Synthesis of Chiral Trifluoromethylated Amines by Palladium-Catalyzed Diastereoselective Hydrogenation-Hydrogenolysis Approach

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Abstract: The synthesis of chiral 2,2,2-trifluoro-1-phenylethylamines by palladium-catalyzed diastereoselective heterogeneous catalytic hydrogenation is described. The one-pot process involves two steps; the diastereoselective hydrogenation of chiral 2,2,2-trifluoro-1-phenylethyl-*N*-1′-phenylethylimines and the hydrogenolysis of the methylbenzyl group on the amino function. During both the hydrogenation and hydrogenolysis steps favorable stereoinduction was observed, and the products were obtained in 90–93% ee and 50–55% yield.

Keywords: asymmetric heterogeneous catalysis; diastereoselective hydrogenation; hydrogenolysis; palladium; 2,2,2-trifluoro-1-phenylethyl amines

The interest in the synthesis of organofluorine compounds has been increasing ever since the discovery of the biological activity of 9α-fluorohydrocortisone.[1] The unique character of fluorine compounds provided a rational base for systematic drug design, and made possible the synthesis of numerous fluorinated antibiotics, antiviral and anticancer agents.[2]

Trifluoromethylated amines are important building blocks in the synthesis of fluorinated pharmaceuticals.[2] Although, the preparation of various chiral trifluoromethylated amines has attracted extended attention,[3] e.g., nucleophilic trifluoromethylation of *N*-(*tert*-butylsulfinyl)-imines was found to be a versatile method, developing an economic,[3] environmentally friendly process is still a challenge. The asymmetric hydrogenation[4,5] of suitable R-C(CF_3)=NX precursors could be a novel alternative. Although several useful methods have been developed for the preparation of chiral non-fluorinated amines and amino acids,[6] heterogeneous catalytic hydrogenation is very rarely applied for the synthesis of trifluoromethylated amines. In the light of the recent developments in metal-catalyzed asymmetric heterogeneous hydrogenations[7] this method is expected to be a viable alternative. Although the asymmetric hydrogenation of trifluoromethyl ketones are recently extensively pursued,[8] catalytic hydrogenations of trifluoromethylated imines are almost unknown. The only attempt by Pirkle and Hauske[9] describes the synthesis of 2,2,2-trifluoro-1-phenylethylamine enantiomers by reductive amination of trifluoroacetophenone using Red-Al as the reducing agent. Certainly, metal-catalyzed catalytic hydrogenation, especially its heterogeneous variation, is a much more economic and environmentally friendly way to carry out such reductive processes. The authors in their only attempt to carry out catalytic reduction used the Pd/C catalyst (25–28% de) that is a well-known and active catalyst; however, its selectivity in asymmetric hydrogenations is not well documented. In the light of recent findings,[7] it is clear that the catalyst (support, preparation, pretreatment method, etc.) and the experimental conditions are crucial factors in determining enantio- or diastereoselectivity. Accordingly, our recent interest in asymmetric catalytic hydrogenations, as well as in developing new methods for the synthesis of chiral trifluoromethylated amines, prompted us to carry out a detailed investigation in this area.

Herein, we report the synthesis of chiral 2,2,2-trifluoro-1-phenylethylamines by palladium-catalyzed diastereoselective heterogeneous catalytic hydrogenation of chiral 2,2,2-trifluoro-1-phenyl-*N*-1′-phenylethylimines through a sequential hydrogenation-hydrogenolysis approach (Scheme 1).

First, we studied the effect of different catalysts under constant experimental conditions. According to literature preliminaries[9] related to similar systems ethanol was used as a solvent. The results are tabulated in Table 1.

As Table 1 shows, Pt catalysts and Raney-Ni were found to be completely inactive in the reaction. The catalysts were likely poisoned by the substrate, for example, after the reaction Raney-Ni did not show any pyrophoric character, that is common for these catalysts.

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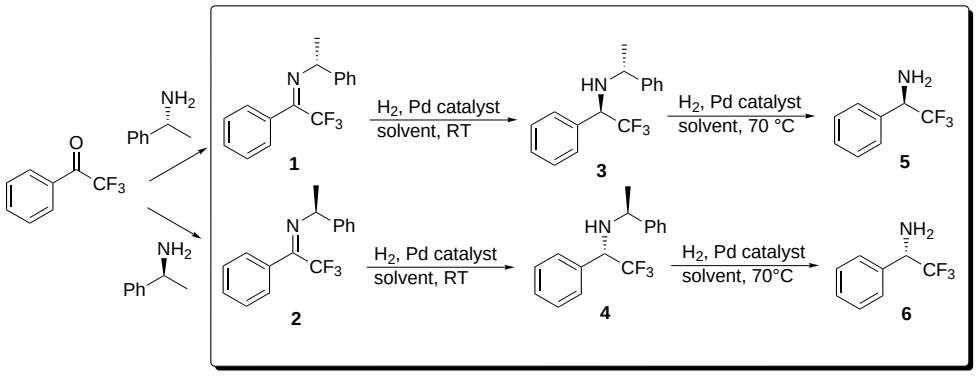


Scheme 1.

