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Base-Free Synthesis of Furfurylamines from Biomass Furans Using Ru Pincer Complexes

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Abstract: We report the first example of employing homogeneous organometal-catalyzed transfer hydrogenation for the selective reductive amination of furfurals to furfurylamines. An efficient, chemoselective, and base-free method is described using Ru-MACHO-BH as catalyst and *i*PrOH as H donor. The method tolerates a range of substituents affording moderate to excellent yields.

Keywords: transfer hydrogenation; furfurals; furfurylamine; reductive amination; Ru-MACHO

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1. Introduction

The development of sustainable techniques to transform biomass into useful compounds is one of the biggest challenges of modern chemistry [1]. The introduction of nitrogen in biomass-derived compounds adds value and expands their industry applicability [2]. Furfurals are aldehydes derived from biomass and are identified as one of the key chemicals produced by the lignocellulosic biorefineries. Around 280 kTon are produced globally per year [3]. Furfurylamines (amines derived from furfurals) present diverse applications in the industry, including the preparation of pharmaceutical compounds such as Furesomide, Furtrethonium, an anti-hepatitis-B, and Barmastine (Figure 1), as well as polymers, antiseptic agents, agrochemicals, pesticides, and synthetic resins [1,2,4].

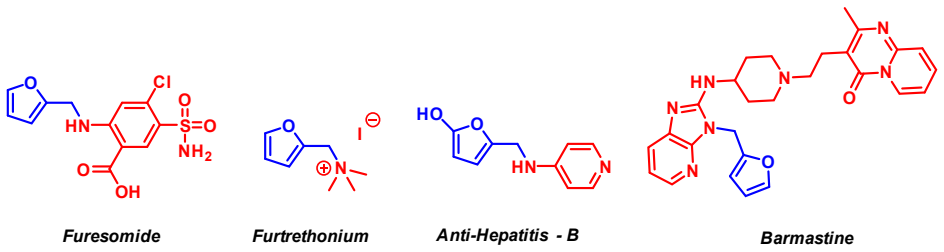


Figure 1. Pharmaceutical compounds containing furfurylamines.

The synthesis of furfurylamines from furfurals by reductive amination has been investigated using diverse reducing agents and catalysts. Studies involving hydrogen gas, silanes, borohydrides, and formic acid as reductants have been reported in the literature. Hydrogen gas as reductant is an interesting green tool; however, the method needs to operate under pressure of a highly flammable gas, increasing the operating cost. Nevertheless, there are many examples in the literature using H_2 as reductant for reductive amination with noble and non-noble metal catalysts such as Ru, Au, Ir, Pt, Ni, Co and Fe [5–11]. Although silane is obtained from waste residues of the silicon industry, their use is still in stoichiometric amounts, generating excessive amounts of waste [12–14]. The use of formic acid as H donor for the reductive amination of furfural was demonstrated as well. Cao and co-workers synthesized N-(furan-2-ylmethyl)aniline in 93% yield from nitrobenzene and furfural using Au/TiO_2-R as catalyst at 80 °C for 4 h [15]. Smith Jr and co-workers also employed formic acid as H donor, but used formamide as N source [16]. To the best of our

knowledge, the only work involving an alcohol as H donor (*i*PrOH) for the synthesis of furfurylamines from furfural was reported by Yus [17]. In this work, the reaction between furfural and heptylamine using 20 mol% of NiNPs at 76 °C for 48 h afforded 30% yield of the furfurylamine.

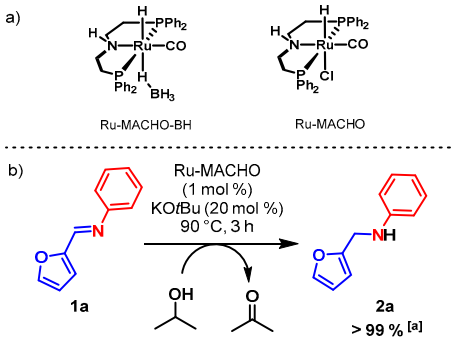
One of the most powerful and robust methods for effective C–N bond formation of amines is the reductive amination of carbonyl compounds. [4,18–30]. This transformation features compelling advantages, such as simple operating setups, mild reaction conditions, direct use of available substrates, and inexpensive reagents [31]. The reductive amination using transfer hydrogenation for the synthesis of furfurylamines from furfurals is limited, even though this transformation as a synthetic tool is non-toxic, environmentally friendly, does not require flammable gasses, and employs a stable, easy to handle, and inexpensive source of hydrogen [4,32–37]. However, transfer hydrogenation catalysts typically require strong bases to be active, which can be detrimental for substrates that are base-sensitive [38]. Therefore, studies applying base-free conditions must be developed to avoid this drawback.

