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Enantioselective Synthesis of β-Trifluoromethyl α-Amino Acids

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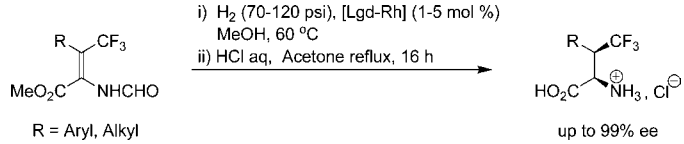
ABSTRACT



We report herein the three-step enantioselective synthesis of β-trifluoromethyl α-amino acids including trifluorovaline (TFV) using stereoselective hydrogenation with [((*R*)-trichickenfootphos)Rh(cod)]BF_4 catalyst as the key step.

An increasing number of fluorinated derivatives, particularly amino acids,[1] have found innovative and valuable applications in medicinal chemistry and biochemistry. Indeed, these derivatives have the capacity to enhance helical protein stability by taking advantage of the hydrophobicity of fluorinated hydrocarbon chains, increasing the protein−protein interaction's selectivity in peptide and protein designs.[2] Fluorine has been successfully used to increase drug activity as it is capable of inhibiting pyridoxal enzymes.[3] The small sterical change and therefore minimal protein structural perturbations involved in the use of fluorine has permitted Tirell and co-workers to successfully insert 5,5,5-trifluoroisoleucine (TFI) in proteins and enzymes using in vitro and in vivo protein engineering method using *E. coli*.[4]

There have been constant efforts in the development of new methods for the synthesis of enantiomerically pure fluorinated amino acids.[5] Optically pure 4,4,4-trifluorovaline (TFV) was first isolated by Kumar and co-workers using enzymatic resolution.[6] Later on, Qing and co-workers developed a practical diastereoselective allylation method for the synthesis of TFV and TFI.[7] Recently, Hu and co-workers were the first to report the application of chiral hydrogenation technology to synthesize various fluoro-containing amino acids.[8] However, this hydrogenation was limited to trisubstituted alkenes. A three-step synthesis of TFV and analogues using catalytic and asymmetric hydrogenation of tetrasubstituted trifluoromethyl alkene precursors as the key step is reported. Numerous ligands, conditions, and their effects upon the yield and selectivity of the process were examined in this study.

The prochiral alkenes (Scheme 1) were prepared using Schollkopf's procedure,[9] which generates a formyl protective group on the nitrogen that requires very mild deprotection conditions.

A benefit of using a formyl group versus an acetyl was reported by Feringa and co-workers who observed no racemization upon deprotection.[10,11] Alkenes **1a**−**f** were

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(2) Chiu, H.-P.; Yuta, S.; Gullickson, D.; Ahmad, R.; Kokona, B.; Fairman, R.; Cheng, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 15556.
(3) (a) Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.; Kuhar, V. P.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **1994**, *5*, 2009. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (c) Sakai, T.; Yan, F.; Kashino, S.; Uneyama, K. *Tetrahedron* **1996**, *52*, 233. (d) Kollonitsch, J.; Patchett, A. A.; Marburg, S.; Maycock, A. L.; Perkins, L. M.; Doldouras, G. A.; Duggan, D. E.; Aster, S. D. *Nature* **1978**, *274*, 906.
(4) Wang, P.; Tang, Y.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 6900.
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(8) Hu, Z.; Han, W. *Tetrahedron Lett.* **2008**, *49*, 901.
(9) Enders, D.; Chen, Z.-X.; Raabe, G. *Synthesis* **2005**, 306.

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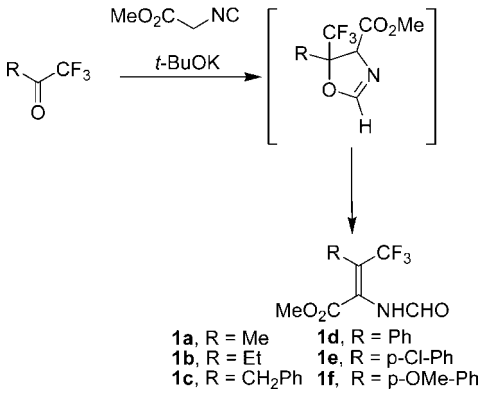
Scheme 1. Synthesis of Prochiral Compounds Using Schollkopf's Procedure

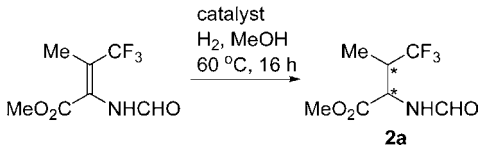


prepared in 60−80% yield and purified by chromatography before being subjected to asymmetric hydrogenation.

