

Catalytic Asymmetric Hydrogenation of α -CF₃- or β -CF₃-Substituted Acrylic Acids using Rhodium(I) Complexes with a Combination of Chiral and Achiral Ligands**

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Dedicated to Professor Manfred T. Reetz on the occasion of his 70th birthday

The introduction of trifluoromethyl (CF₃) groups into organic molecules can substantially modify the lipophilicity, metabolic stability, and bioavailability of the biologically interesting molecules, and thus has attracted much attention from synthetic chemists over recent years.^[1,2] Optically active carboxylic acids with CF₃ substituents are versatile chiral building blocks for the synthesis of pharmaceuticals, agrochemicals, natural products and fragrances.^[3] Accordingly, the development of methodologies for the enantioselective construction of trifluoromethylated carboxylic acid derivatives is highly desirable and has become an important research area.^[2] However, the catalytic asymmetric synthesis of optically active α -CF₃- or β -CF₃-substituted propanoic acid derivatives is less explored, with α -trifluoromethylation of some specific carbonyl compounds^[4] and conjugate addition of β -trifluoromethylated acrylic acid derivatives being among the few documented examples.^[5] In this context, asymmetric hydrogenation (AH) of α - or β -trifluoromethylated acrylic acid derivatives, one of the most straightforward and environmentally benign approaches, still remains a big challenge,^[6,7] probably because of the highly electron-withdrawing nature of the CF₃ group in the olefinic substrates, despite the fact that numerous chiral catalysts have been successfully developed for the AH of various nonfluoro-substituted acrylic acids. Even though a few Ru^{II} or Rh^I complexes with chiral bisphosphine ligands catalyze the hydrogenation of some specific α -CF₃- or β -CF₃-substituted acrylic acids, the procedures are usually associated with only a single substrate.^[6,7] Herein, we report a highly enantioselective AH of a broad range of α -CF₃- or β -CF₃-substituted acrylic acids, using a Rh^I complex generated in situ with a mixture of a chiral secondary phosphine oxide (SPO) and an achiral triarylphosphine ligand, as the catalyst.

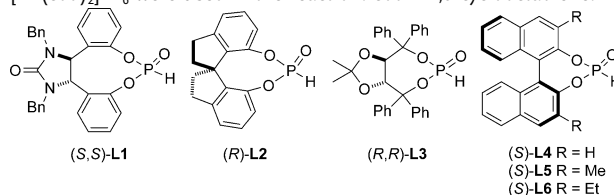
The research project was inspired by the excellent performance of chiral SPO molecules as preligands in Rh^I-

catalyzed AHs of a variety of olefinic substrates.^[8] The feasibility of using Rh^I/SPO-type catalysts in AHs of CF₃-substituted acrylic acid derivatives was first investigated by screening several SPO ligands (**L1–L6**) with α -CF₃-substituted cinnamic acid ((*Z*)-**1a**) as a model substrate (Table 1).

Table 1: Effect of PPh₃ on the Rh^I-catalyzed asymmetric hydrogenation of (*Z*)-**1a** in the presence of SPO preligands **L1–L6**.^[a]

Entry	L ([mol %])	Ph ₃ P [mol %]	Conv. [%] ^[b]	ee [%] ^[c]
1	(<i>S,S</i>)- L1 (2)	1	30	37 (<i>S</i>)
2	(<i>R</i>)- L2 (2)	1	44	58 (<i>R</i>)
3	(<i>R,R</i>)- L3 (2)	1	95	23 (<i>S</i>)
4	(<i>S</i>)- L4 (2)	1	74	11 (<i>R</i>)
5	(<i>S</i>)- L5 (2)	1	80	84 (<i>R</i>)
6	(<i>S</i>)- L6 (2)	1	82	92 (<i>R</i>)
7 ^[d]	(<i>S</i>)- L6 (2)	1	> 99	98 (<i>R</i>)

[a] Reaction conditions: 1 mol % [Rh(cod)₂]BF₄, [**1a**] = 0.1 M. [b] Determined by ¹⁹F NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase after **2a** was transformed to its corresponding methyl ester with CH₂N₂. The absolute configurations were assigned by comparison of their optical rotations with reported values (see the Supporting Information). [d] The solvent mixture CHCl₃/H₂O (4/1) and [Rh(cod)₂]PF₆ were used in the reaction. cod = 1,5-cyclooctadiene.