The use of homogenous metal catalysis has demonstrated great reactivity for transfer hydrogenation of carbonyl compounds and has been proven to hold many advantages [38–41]. In 2018, De Vries reported a base-free transfer hydrogenation of α,β-unsaturated ketones and aldehydes using the PNP pincer complex carbonylhydrido (tetrahydroborato)[bis(2-diphenylphosphinoethyl)amino]ruthenium(II) (Ru-MACHO-BH) as catalyst, in the presence of EtOH or *i*PrOH as H source and showed high activity and selectivity [42]. The amino-based Ru-PNP complexes are also very efficient catalysts for hydrogenation [43–49] and dehydrogenation [50–57] reactions. The high activity of these Ru PNP complexes in hydrogenations is often attributed to the presence of the Ru–H unit and N–H group [58].

Inspired by these works, we investigated the use of Ru-MACHO [59] (carbonylhydrido (tetrahydroborato)[bis(2-diphenylphosphinoethyl)amino]ruthenium(II)) and Ru-MACHO-BH complexes as potential catalysts for the transfer hydrogenation of the reductive amination in this work.

2. Results and Discussion

Our studies commenced with testing Ru-MACHO (1 mol%) as the catalyst for the transfer hydrogenation of the aldimine **1a** (Figure S1) in the presence of *i*PrOH (0.2 M of **1a**) as hydrogen source and KO*t*Bu (20 mol%) as additive at 90 °Cfor 3 h (Scheme 1). To our delight, the reaction afforded >99% conversion to furfurylamine **2a**. We then set out to evaluate the transfer hydrogenation of **1a** using varying catalyst loading, additives, temperatures, and reaction times with the aim of developing a mild protocol for this reaction.



Scheme 1. (**a**) Ru-PNP catalysts used in this work. (**b**) Transfer hydrogenation of aldimine using Ru-MACHO. [a] Measured by ^{1}H NMR spectroscopy analysis of the crude reaction mixture.

Reducing the reaction time to 15 min, the catalyst loading of Ru-MACHO to 0.5 mol%, and the KO*t*Bu loading to 10 mol% still led to full conversion (Table 1, Entry 3). In fact, after 5 min, 51% was already converted (Entry 4). Changing the additive to NaOH had

a detrimental effect, and only 18% conversion was observed. Likewise, lowering the catalyst loading to 0.1 mol% afforded less than 5% conversion. Changing the catalyst to Ru-MACHO-BH showed very low activity within 15 min, both with and without additive (Entries 6 and 7, respectively).

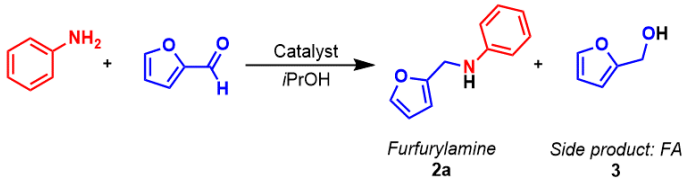
Table 1. Transfer hydrogenation of aldimines: Initial studies.

Entry [a]	Catalyst (mol%)	Additive [b]	Time	Conv. [c] (%)
1	Ru-MACHO (0.5)	KO*t*Bu	1 h	>99
2	Ru-MACHO (0.5)	KO*t*Bu	30 min	>99
3	Ru-MACHO (0.5)	KO*t*Bu	15 min	>99
4	Ru-MACHO (0.5)	KO*t*Bu	5 min	51
5	Ru-MACHO (0.5)	NaOH	15 min	18
6	Ru-MACHO (0.1)	KO*t*Bu	15 min	<5
7	Ru-MACHO-BH (0.5)	-	15 min	<5

[a] Reactions were carried out using 1.3 mmol of furfural and aniline in 7 mL *i*PrOH at 90 °C. [b] 10 mol% additive used. [c] Measured by ^{1}H NMR spectroscopy analysis of the crude reaction mixture.

