifluoroethanol³⁸ or ionic liquid³⁹ as solvent. The literature data showed possibility to carry out the reaction using NaBH₄ with Ti(Oi-Pr)₄⁴⁰ between aromatic aldehyde and secondary amine in good yield (82%).

Reductive Amination with NaBH₃CN

Five substrates were obtained in 57–99% vields using the unified procedure with NaBH₃CN. Despite the softness of NaBH₃CN, it did not afford to obtain all the substrates using the procedure without modifications. Necessity to carry out the reaction in the presence of AcOH provokes side aldol condensation particularly for 3-phenylpropanal. As in the case of sodium borohydride. Ti $(Oi-Pr)_{4}$ can be used to increase yields for some substrates (Table 3). We decided to try it for reductive amination with NaBH₃CN. It was confirmed by increasing of the process efficiency for 5 (from 23% to 65%), 6 (from 33% to >99%), 8 (from 6% to 71%), and 10 (from 57% to 79%) (Table 3). This means that sodium cyanoborohydride is an effective reducing agent in reductive amination, however, its drawbacks make it necessary to conduct the reactions in a certain pH interval with requirement of specialized disposal of highly toxic reaction byproducts such as HCN. It is commonly believed that NaBH₃CN does not reduce carbonyl compounds under conditions of reductive amination, but our experimental results showed that NaBH₃CN is able to reduce carbonyl compounds.

Reductive Amination with NaBH(OAc)₃

Six substrates were obtained in 52–99% yields (Table 2) using unified procedure with NaBH(OAc)₃ (Figure 1). The described method with AcOH²⁴ led to an increase of the yield of **5** up to 69% during 22 hours, while according to authors' data the outcome of the same compound comprises 55% for 10 days. The opposite scenario was obtained for **9**. In literature data,²⁴ the yield of this compound was 88%, although no precise protocol for this product was described. In our hands, an average outcome of four equal experi-

ments constituted 60–71%. Besides, we managed to increase the yield of **8** up to 54% thanks to prolonged reaction times. Similar to NaBH₃CN, in the case of NaBH(OAc)₃ we observed that it can reduce carbonyl compounds. We found the corresponding alcohols in the reaction mixtures (Table 2, 6, 9).



Figure 1 Number of products synthesized using unified procedure

Reductive Amination with CO/Rh₂(OAc)₄

Despite the fact that there are many protocols for reductive amination with CO, we chose $Rh_2(OAc)_4$ as it is commercially available and most versatile.⁷ Eight substrates were obtained in 60-99% yields using unified procedure with CO/Rh₂(OAc)₄ (Figure 1). Optimization was conducted for reductive amination products 6, 7, and 9. While other reducing agents turned out to be completely useless in the synthesis of product 7 from camphor and anisidine, use of $CO/Rh_2(OAc)_4$ allowed us to obtain this product in 8% using unified conditions. At higher temperature and prolonged reaction times the outcome increased up to 69%. It is worth to mention that only exo-diastereomer of the product is formed. In addition, we managed to increase outcome of product 6 from 21–25% to 40% and product 9 from 18% to 63%, although, multiple aldol condensations appeared to be a side processes in the case of **6**. It is worth noting that there are other catalysts for conducting process with carbon monoxide such as Rh on Carbon Matrix,⁴¹ [(C₄Et₄)Rh(pxylene)]PF₆,⁸ anthracene rhodium complexes,⁴² and RuCl₂,⁴³ which might provide such transformations. However, as for H_2/Pd we did not try any other catalysts.



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 Table 4
 Reaction Mass Efficiency (RME, %)

R^{1} R^{2} + R^{3} R^{4} + reducing + solvent R^{3} R^{4} + by-products R^{1} R^{2} R^{2} R^{3} R^{4} + R^{4} + R^{3} R^{4} + R^{4} + R^{3} R^{4} + R^{4} + R^{3} R^{4} + R						
Product	Rh/CO	NaBH ₄	NaBH(OAc) ₃	NaBH ₃ CN	H ₂ /Pd	
	77%	63%	44%	51%	0%	
HO 2	75%	64%	39%	44%	42%ª	
N N N N N N N N N N N N N N N N N N N	67%	62%	34%	47%	34%ª	
O ₂ N 4	67%	21% ^b	34%	55%	0%	
	72%	24% ^b	23%	15% ^b	0%	
Ph N H 6	19%	26% ^b	23%	25%	39%	
	65%	0%	0%	0%	0%	
Ph N	76%	0%	12% ^b	17% ^b	34%	
	75%	9%	33%	29%	38%	
	47%	0%	13% ^b	6% ^b	3%ª	