It has been widely reported that only a few ligands are able to achieve good enantioselectivity and conversion on tetrasubstituted dehydroamino acids.[12−14] Indeed, these substrates are more challenging for chiral hydrogenation as the olefin is sterically more hindered and electronically enriched. These few ligands are very substrate specific, and thus, a slight change in substrate can have a dramatic impact on the performance of the hydrogenation.

Screening was carried out using two different conditions: 120 psi with S/C 20 and 70 psi with S/C 100.[15] A summary of the best results obtained on alkene **1a** is reported in Table 1.

Table 1. Asymmetric Hydrogenation of **1a**: Screening of Various Conditions with Various Catalysts[a]



entry	catalyst	method	convn (%)	ee (%)
1	L_1 + $Rh(nbd)_2BF_4$	B	100	79 (2*S*,3*S*)
2	L_2 + $Rh(nbd)_2BF_4$	B	85	72 (2*R*,3*R*)
3	L_3	B	95	87 (2*R*,3*R*)
4	L_4	A	100	89 (2*S*,3*S*)
5	L_5	A	100	78 (2*S*,3*S*)
6	L_6	B	100	92 (2*S*,3*S*)
7	L_7	B	100	>99 (2*R*,3*R*)

[a] Reactions were performed on 1 mmol of substrate at 60 °C with a substrate concentration of 0.4 M. Method A is performed at 120 psi of H_2 with S/C 20, and method B is performed at 70 psi of H_2 with S/C 100. Each reaction was stopped after 16 h. Enantiomeric excesses were determined via chiral GC as described in the Supporting Information.

Our initial screening comprised of Johnson-Matthey ligands (Phanephos and Me-BoPhoz) known to have good activity on tetrasubsituted dehydroamino acids.[13,14] Unlike the trend reported on similar substrates, these ligands gave stereochemical induction of less than 15% ee. A secondary screen was run using ferrocennyl-based ligands from Solvias. Their long shelf life and stability to air makes them an attractive set of ligands. Initially, low enantioselectivities (<50% ee) were obtained using the Josiphos and Mandiphos ligands.

However, more promising results were obtained using ligands from the Walphos family (Figure 1).[16] W003-1 ($\mathbf{L_1}$)

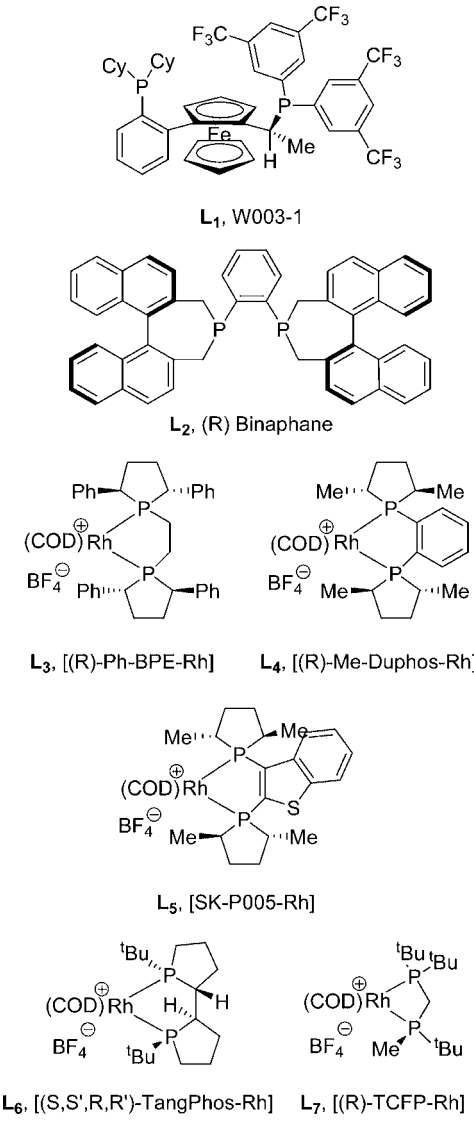


Figure 1. Best chiral catalysts and ligands screened.