As shown in Table S1 in the Supporting Information, only very poor conversions (16 h, < 15 %) were obtained under the initially tested conditions, indicating that the complexes generated with Rh^I and these SPO ligands are not adequately active for catalysis. Gratifyingly, when we investigated the reaction using Rh^I complexes with SPO/PPh₃^[9] monodentate ligand mixtures,^[10–16] the addition of achiral PPh₃ had a profound influence on the catalysis, as evidenced by the substantial improvement in the catalytic performance (30–95 % conversions, 11–92 % ee, Table 1, entries 1–6). Such a dramatic change in catalytic behavior upon addition of PPh₃ can be attributed to an active Rh^I species, coordinated

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Table 3: Rh^I-catalyzed asymmetric hydrogenation of β-CF₃-substituted acrylic acids **3a–s**.^[a]

$ \begin{array}{c} \text{Rf} \\ \\ \text{R} - \text{C} = \text{C} - \text{COOH} \\ \text{(E)- or (Z)-3a–3s} \end{array} + \text{H}_2 \xrightarrow[20 \text{ atm}]{\begin{array}{c} [\text{Rh}(\text{cod})_2\text{PF}_6] (1 \text{ mol}\%) \\ (\text{S})\text{-L6} (2 \text{ mol}\%), \text{PPh}_3 (1 \text{ mol}\%) \\ \text{morpholine} (10 \text{ mol}\%) \\ \text{CHCl}_3/\text{H}_2\text{O} (4/1), \text{RT}, 16 \text{ h} \end{array}} \begin{array}{c} \text{Rf} \\ \\ \text{R} - \text{CH} - \text{CH}_2 - \text{COOH} \\ \text{4a–4s} \end{array} $							
Entry	Substrate	Product	Ee [%]	Entry	Substrate	Product	Ee [%]
1			99 (R)	11			97 (R)
2 ^[b]			> 99 ^[e]	12			> 99 (R)
3 ^[b,c]			> 99 ^[e]	13			98 (R)
4 ^[b,c]			94 ^[e]	14 ^[b]			> 99 (R)
5			> 99 (R)	15			99 (R)
6			> 99 (R)	16 ^[d]			90 ^[e]
7			> 99 (R)	17			> 99 (R)
8			98 (R)	18			97 (S)
9			> 99 (R)	19			> 99 (R)
10			97 (R)	20 ^[d]			92 ^[e]

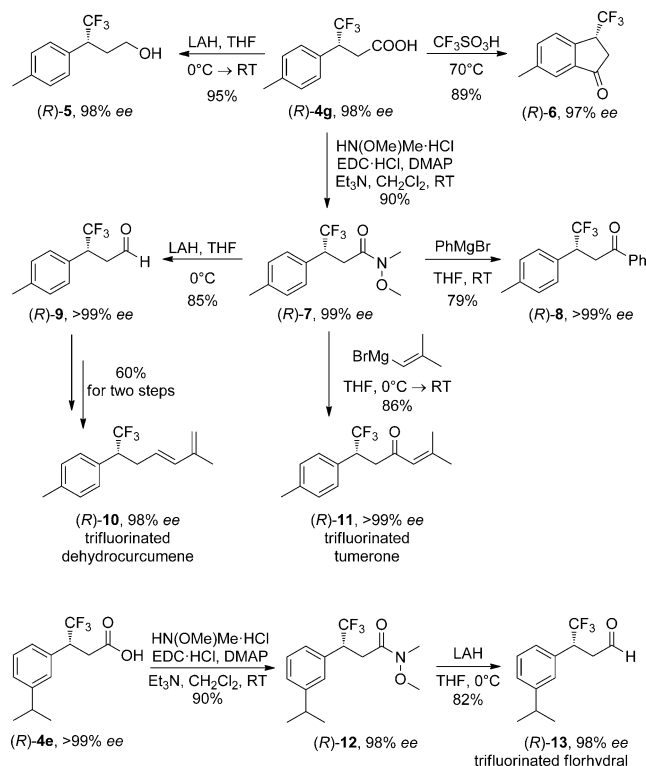
[a] Reaction conditions: [3] = 0.10 M. All conversions were higher than 99%, as determined by ¹⁹F NMR spectroscopy. The ee values were determined by HPLC on a chiral stationary phase after the acids were transformed to their corresponding methyl esters with CH₂N₂, and the absolute configurations of the products were deduced by comparison of their Cotton effects with that of (R)-(-)-4f in the CD spectra (see the Supporting Information). [b] 50 atm H₂, 24 h. [c] 2 mol% catalyst. [d] The ee values were determined directly by GC on a chiral stationary phase. [e] The absolute configuration was not assigned.