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Table 4 (continued)						
	Product	Rh/CO	NaBH ₄	NaBH(OAc) ₃	NaBH ₃ CN	H ₂ /Pd
	NHCBz H 11	61%	30%	31%	55%	0%
Average RME		64%	27%	25%	31%	17%
Generalized RME ^c		14.3%	0.55%	4.11%	0.99%	0.78%

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^a Reaction conditions: 10% Pd/C (1%), 5 atm H₂, r.t.

^b Procedure with Ti(O*i*-Pr)₄.

^c Solvents are taken into account in the calculation.

Functional Group Tolerance

Obviously, according to our results H₂/Pd showed the worst tolerance to potentially reducible functional groups. Nitro group was reduced by this agent, cleavage of C-N bond in Cbz-protected amine as well as N-benzyl containing products was observed. Aldehydes and ketones were reduced to the corresponding alcohols. Notably, no reducing agent was tolerant to starting carbonyl compounds. Returning to Scheme 1, it can be said that in spite of statements in textbooks that NaBH₃CN and NaBH(OAc)₃ cannot reduce carbonyl compounds, our experiments (Table 2, 6, 9) and other literature data^{4,13,24} pointed out the presence of the corresponding alcohols in reaction mixtures (Scheme 2). However, sterically hindered ketones like camphor were not reduced by tested reducing agents. Surprisingly, C-N bond in Cbz-protected amine was cleaved by NaBH₄, but nitro group persisted under reductive amination conditions using NaBH₄, although according to literature data the reduction of NO₂ group is possible.⁴⁴ Such functional groups as halogen, OH, pyridine fragments are resistant under used conditions.

To sum up our results, several recommendations can be given. First, for aromatic aldehydes and amines without potentially reducible functional groups any of standard methods except for H_2/Pd can be used. Second, if such groups, for example, NO_2 and Cl, are present in molecules, it is worth to use more soft and selective NaBH₃CN, NaBH(OAc)₃, or CO/Rh system. Third, to prevent side reduction of carbonyl compounds, aldol condensation and also to increase reactivity of ketones, additives such as Ti(Oi-Pr)₄ or TiCl₄ can be used. Finally, for the synthesis of sterically hindered amines by reductive amination CO/Rh system is more suitable.

Green Chemistry Metrics

To prove the efficiency and purity of the described methods from the ecological point, we decided to count a green chemistry metric for all of them, namely reaction mass efficiency (RME).⁴⁵ RME is the ratio of the mass of a product to the mass of reagents. It shows if a method pro-

duces lots of waste (low RME) or it is ecologically friendly and usage of all the reagents is reasonable (high RME). RME is an actually illustrative green chemistry metric because it takes into account the yield of a product, which means that it shows overall efficiency of the method. It is obvious from Table 4 that using the hydride reagents, even if they furnish the desired amines in good to excellent yields in many cases, it still means producing solid wastes and average reaction mass efficiencies of 25-31%. CO/Rh system showed the highest average RME (64%), because it does not produce any solid wastes and allows to obtain most of the desired products in good to excellent yields. Notably, H₂/Pd system showed not as low RMEs as we could expect (17% average, 42% the highest), because despite its low selectivity towards most of the reported reductive aminations, reductions by H₂ are almost zero-waste. Significantly, when the RMEs are counted taking into account the amounts of solvents (Generalized RME, for more details see Supporting Information), the values significantly decrease, which points at the necessity of using less solvents in the reactions.