Motivated by these initial positive results, the reductive amination of furfural with aniline was further investigated. Thus, in the presence of 10 mol% KO*t*Bu, 0.5 mol% of Ru-MACHO afforded >99% conversion after 18 h at 90 °C. However, the furfuryl alcohol (FA, **3**) appeared as a significant side product in a proportion of 7:3 (**2a**/**3**) (Scheme 2). Fortunately, introducing $MgSO_4$ as drying agent led to >99% conversion selectively to the desired product in 3 h (Table 2, Entry 2). Reducing the reaction time to 1 h decreased the selectivity to 93:7. Using Ru-MACHO-BH (0.5 mol%) and $MgSO_4$ but without the basic additive still resulted in 93% conversion after 1 h and with **2a** as the sole product by ^{1}H NMR analysis (Entry 3). Increasing the amount of aniline from 1.0 to 1.2 equivalent afforded >99% **2a** under otherwise identical conditions (Entry 5). Unfortunately, it was not possible to further reduce the reaction time without compromising the conversion and selectivity (Entries 6–8). Decreasing the amount of Ru-MACHO-BH to 0.25 mol% also led to a low conversion of 11% (Entry 9). Lowering the temperature to 70 °C resulted in practically no conversion (<5%, Entry 10). However, by increasing the temperature to 120 °C, it was possible to achieve exclusively **2a** with >99% conversion within 30 min (Entry 11).

A number of drying agents were then tested. Using Na_2SO_4 at 90 °C afforded >99% conversion in 1 h. However, the selectivity decreased to 97:3 (**2a**/**3**) (Entry 12). Decreasing the time further to 15 min maintained the full conversion but led to even lower selectivity, down to 57:42 (**2a**/**3**) (Entries 13–15). These observations suggest that the formation of **3** is highly reversible, and that **1a** is regenerated from **3** throughout the course of the reaction. Moreover, decreasing the reaction temperature to 70 °C led to merely 17% conversion (Entry 16). Molecular sieves (4 Å) were also evaluated and showed full conversion after 1 h, albeit with slightly lower selectivity (94:6 **2a**/**3**) (Entry 17). Decreasing the time further to 15 min maintained the full conversion but also led to lower selectivity, (71:29 **2a**/**3**) (Entry 18). The temperature was evaluated, and carrying out the reaction at 70 °C led to 71% conversion and 96:4 (**2a**/**3**) of selectivity (Entry 19).



Scheme 2. Reductive amination between furfural and aniline.

Table 2. One-pot synthesis of furfurylamines: Optimization.

Entry [a]	Catalyst (mol%)	Additive [b]	Temperature (°C)	Time	Conversion [c] (%)	2a [c] (%)	3 [c] (%)
1	Ru-MACHO (0.5)	KO*t*Bu	90	18 h	>99	70	30
2	Ru-MACHO (0.5)	KO*t*Bu + $MgSO_4$	90	3 h	>99	>99	-
3	Ru-MACHO (0.5)	KO*t*Bu + $MgSO_4$	90	1 h	>99	93	7
4	Ru-MACHO-BH (0.5)	$MgSO_4$	90	1 h	93	>99	-
5 [d]	Ru-MACHO-BH (0.5)	$MgSO_4$	90	1 h	>99	>99	-
6 [d]	Ru-MACHO-BH (0.5)	$MgSO_4$	90	45 min	75	86	14
7 [d]	Ru-MACHO-BH (0.5)	$MgSO_4$	90	30 min	30	73	27
8 [d]	Ru-MACHO-BH (0.5)	-	90	30 min	15	52	48
9 [d]	Ru-MACHO-BH (0.25)	$MgSO_4$	90	1 h	11	-	>99
10 [d]	Ru-MACHO-BH (0.5)	$MgSO_4$	70	1 h	<5	-	-
11 [d]	Ru-MACHO-BH (0.5)	$MgSO_4$	120	30 min	>99	>99	-
12 [d]	Ru-MACHO-BH (0.5)	Na_2SO_4	90	1 h	>99	97	3
13 [d]	Ru-MACHO-BH (0.5)	Na_2SO_4	90	45 min	>99	90	10
14 [d]	Ru-MACHO-BH (0.5)	Na_2SO_4	90	30 min	>99	76	24
15 [d]	Ru-MACHO-BH (0.5)	Na_2SO_4	90	15 min	>99	57	42
16 [d]	Ru-MACHO-BH (0.5)	Na_2SO_4	70	1 h	17	72	28
17 [d]	Ru-MACHO-BH (0.5)	MS 4 Å	90	1 h	>99	94	6
18 [d]	Ru-MACHO-BH (0.5)	MS 4 Å	90	15 min	>99	71	29
19 [d]	Ru-MACHO-BH (0.5)	MS 4 Å	70	1 h	71	96	4

