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PN-Ligands for Asymmetric Reduction of Ketones

Ru-(phosphino-oxazoline) complexes are effective, industrially viable hydrogenation catalysts for the enantioselective hydrogenation of aryl ketones

The enantioselective reduction of aryl ketones is an important transformation both from an academic/synthetic as well as an industrial point of view [1]. Besides biocatalytic and hydride reduction methods, two different effective hydrogenation methods have been developed:

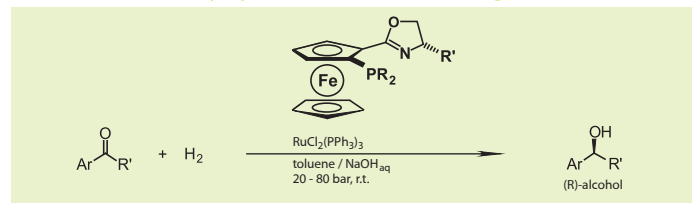
- transfer hydrogenation, where the reducing agent is a hydrogen donor such as formic acid or isopropanol [2]
- the catalytic addition of H₂ to the ArCO double bond [1a].

Oxazoline-based ligands have attracted a lot of attention in the past 15 years especially due to their ease to prepare in enantio-pure form, coordination properties towards a large variety of metals and the generally high enantioselectivities they are associated to for various asymmetric catalytic reactions. Indeed level of enantioselectivities above 95% have been obtained using oxazoline based ligands in various catalytic reactions such as: Hydrosilylation, Diels-Alder, allylic alkylation, cyclopropanation, hydrogenation of olefins, transfer hydrogenation of ketones. For the later Helmchen, Uemura and Samakia [3] have reported in the late 90's several Ru-phosphino-oxazoline catalysts which transfer hydrogenate aryl ketones with % ee > 95% using iPrOH as a proton source. The limitation of this method is that the concentration of the ketone must be low (0.04 to 1 M [ketone]), the S/C maximum 400, and the ee is subject to erosion at long reaction times. Although attractive for its simplicity and the high enantioselectivity of the catalyst, this method is not suited for industrial purposes.

Solvias circumvented these drawbacks and developed a hydrogenation process which hydrogenate aryl ketones with [ketone] = 3 M to neat, S/C = 10'000 to 50'000 and without erosion of the ee upon longer reaction time.

To the best of our knowledge this is:

- The first system which is amenable to both transfer hydrogenation and hydrogenation with high ee and activity.
- The first Ru/ligand catalyst which can hydrogenate aryl ketones with high ee and activity without a N-H containing ligand.
- The first industrial catalytic process with an oxazoline based ligand.



References:

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- [2] (a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* 1997, 30, 97. (b) M.J. Palmer, M. Wills, *Tetrahedron: Asymmetry* 1999, 10, 2045.
- [3] (c) G. Zassinovich, G. Mestroni, S. Gladioli, *Chem. Rev.* 1992, 92, 1051.
- [3] (a) T. Sammakia, E.L. Stangeland, *J. Org. Chem.* 1997, 62, 6104. (b) Y. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* 1999, 18, 2291. (c) T. Langer, G. Helmchen *Tetrahedron Letters* 1996, 37 (89), 1381.

Catalyst RuCl₂(PPh₃)₃ + PR'₂-Fc-oxa R' s/c: 50'000, p(H₂) 20-40 bar, 25 °C, Toluene, NaOH_{aq}; Ru = 100, 3 M-Neat

Substrate								
Ligand								
	Yield [%]	all 100 in 2 h - 4 h					99 ^a	98*
	ee [%]	95	92	94	93	98	>98 ^a	>95*
	Yield [%]	all 100 in 2 h - 4 h						
	ee [%]	92	94	92	94	98		
	Yield [%]	all 100 in 2 h - 4 h						
	ee [%]	92	89	96	95	97		

A total of 300 kg manufactured in less than 2 months from screening to production plant. Solvias in cooperation with Rohner AG, Pratteln Switzerland

* RuCl₂(PPh₃)₃ PPh₂-Fc-oxa iPr, s/c = 20'000, sm loading > 10% weight, p(H₂), 20 bar, 25 °C
Toluene, NaOH_{aq}; Ru = 100
^a s/c = 20'000

Industrial Success with Tunability and Modularity

New aryl ortho-substituted ligands

R	Ketone				
	SL-N003-2	90 (100)	83 (100)	92 (100)	rac (100)
	SL-N012-2	94 (100)	85 (100)	n.d.	56 (90)
	SL-N011-2	96 (100)	97 (100)	97 (100)	90 (100)

Increased enantioselectivities with ortho-substituted aryl phosphines

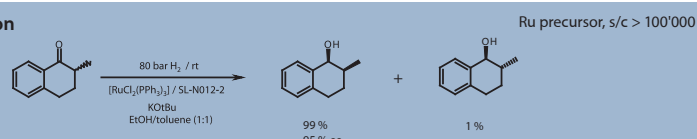
ee values (figures in bold); conversion: values in parenthesis

Solvias Ligand Kit

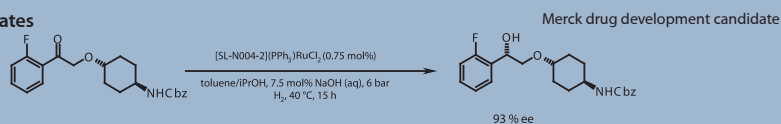
Broad selection for your screening

Solvias ligands available from Sigma-Aldrich, Strem Chemicals, Wako

Dynamic kinetic resolution



Real-life substrates



Work performed by Merck, details available: D.M. Tellers et al. *Tetrahedron Asymmetry* 2006, 17, 550.