Conclusions

We have conducted a comparative study of five powerful methods of reductive amination. Various types of amines were synthesized using these protocols, and comparison of the corresponding yields of the products allowed us to evaluate the effectiveness and selectivity of each method. We showed that hydride reducing agents, which are thought to be the most selective towards reductive amination are indeed effective in many cases, however, they are not always as perfect as it seems. In spite of common viewpoint, we found that soft and selective NaBH₃CN and NaBH(OAc)₃ are able to reduce aldehydes, which was confirmed by analysis of literature data.³⁻⁵ Moreover, in cases where sterically hindered substrate such as camphor is used, CO/Rh system appeared to be the only effective reducing agent. Molecular hydrogen on Pd, being one of the most atom-economical reducing agents, showed low selectivity and is only effective in two cases reviewed herein. To con-

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clude, we hope that this paper will be useful for understanding which method of reductive amination a chemist should choose in different cases.

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification, THF was distilled over Na/benzophenone. CO of >98% purity was obtained from NII KM (Moscow, Russia). ¹H and ¹³C spectra were recorded in CDCl₃ and DMSO-*d*₆ on Bruker Avance 300, Bruker Avance 400, Varian Inova 400 spectrometers. Chemical shifts δ are reported in ppm relative to the solvent resonance signal as an internal standard. Standard abbreviations were used to designate chemical shift multiplicities. Coupling constants are given in hertz (Hz).

Unified General Procedures

We consider that determining the yields by NMR with internal standard is highly reliable for comparing different protocols and gives less error of measuring than isolated yields.

General Procedure for Reductive Amination with CO/Rh

A glass vial in a 10 mL stainless autoclave was charged with Rh₂(OAc)₄ (0.7 mol%), amine (1.98 mmol), and carbonyl compound (1.65 mmol). anhydrous THF (0.7 mL) was added and the autoclave was sealed, flushed three times with 3 atm of CO, and then charged with 50 atm CO. The reactor was placed in an oil bath preheated to 120 °C. After heating for 22 h, the reactor was cooled to r.t. and depressurized. The reaction mixture was transferred to a flask and the autoclave was washed with CH₂Cl₂. The filtrate was passed through a small pad of silica gel in order to remove the catalyst and the solvents were removed on a rotary evaporator. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH₄

A 10 mL round-bottomed flask was charged with carbonyl compound (0.24 mmol), amine (0.2 mmol), and MeOH (2 mL) and the mixture was refluxed for 2 h. NaBH₄ (0.4 mmol) was added to the reaction mixture and the suspension was stirred at r.t. overnight. Then, the mixture was refluxed for an additional 2 h. After reaction completion, the mixture was diluted with H₂O, and the product extracted with EtOAc. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH(OAc)₃

A 10 mL round-bottomed flask with an inlet for argon was charged with carbonyl compound (0.2 mmol), amine (0.2 mmol), and 1,2-dichloroethane (0.7 mL). The mixture was stirred at r.t. under argon atmosphere for 15 min. NaBH(OAc)₃ (0.28 mmol) was added to the mixture and the suspension was stirred at r.t. under argon atmosphere for 18 h. The reaction mixture was quenched by adding sat. aq NaHCO₃, and the product extracted with EtOAc. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH₃CN

A penicillin vial was charged with amine (0.2 mmol), glacial AcOH (0.2 mmol), and MeOH (2 mL). After that, carbonyl compound (0.2 mmol) and a solution of NaBH₃CN (0.4 mmol) in MeOH (1 mL) were added. The reaction mixture was stirred at r.t. overnight. After reac**Special Topic**

tion completion, the mixture was diluted with H₂O, and the product extracted with CH₂Cl₂. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with H₂/Pd

A glass vial in a 10 mL stainless autoclave was charged with 10% Pd/C (5 mol %), amine (0.2 mmol), carbonyl compound (0.2 mmol), and a magnetic stir bar. EtOH (0.5 mL) was added and the autoclave was sealed and charged with 5 atm H_2 at 40 °C. After heating for 24 h, the reactor was cooled to r.t. and depressurized. The reaction mixture was transferred to a flask and the autoclave was washed with CH₂Cl₂. The combined solvents were removed on a rotary evaporator. The yield of product was determined by ¹H NMR with an internal standard.