gave complete conversion with 79% ee (entry 1). Interestingly, with an additionnal test using this ligand at 70 psi,

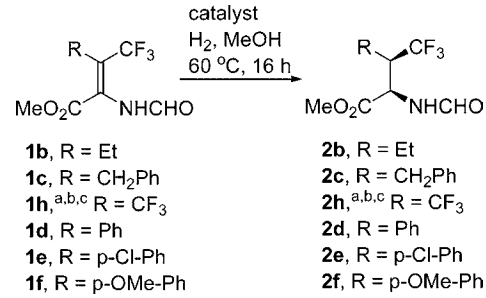
(10) Panella, L.; Aleixandre, A. M.; Kruidhof, G. J.; Robertus, J.; Feringa, B. L.; De Vries, J. G.; Minnaard, A. J. *J. Org. Chem.* **2006**, *71*, 2026.
(11) Sheehan, J. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1154.
(12) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (b) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375.

we were able to increase the S/C ratio to 1000 and still obtain 91% conversion with 75% ee. Our next catalyst screening involved the well-known BINAP family. Higher selectivity (86% ee) was obtained with [Binap-Ru] preformed complex but with only a 45% conversion with S/C 50 in methanol. The conversion was successfully increased to 95% by using a more acidic solvent, trifluoroethanol. Unfortunately, it was accompanied with a significant loss of selectivity (57% ee). The best result from this series was using binaphane ($\mathbf{L_2}$) with complete conversion at S/C 100 with reasonable enantioselectivity (72% ee, entry 2). DUPHOS[12] and BPE are the most widely used family of ligands for asymmetric hydrogenation of tetrasubstituted dehydroamino acids. Therefore, it is with no surprise that we observed selectivities of up to 89% using these ligands.

Ph-BPE ($\mathbf{L_3}$)-catalyzed reaction could be accomplished with 1 mol % of catalyst. Higher pressure and higher catalytic amounts seemed to be necessary for complete conversion with both Me-Duphos ($\mathbf{L_4}$) and its analogue SK-P005 ($\mathbf{L_5}$) (entries 3−5). Finally, high enantioselectivity (92% ee) was obtained using Tangphos ($\mathbf{L_6}$) (entry 6),[17] a ligand which holds chirality on both carbon and phosphorus.Another chiral phosphorus-type ligand was then screened: trichickenfootphos-Rh, TCFP-Rh ($\mathbf{L_7}$). It was developed by Hoge and coworkers[18] who reported outstanding results such as high TON (up to 27000) and nearly perfect enantioselectivity (>98% ee) on various trisubstituted olefins and a few symmetrical tetrasubstituted α-dehydroamino acids. We were able to successfully use the $\mathbf{L_7}$ catalyst in the hydrogenation of substrate **1a** giving complete conversion and a very high selectivity of above 99% ee (entry 7). We then decided to extend the scope of our work by substituting the β-methyl group with other alkyl or aryl groups (Table 2). A consistent stereochemical induction was observed going from methyl-substituted alkene **1a** to ethyl-substituted akene **1b** with catalyst $\mathbf{L_7}$ (>99% ee, Table 2, entry 1).

The introduction of the benzyl group (**1c**) allowed for study of steric effects, and once again, not only was the conversion high but the selectivity was also found to be excellent (99% ee, Table 2 entry 3). The benzyl and the hexafluoro olefin (**1c** and **1h**) seem to be very unique as most catalysts tested apart from $\mathbf{L_7}$ gave conversion below 20% with low selectivity (<20% ee). This was surprising as one can usually expect to achieve some good conversions and potentially some good selectivities in at least a couple of other similar catalysts. We next investigated the impact of steric and electronic effect using aromatic substituents (**1d**−**f**). First, we demonstrated that the hydrogenation of these substrates needed to be run with a mimimum of 5 mol % of catalyst and higher pressure of 250 psi to get full conversion (method C) in 16 h. Unfortunately, having the aryl directly attached to the double bond seems to lower the reactivity of the substrates toward the $\mathbf{L_7}$ catalyst. The reactions ranged from 14 to 78% completion within 16 h, with selectivities under 50% ee. The best results were obtained with $\mathbf{L_3}$, which gave around 90% ee on three different substrates (Table 2, entries 7, 9, and 11). Having these results in hand, we concluded that $\mathbf{L_7}$ requires a methylene group to get very high selectivity and/or conversion (Scheme 2).