[a] Reactions were carried out using 1.3 mmol of furfural, aniline, and 1.3 mmol of drying agent in 7 mL *i*PrOH. [b] 10 mol% of KOtBu used. [c] Measured by ^{1}H NMR spectroscopy analysis of the crude reaction mixture. [d] Reactions were carried out using 1.2 equivalent of aniline. MS = Molecular sieves.

As seen in Figure 2, the levels of **1**–**3** differed significantly throughout the course of the reaction, depending on whether Na_2SO_4 or $MgSO_4$ was employed. Within 15 min, almost all **1a** had disappeared and 60% of **2a** had already been generated when using Na_2SO_4. Surprisingly, 35% of **3** was observed at this point. Hereafter, the reaction slowed significantly, and after 30 min, merely 70% of **2a** had been produced and **3** had only dropped to 22%. By contrast, with $MgSO_4$ the level of **3** did not exceed 15% throughout the entire course of the reaction, and after 30 min, it was 12%. At this time, there was still an ample amount of **1a** (45%) to undergo hydrogenation, and 43% of **2a** had been produced. This difference in amount of **1a** present during the course of the reaction might explain the superiority of $MgSO_4$ as drying agent after 60 min.

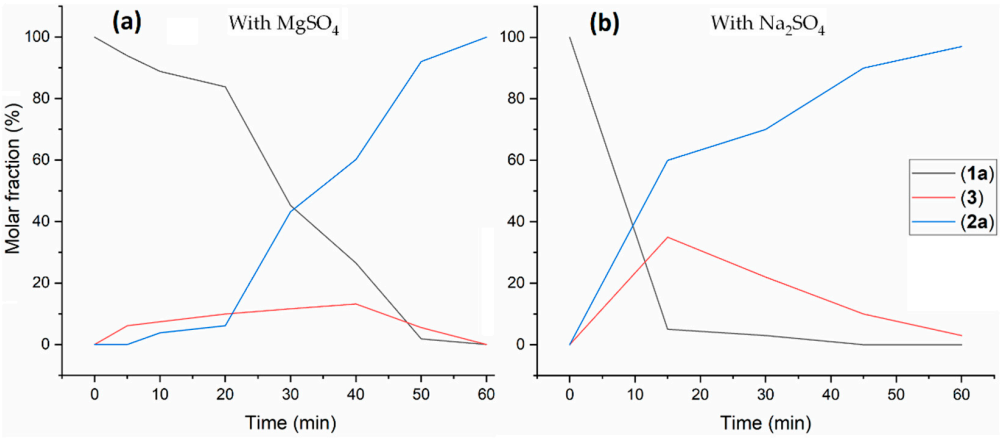
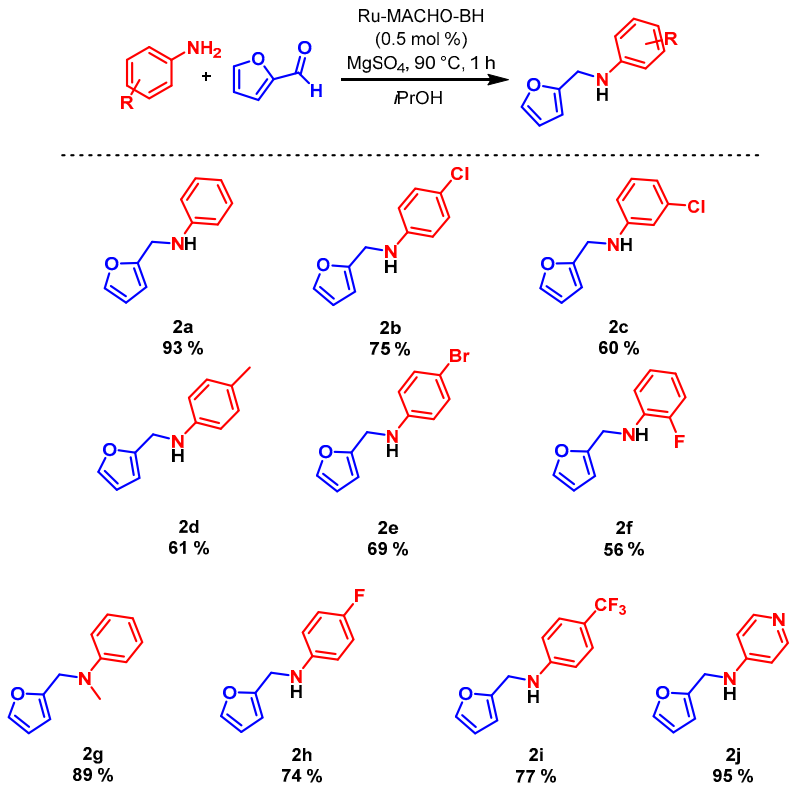