Table 1. Diastereoselective hydrogenation of (*R*)-2,2,2-trifluoro-1-phenylethyl-*N*-1′-phenylethylimine (**1**) to secondary amine (**3**) in ethanol over various supported Pd catalysts at ambient temperature (15 bar hydrogen pressure).

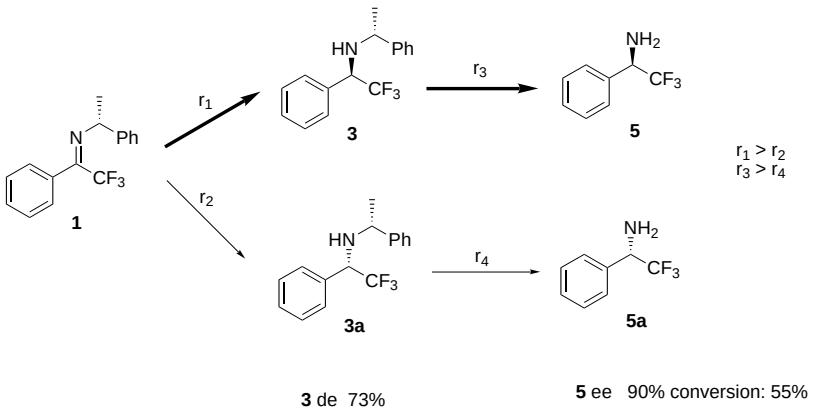
Catalyst	Origin/Code	Reaction Time [h]	Conversion [%]	de [%]
5% Pt/Al_2O_3	Engelhard 4759	18	–	–
5% Pt/K-10	Ref.[10]	18	–	–
Raney-Ni	Aldrich	18	–	–
5% Pd/Al_2O_3	Engelhard 40692	5	100	40
5% Pd/Al_2O_3	Aldrich	5	100	42
5% $Pd/BaCO_3$	Aldrich	18	60	61
5% Pd/C	Engelhard Selcat 103	18	100	10
5% Pd/C	Aldrich	18	100	28
5% $Pd/BaSO_4$	Aldrich	18	100	15
5% Pd-black	Aldrich	4	100	62

Table 2. Diastereoselective hydrogenation of (*R*)-2,2,2-trifluoro-1-phenylethyl-*N*-1-phenylethylimine (**1**) to secondary amine (**3**) under various experimental conditions over 5% $Pd/BaCO_3$ catalysts at ambient temperature.

Solvent	Hydrogen Pressure [bar]	Reaction Time [h]	Conversion [%]	de [%]
EtOH	5	18	23	60
EtOH	15	18	60	61
EtOH	50	18	100	33
toluene	15	18	5	92
toluene	15	30	8	93
THF	15	18	85	73
DMF	15	18	74	43
EtOAc	15	18	53	51

Although these results are rather surprising, they are in agreement with the literature reports.[11] Pd catalysts, however, showed excellent to satisfactory activity. (*R*,*R*)-diastereomer (**3**) is formed in excess and according to our expectations the diastereomeric excesses (de %) strongly depended on the catalyst used, Pd-black, and $Pd/BaCO_3$ gave the best diastereoselectivities. Therefore, we have chosen the $Pd/BaCO_3$ catalyst to optimize the experimental conditions. We studied the effect of different solvents and hydrogen pressure. Ultrasonic pretreatment as a possible technique[12] to improve selectivities failed or showed only a negligible effect. The results are shown in Table 2.

As it is shown, the hydrogen pressure has no significant effect on the diastereoselectivity in the lower pressure range, however, at higher pressures (50 bar) the de values dropped considerably. As the results also show, toluene was found to be an excellent solvent with respect to the diastereoselectivity (up to 93% de), however, the conversion is very low even after 30 h. In tetrahydrofuran, although the diastereoselectivity is lower, the conversion is reasonable. Therefore, we studied the last step, the hydrogenolysis of the methylbenzyl group in THF. During the hydrogenolysis of **3** we observed that the diastereomeric excess of the starting material (73% de) gradually changed, the (*R*,*R*)-diastereomer reacted with a significantly higher reaction rate than the (*R*,*S*) diastereomer. Similar advantageous secondary kinetic resolution was described in the hydrogenation of 2,3-butanedione by Studer et al.[13] According to the literature the hydrogenation of (*R*)-imine (**1**)[9] initiates the formation of (*R,R*)-secondary amine (**3**) as a major product, while (*R,S*)-amine (**3a**) forms in minor amounts. Our observation agrees with that of the literature studies. Therefore, we targeted the



Scheme 2.

use of (*R*)-imine (**1**) for the preparation of (*R*)-amine (**5**) after hydrogenation and subsequent hydrogenolysis. From this point of view, the kinetic resolution in the hydrogenolysis helps to improve the originally 73% de value. A mechanistic scheme is illustrated on Scheme 2.