However, the sterically more crowded substrates required higher hydrogen pressure (50 atm), a longer reaction time (24 h), and/or a higher catalyst loading (2 mol%) for complete conversions (Table 3, entries 2–4). Remarkably, AHs of *E* or *Z* isomers of **3c** gave the products (–)-**4c** or (+)-**4c**, respectively, with the same level of enantioselectivity (94% ee), but the opposite sense of asymmetric induction (Table 3, entry 3 vs. entry 4), suggesting a directing effect of carboxy group.^[9,18] The AH of analogous substrates containing pyrrol-2-yl or indol-3-yl at the β position of acrylic acid

proceeded with excellent enantiocontrol to give the corresponding hydrogenated products (R)-**4m** or (R)-**4n**, respectively, in more than 99% ee (Table 3, entries 14 and 15). The catalyst system also worked very well for β-alkyl-β-CF₃-substituted acrylic acid derivatives (E)-**3o** and (E)-**3p** (Table 3, entries 16 and 17), as well as β-difluoromethyl- and pentafluoroethyl-substituted cinnamic acids ((Z)-**3q** and (E)-**3r**; Table 3, entries 18 and 19), to afford full conversion of the substrates with excellent enantioselectivities. Furthermore, the AH of (E)-**3s**, a β-CF₃-substituted acrylic acid with

an α -methyl substituent, provided the corresponding product with 92 % *ee* (Table 3, entry 20). It should be noted that some of the obtained hydrogenation products are highly valuable chiral synthons or bioactive molecules. For example, (*R*)-**4f** (>99 % *ee*) is the key intermediate in the synthesis of an inhibitor of β -amyloid production,^[6c] while (*R*)-**4m** (>99 % *ee*) has been used as a key intermediate for the synthesis of a biologically interesting heliotridane analogue.^[5a] Compound (*R*)-**4n** (>99 % *ee*) itself is a plant growth regulator (TFIBA),^[5b] while (*S*)-**4o**^[19] and **4s**^[19c,20] are well-known intermediates for pharmacologically active compounds that contain a trifluoromethyl group, such as amino acid antagonists or inhibitors.

Apart from the useful hydrogenation products **4f**, **4m**, **4n**, and **4o** mentioned above, the synthetic utility of the present procedure was further demonstrated with a series of transformations of (*R*)-**4g** into the corresponding alcohol **5**, cycloketone **6**,^[21] and Weinreb amide **7** without any loss of enantiopurity (Scheme 1; for details, see the Supporting Information). As a synthetically versatile intermediate, the



Scheme 1. Transformation of hydrogenation products to optically active CF_3 -substituted synthons and bioactive molecules. DMAP = 4-dimethylaminopyridine, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, LAH = lithium aluminum hydride.

Weinreb amide **7** was further transformed into a variety of useful chiral products (**8–11**), including trifluorinated natural products,^[3b] such as dehydrocurcumene **10** and tumerone **11**. Finally, (*R*)-**4e** was transformed into a trifluorinated analogue of florhydral through a two-step sequence without significant loss of optical purity.

In summary, a Rh^I catalyst containing a simple chiral SPO ligand (*S*)-**L6** and an achiral Ph_3P ligand was developed for highly efficient asymmetric hydrogenations of various α - CF_3 - or β - CF_3 -substituted acrylic acids with excellent enantioselectivities. This catalyst system provides a straightforward approach to diverse optically active α - CF_3 - or β - CF_3 -substituted propanoic acid derivatives with biological importance. The resultant products were readily transformed to a variety of optically active CF_3 -substituted synthons and bioactive molecules.

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