Figure 2. Monitoring the reaction of furfural with aniline using either $MgSO_4$ as drying agent (**a**) or Na_2SO_4 as drying agent (**b**). Reactions were carried out using 1.3 mmol of furfural, 1.2 equivalent aniline, and 1.3 mmol of drying agent in 7 mL *i*PrOH.

Therefore, although Na_2SO_4 and molecular sieves demonstrate higher conversion rates than $MgSO_4$, the latter drying agent was chosen due to the higher yield provided

after 1 h of reaction time. Therefore, the conditions described in the Entry 5 in Table 2 were defined as standard conditions for the scope.

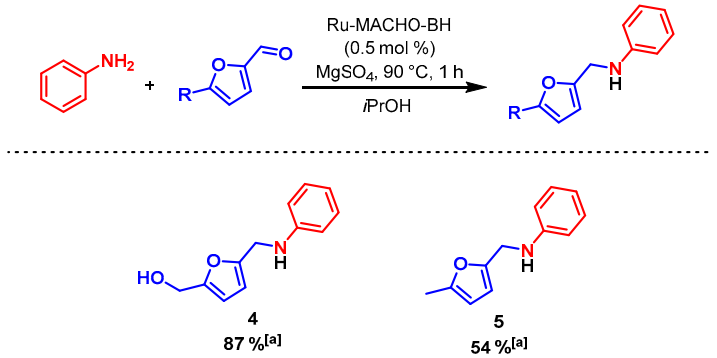
To assess the general applicability of the Ru-MACHO-BH as a catalyst for the one-pot synthesis of furfurylamines from furfurals and amines, various anilines were evaluated using the standard conditions (Scheme 3). Generally, moderate to excellent yields were obtained. The parent aniline afforded an excellent 93% of isolated product. Comparing the anilines containing either electron-donating or -withdrawing substituents, the latter group showed superior yield. As such, 4-F-$C_6H_4NH_2$, 4-CF_3-$C_6H_4NH_2$, and 4-aminopyridine generated the best yields of the substituted anilines with 74-95% of isolated products **2h**–**j**. The product **2j** is analogous to the anti-hepatitis-B compound shown in Figure 1, which demonstrates the direct applicability of the method for the synthesis of pharmacological activity compounds. On the other hand, a donating group (4-CH_3-$C_6H_4NH_2$) afforded lower yield of 61% of **2d**. This observation can perhaps be explained by the increased electronic deficiency of the imines when employing 4-CF_3-$C_6H_4NH_2$ as reagent [1]. Various halogens were tested as well and showed moderate to good yields (**2b**, **2e**, **2h**). Compounds with substituent in different positions, such as 3-Cl-$C_6H_4NH_2$ and 2-F-$C_6H_4NH_2$, showed good tolerance, yielding 60% and 56% of **2c** and **2f**, respectively. The method was also tested with the secondary amine *N*-methylaniline, which afforded the tertiary amine **2g** in high yield (89%). Unfortunately, no products were observed when employing various primary and secondary alkyl amines (*t*BuNH_2, *n*HepNH_2, Me_2NH, morpholine).