As the scheme shows, based on the considerable difference in the rate of hydrogenolysis between the two diastereomers, at very low conversion (2–3%), the primary amine can be obtained with very high enantioselectivity (up to 97–98% ee), which gradually declines as we approach complete conversion. Certainly, at 100% conversion the final ee for **5** is 73%, which exactly corresponds to the purity of the diastereomeric secondary amine (**3**). According to this pattern, the hydrogenolysis should be stopped at about 50–60% conversion, when the majority of the (*R,S*)-amine (**3a**) starts reacting. We can reach the best possible ee conversion values in this way under the present experimental conditions. The experimental results showed a reasonable match with the theory, and both (*R*)-2,2,2-trifluoro-1-phenylethylamine (90% ee), and the (*S*)-enantiomer (93% ee) were obtained with high selectivity, at 50–55% conversion.

In conclusion, supported palladium catalysts (especially $Pd/BaCO_3$) were found to be effective and selective catalysts for the preparation of chiral 2,2,2-trifluoro-1-phenylethylamines through the diastereoselective hydrogenation of the corresponding *N*-phenylethylimines and the subsequent hydrogenolysis of the methylbenzyl group. Under the best experimental conditions 90–93% ee in 50–55% conversion can be achieved for the trifluoromethylated primary amines. The application of the combined diastereoselective hydrogenation-hydrogenolysis process may open up a new way for the synthesis of trifluoromethylated amines. The extended application of the approach for the preparation of other substituted derivatives will be forthcoming.

Experimental Section

Materials

1,1,1-Trifluroroacetophenone was available from Aldrich, while chiral 2,2,2-trifluoro-1-phenylethyl-*N*-1′-phenylethylimines[14] were synthesized by our recently developed method. The optical purity of (*R*)- and (*S*)-phenylethylamines used for the preparation of the imines were 99.5% ee (Chiraselect grade) and were Fluka products. Solvents with minimum purity of 99.5% were Mallinckrodt and Aldrich products. Catalysts used in the hydrogenations were well-known, commercially available samples from Aldrich and Engelhard. The catalysts were subjected to a reductive pretreatment in the reaction solvent (30 min, RT, 20 bar H_2) prior to reactions.

The intermediate secondary, and the product primary amines were identified by NMR spectroscopy and mass spectrometry. The ^1H, ^{13}C and ^{19}F NMR experiments were carried out using a 300 MHz superconducting NMR spectrometer, in $CDCl_3$ as a solvent. TMS and CCl_3F were used as internal standards. The mass spectrometric analysis including the gas chromatographic separation was carried out using a Hewlett-Packard 5890GC-5971MS GC-MS (70 eV EI ionization, 30 m long DB-5 column).

Diastereoselective Catalytic Hydrogenation of 2,2,2-Trifluoro-1-phenylethyl-*N*-1′-phenylethylimines

The hydrogenations were performed in a Berghof HR-100 autoclave with a teflon liner at room temperature (25 °C). The catalytic system (standard conditions: 50 mg of catalyst, 5 mL of solvent) was prehydrogenated (20 bar hydrogen pressure, 30 min, RT) and subsequently the reactant (0.5 mmol) was introduced. After that the autoclave was flushed with hydrogen several times, filled to the desired pressure and the reaction mixture was stirred (1000 rpm) for the required reaction time. The product identification and the determination of diastereomeric excesses {de $\%=(|[R,R]-[R,S]|)\times 100/([R,R]+[R,S])$} were carried out by ^{19}F NMR spectroscopy using CCl_3F as an internal standard [^{19}F NMR chemical shifts of CF_3 group; $\delta = -71.5$ ppm (**1**), -73.5 ppm (**3**), -74.5 ppm (**3a**)].

Hydrogenolysis of the Methylbenzyl Group

The hydrogenolysis was carried out after the diastereoselective hydrogenation in the same reaction vessel, without isolation of the secondary amines. 0.5 mL 0.1 M HCl in ether was added to the mixture of diastereomers, and the mixture was hydrogenated under 10 bar hydrogen pressure at 70 °C for the required time, and then the reaction was stopped. The solvents were evaporated, then the remaining ammonium salt was dissolved in water, and neutralized with 5% aqueous NaOH. The free amines then were extracted with ether and analyzed by GC-MS and ^{19}F NMR. The enantiomeric excesses {ee %=$(|[R]-[S]|)\times 100/([R]+[S])$} of the final product primary amines were determined by gas chromatography (Varian 3400GC, 30 m Beta-Dex capillary column, flame ionization detector).

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