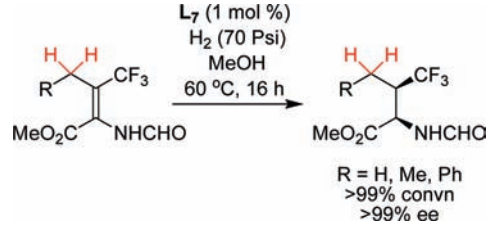
Table 2. Hydrogenation of (*Z*)-Alkyl- or -Aryl-4,4,4-trifluoro-2-formamido-3-methylbut-2-enoate[a]



entry	catalyst	method	product	convn (%)	ee (%)
1	L_7	B	**2b**	100	>99
2	L_3	B	**2b**	100	60
3	L_7	B	**2c**	100	99
4	L_3	B	**2c**	0	N/A
5	L_7	B	**2h**	100	86
6	L_7	C	**2d**	78	50
7	L_3	C	**2d**	100	93
8	L_7	C	**2e**	14	50
9	L_3	C	**2e**	100	91
10	L_7	C	**2f**	65	39
11	L_3	C	**2f**	100	90

[a] Reactions were performed on 1 mmol of substrate at 60 °C with a substrate concentration of 0.4 M. Method B was performed at 70 psi of H_2 with S/C 100 and method C at 250 psi of H_2 with S/C 20. Each reaction was stoppped after 16 h. Enantiomeric excesses were determined via chiral GC or HPLC as described in the Supporting Information. Key: (a) for olefin preparation, see the Supporting Information; (b) starting material and product bearing an acetamide instead of formamide; (c) ethyl ester.

Scheme 2. Generalized Reaction for Highly Stereoselective Hydrogenation with [TCFP-Rh] ($\mathbf{L_7}$) Catalyst



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(15) S/C means substrate over catalyst ratio; S/C 20 = 5 mol % of catalyst; S/C 100 = 1 mol % of catalyst.

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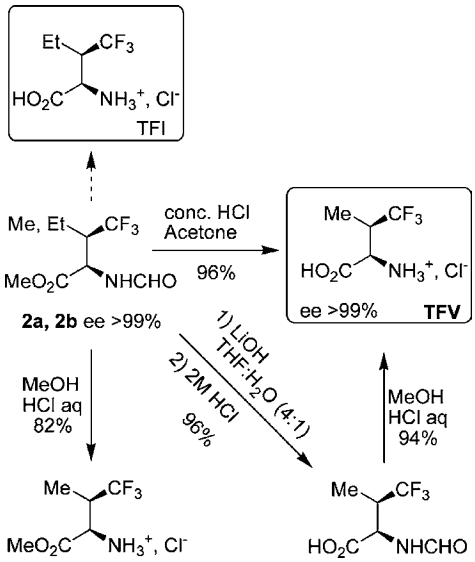
Scheme 3. Synthesis of Enantiopure TFV and Derivatives



During the hydrogenation screening of all alkenes, diastereoisomers were never observed with chiral catalysts, but a maximum of 40% de was obtained while preparing racemic compounds (**2a**−**f**) with Pd/C for chiral HPLC references.[19]

(19) Reactions were performed on 1 mmol of substrate at 60 °C with a substrate concentration of 0.4 M in MeOH with 15% Pd/C (10%) at 250 psi of H_2.

Finally, we demonstrated that the asymmetric hydrogenation approach could be used to generate enantiopure amino acids. A simple treatment with concentrated HCl in acetone afforded optically pure TFV from **2a** (Scheme 3). The same conditions applied on **2b** would lead to enantiopure trifluoroisoleucine (TFI). It is also possible to generate many other derivatives such as amino esters or *N*-formyl-protected amino acids using simple transformations described in Scheme 3, with preservation of stereochemical integrity.

In conclusion, we report the first synthesis of β-trifluoromethyl-α-amino acid precursors (**2a**−**g**) using stereoselective hydrogenation and its application to the synthesis of fluorinated amino acids such as TFV. We believe the same approach can be used for the preparation of other analogues such as TFI and/or aromatic analogues.

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Supporting Information Available: Experimental procedures and compound characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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