Scheme 3. One-pot synthesis of furfurylamines catalyzed by Ru-MACHO-BH. Reactions were carried out using 1.3 mmol of furfural, 1.56 mmol of aniline, and 1.3 mmol of $MgSO_4$ in 7 mL *i*PrOH. All yields are isolated.

5-(hydroxymethyl)furfural (HMF) and 5-methylfurfural are other important biomass-derived furans with industrial applications [60,61]. The furfurylamines derived from HMF are used in the synthesis of biopolymers (polyamides) and pharmaceuticals [4]. The *N*-(5-methylfurfuryl)aniline is a very important compound used in the synthesis of epoxyisonindoles and bioactive compounds such as anti-bacterial, anti-tuberculosis, anti-tumor, and anti-inflammatory entities [62–70]. Therefore, the method is an interesting

alternative for the production of these valuable compounds. Hence, we also evaluated this compound as a potential substrate (Scheme 4). The reactions afforded a high yield of **4** (87%) and a moderate yield of **5** (54%).



Scheme 4. One-pot synthesis of furfurylamines catalyzed by Ru-MACHO-BH. Reactions were carried out using 1.3 mmol of furfural, 1.56 mmol of aniline and 1.3 mmol of $MgSO_4$ in 7 mL of *i*PrOH. [a] Isolated yield.

3. Materials and Methods

3.1. Materials

Most chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. Hydroxymethylfurfural (HMF, 99%) (Sigma-Aldrich, St. Louis, MO, USA), furfural (99%) (Sigma-Aldrich, St. Louis, MO, USA), 5-methylfurfural (99%, Sigma-Aldrich, St. Louis, MO, USA), KO*t*Bu (99%, Sigma-Aldrich, St. Louis, MO, USA), *i*PrOH (anhydrous, 99.5%, Sigma-Aldrich, St. Louis, MO, USA), Ru-MACHO (Sigma-Aldrich, St. Louis, MO, USA), and Ru-MACHO-BH (Strem Chemicals, Newburyport, MA, USA) are commercially available and were used without further purification. All reactions dealing with air or moisture-sensitive compounds were performed using standard Schlenk techniques or in an argon-filled glovebox. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer (Bruker, Billerica, MA, USA) and were referenced to the solvent peak. The software MestReNova version 11.0.0-17609 (Mestrelab, Escondido, CA, USA, 2016) was used for NMR analysis. The software OriginPro 2019 9.6.0.172 (Academic) (OriginLab, Northampton, MA, USA, 2019) was used for graphic plot. All the products are literature known compounds, and the experimental data (^{1}H and $^{13}C\{^{1}H\}$ NMR spectra) fit those reported.

3.2. Methods

3.2.1. Preparation of Aldimine 1a

A mixture of furfural (54 mmol), aniline (54 mmol) and methanol (0.5 M) in the presence of MS (4 Å) was stirred at room temperature for 3 h. After completion of the reaction, the crude mixture was filtered off and evaporated under reduced pressure. The product **1a** was obtained as a brown oil, 7.83 g, 85%.

3.2.2. General Procedure for Transfer Hydrogenation of Aldimine 1a Catalyzed by Ru-PNP Complexes

A Schlenk pressure vessel containing catalyst, additive and magnetic bar was sealed and flushed with argon (three times). The solvent and H-donor (*i*-PrOH) was introduced by a needle and stirred at 90 °C. After 10 min, the aldimine **1a** was added to the solution. After a certain reaction time (5–18 h), the reaction was stopped, and the crude was analyzed. The conversion was determined by spectroscopy ^{1}H NMR.