General Procedures Under Optimized Conditions

General Procedure for Reductive Amination with CO/Rh

The optimized conditions differ from unified ones by temperatures, reaction times, solvents, and equivalents of reagents. Details are set out in Supporting Information.

General Procedure for Reductive Amination with NaBH4 and Ti(Oi-Pr)₄

After removing traces of moisture and oxygen of air from the Schlenk glassware, it was charged with carbonyl compound (0.24 mmol), amine (0.2 mmol), Ti(Oi-Pr)₄ (0.4 mmol), and anhydrous THF (1.5 mL). The reaction mixture was stirred at r.t. for 3 h under argon. Then, THF was evaporated under reduced pressure. NaBH₄ (0.4 mmol) and MeOH (2 mL) were added and the reaction mixture was refluxed for 4 h. After reaction completion, the mixture was diluted with H₂O, and the product extracted with CH₂Cl₂. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH₄ and TiCl₄

After removing traces of moisture and oxygen of air from the Schlenk glassware, it was charged with carbonyl compound (0.24 mmol), amine (0.2 mmol), TiCl₄ (0.1 mmol), and anhydrous THF (1.5 mL). The reaction mixture was stirred at r.t. for 3 h under argon. Then, THF was evaporated under reduced pressure. NaBH₄ (0.4 mmol) and MeOH (2 mL) were added and refluxed for 4 h. After reaction completion, the mixture was diluted with H₂O, and the product extracted with CH₂Cl₂. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH(OAc) $_3$ and AcOH

A 10 mL round-bottomd flask with an inlet for argon was charged with carbonyl compound (0.2 mmol), amine (0.2 mmol), glacial AcOH (0.2 mmol), and 1,2-dichloroethane (0.7 mL). The mixture was stirred at r.t. under argon atmosphere for 15 min. NaBH(OAc)₃ (0.28 mmol) was added to the reaction mixture. The suspension was stirred at r.t. under argon atmosphere for 22 h. The mixture was quenched by adding sat. aq NaHCO₃, and the product extracted with EtOAc. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH(OAc) $_3$ and Ti(Oi-Pr) $_4$

After removing traces of moisture and oxygen of air from Schlenk glassware, it was charged with carbonyl compound (0.2 mmol), amine (0.2 mmol), Ti(Oi-Pr)₄ (0.4 mmol), and anhydrous THF (1.5 mL). The reaction mixture was stirred at r.t. for 3 h under argon. Then, THF was evaporated under reduced pressure. NaBH(OAc)₃ (0.28 mmol) and 1,2-dichloroethane (0.7 mL) were added and the mixture was stirred at r.t. for 18 h. After reaction completion, the mixture was diluted with H₂O and the product extracted with CH₂Cl₂. The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with NaBH_3CN and $Ti(Oi\mbox{-}Pr)_4$

After removing traces of moisture and oxygen of air from Schlenk glassware, it was charged with carbonyl compound (0.2 mmol), amine (0.2 mmol), Ti(Oi-Pr)₄ (0.4 mmol), and anhydrous THF (1.5 mL). The reaction mixture was stirred at r.t. for 3 h under argon. Then, THF was evaporated under reduced pressure. NaBH₃CN (0.4 mmol) and MeOH (2 mL) were added and stirred at r.t. overnight. After reaction completion, the mixture was diluted with H₂O, and the product was extracted with CH_2Cl_2 . The organic layer was dried (anhydrous Na₂SO₄), filtered, and evaporated. The yield of product was determined by ¹H NMR with an internal standard.

General Procedure for Reductive Amination with H₂/Pd

A glass vial in a 10 mL stainless autoclave was charged with 10% Pd/C (1 mol %), amine (0.2 mmol), carbonyl compound (0.2 mmol), and a magnetic stir bar. EtOH (0.5 mL) was added and the autoclave was sealed. The reaction mixture was stirred overnight at r.t. Then autoclave was charged with 3 atm H₂ and the contents were stirred at r.t. for 15 h. After reaction completion, the reactor was depressurized. The mixture was transferred to a flask and the autoclave was washed with CH_2CI_2 . The combined solvents were removed on a rotary evaporator. The yield of product was determined by ¹H NMR with an internal standard.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611788.

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