3.2.3. General Procedure for One-Pot Reductive Amination of Furfural

In a Schlenk pressure vessel containing Ru-MACHO-BH (0.5 mol %) and $MgSO_4$ (1.3 mmol), a magnetic stirring bar was added and the vessel was sealed and flushed with argon (three times). During argon flow, 4.5 mL of *i*PrOH was introduced by a needle and the solution was heated at 90 °C and stirred for 10 min. In a flame-dried screw-cap vial, aniline (1.56 mmol) and furfural (1.3 mmol) were mixed with 2.5 mL of *i*PrOH (to provide a solution with furfural concentration of 0.18 M) under argon flow. The atmosphere was replaced with argon and the solution was introduced to the Schlenk pressure vessel. The reaction mixture was kept at 90 °C for 1 h. The crude reaction mixture was evaporated under reduced pressure, and the product was obtained after purification through chromatography column (Ethyl acetate/pentane, 90:10). For the optimization process, the method of employing relative conversions as measured by NMR was confirmed with respect to absolute values by a single duplicate test reaction using mesitylene as internal standard.

4. Conclusions

In conclusion, we report the first example of an efficient base free one-pot transfer hydrogenative reductive amination of furfural for the synthesis of furfurylamines under mild conditions, employing low amounts of the commercially available catalyst Ru-MACHO-BH and *i*PrOH as H donor. The general applicability of the method is demonstrated by the use of furfural and various anilines with different substituents, which afforded yields that varied from moderate to excellent (56–93%). Furthermore, this chemoselective methodology established a high yield (83%) in the synthesis of the furfurylamine derived from HMF and a moderate yield (54%) from *N*-(5-methylfurfuryl)aniline.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11050558/s1, Table S1: Monitoring the reaction of furfural and aniline using $MgSO_4$ as drying agent. Table S2: Monitoring the reaction of furfural and aniline using Na_2SO_4 as drying agent. Figure S1: ^{1}H NMR spectrum of **1a** (400 MHz, $CDCl_3$), Figure S2: ^{13}C NMR spectrum of **1a** (100 MHz, $CDCl_3$), Figure S3: ^{1}H NMR spectrum of **2a** (400 MHz, $CDCl_3$), Figure S4: ^{13}C NMR spectrum of **2a** (100 MHz, $CDCl_3$), Figure S5: ^{1}H NMR spectrum of **2b** (400 MHz, $CDCl_3$), Figure S6: ^{13}C NMR spectrum of **2b** (100 MHz, $CDCl_3$), Figure S7: ^{1}H NMR spectrum of **2c** (400 MHz, $CDCl_3$), Figure S8: ^{13}C NMR spectrum of **2c** (100 MHz, $CDCl_3$), Figure S9: ^{1}H NMR spectrum of **2d** (400 MHz, $CDCl_3$), Figure S10: ^{13}C NMR spectrum of **2d** (100 MHz, $CDCl_3$), Figure S11: ^{1}H NMR spectrum of **2e** (400 MHz, $CDCl_3$), Figure S12: ^{13}C NMR spectrum of **2e** (100 MHz, $CDCl_3$), Figure S13: ^{1}H NMR spectrum of **2f** (400 MHz, $CDCl_3$), Figure S14: ^{13}C NMR spectrum of **2f** (100 MHz, $CDCl_3$), Figure S15: ^{1}H NMR spectrum of **2g** (400 MHz, $CDCl_3$), Figure S16: ^{13}C NMR spectrum of **2g** (100 MHz, $CDCl_3$), Figure S17: ^{1}H NMR spectrum of **2h** (400 MHz, CD_3OD), Figure S18: ^{13}C NMR spectrum of **2h** (100 MHz, $CDCl_3$), Figure S19: ^{1}H NMR spectrum of **2i** (400 MHz, $CDCl_3$), Figure S20: ^{13}C NMR spectrum of **2i** (100 MHz, $CDCl_3$), Figure S21: ^{1}H NMR spectrum of **2j** (400 MHz, $CDCl_3$), Figure S22: ^{13}C NMR spectrum of **2j** (100 MHz, $CDCl_3$), Figure S23: ^{1}H NMR spectrum of **4** (400 MHz, $CDCl_3$), Figure S24: ^{13}C NMR spectrum of **4** (100 MHz, $CDCl_3$), Figure S25: ^{1}H NMR spectrum of **5** (400 MHz, $CDCl_3$), Figure S26: ^{13}C NMR spectrum of **5** (100 MHz, $CDCl_3$).

Author Contributions: D.L.J.P. did the experimental part. M.N. did funding acquisition and project administration. Everything else, from conceptualization to manuscript writing, D.L.J.P. and M.N. did equally. All authors have read and agreed to the published version of the manuscript.

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