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Zinc-Catalyzed Asymmetric Hydrosilylation of Cyclic Imines: Synthesis of Chiral 2-Aryl-Substituted Pyrrolidines as Pharmaceutical Building Blocks

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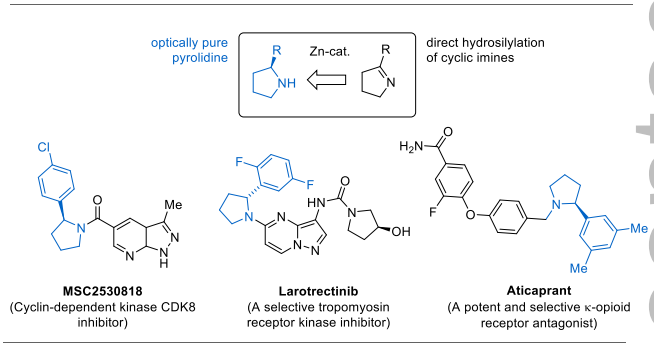
Abstract. The first successful enantioselective hydrosilylation of cyclic imines promoted by a chiral zinc complex is reported. *In situ* generated zinc-ProPhenol complex with silane afforded pharmaceutically relevant enantioenriched 2-aryl-substituted pyrrolidines in high yields and with excellent enantioselectivities (up to 99% *ee*). The synthetic utility of presented methodology is demonstrated in an efficient synthesis of the corresponding chiral cyclic amines, being pharmaceutical drug precursors to the Aticaprant and Larotrectinib.

Keywords: Asymmetric synthesis; Zinc; Reduction; Hydrosilylation; Cyclic imines

Chiral 2-substituted pyrrolidines are important building blocks due to their ubiquitous structural motifs found in many natural products,[1] pharmaceutical compounds[2] and drug candidates.[3] In particular, 2-aryl-substituted pyrrolidine derivatives are pharmaceutically relevant molecules used in the synthesis of drugs e.g. Aticaprant (κ-opioid receptor antagonist effective in the treatment of depression disorder and anxiety) or Larotrectinib (a highly selective inhibitor of neurotrophin receptor kinase recently approved for treating tumors harboring neurotrophin receptor (NTRK) gene fusions) (Scheme 1).[3] Broad application scope in both pharmaceutical and agrochemical industries stimulates intensive studies, and it is of central importance in organic synthesis.[1-3]

In the past decades, numerous catalytic methodologies for the construction of optically pure cyclic amines have been developed,[4] mostly rely on bio-,[5] organo-[6] and transition-metal catalysis.[7] Despite these achievements,[4-7] the alternative synthesis of chiral amines *via* the enantioselective hydrosilylation of cyclic imines appears especially attractive strategy. The advantages of hydrosilylation reactions include its simplicity combined with mild conditions and employing readily available and safe hydrosilanes. In contrast to well-established asymmetric hydrosilylation of acyclic imines promoted by numerous metal-based complexes,[8] the arsenal of known catalysts for hydrosilylation of cyclic imines is restricted to few examples of titanium complexes and platinum-group metals.[9] Therefore the development of efficient and inexpensive catalysts for the hydrosilylation of prochiral cyclic imines is still very challenging and highly desirable goal.



Scheme 1. Biologically active compounds and pharmaceutical drugs containing 2-aryl-substituted pyrrolidine fragments.

A major breakthrough in the enantioselective hydrosilylation of cyclic imines was reported by Buchwald in 1996.[9c] The use of chiral titanocene-complex proceeded highly enantioselectively, however, the proposed catalyst required pre-activation and the substrate scope was mainly limited to a few simple cyclic imines.[9b,9c,10] Following this achievement, the more efficient catalysts were showed by Uemura and Hidai.[9a] Application of ruthenium(II)- and iridium(II)-

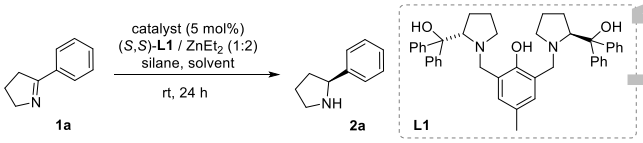
oxazolinyl-ferrocenylphosphine-complexes provided optically pure 2-substituted pyrrolidine derivatives with good enantioselectivities (up to 88% *ee*), whereas replacing substrates to six-membered imines was completely ineffective.[9a] Recently, Speed and co-workers presented an alternative method to this approach by asymmetric hydroboration using chiral phosphenium cations.[4a] Although authors tested several hydrosilanes, the highest yields and enantioselectivites (72–94% *ee*) of the corresponding chiral pyrrolidines and piperidines were obtained in case of the use of HB(pin) as a reducing agent.[4a]

Despite the progress achieved in enantioselective hydrosilylation of prochiral cyclic imines, some areas such as: difficult catalyst preparation, limited availability, high toxicity, and the cost of noble metal complexes, indicate the need for the development of more sustainable reaction conditions. Replacement of platinum-group metals is recently one of the great challenges in organic chemistry, because their usage represents substantial limitations, especially in the synthesis of bioactive compounds.[1-3,9] A promising alternative, still unexplored, is to use in the reduction of cyclic imines, an environmentally benign and easily accessible chiral zinc complexes. Inspired by our previous experience in zinc-catalyzed asymmetric hydrosilylation of ketones[8b,11] and acylic imines,[8a,8b,11] in this paper, we present the first example of a highly efficient and enantioselective hydrosilylation of a wide variety of 2-aryl-substituted pyrrolines promoted by a Trost-type zinc complex.[12] Presented concept requires application of the commercially available ProPhenol ligand and is superior to previously published protocols in terms of reaction efficiency and enantioselectivity.

Our initial aim was to identify the best-suited zinc complex in terms of both reaction conversion and enantioselectivity. After many trials, we found that the readily available chiral Zn-ProPhenol complex is the best catalyst candidate for the hydrosilylation of 2-phenyl-1-pyrroline (**1a**) as a model substrate. Encouraged by the promising results, a series of silanes as reducing agents and various solvents were tested to improve the reaction outcome (Table 1). Data collected in Table 1 indicates that the application of $(EtO)_2MeSiH$ as a hydrogen source in reduction had a significant impact on the reaction selectivity (Table 1, entry 5). From among the tested solvents, only tetrahydrofuran (THF) proved to be the best choice with respect to efficiency and enantioselectivity up to 66% *ee* of the newly formed product (**2a**) (Table 1, entry 5). Considering further improvement of reaction enantioselectivity, the optimal amount of employed hydrosilane was evaluated in the presence of 5 mol% of the catalyst (Table 1). We found that the increased values of equivalents of this particular hydrosilane played a crucial role in asymmetric induction and reaction efficiency. To our delight, higher silane loading (4 equiv.) from the initially used amount of $(EtO)_2MeSiH$ resulted in the formation of desired amine **2a** in 98% yield and with a high level of enantioselectivity in the range of 88% (Table 1, entry 10 vs. 5). The use of the (*R*,*R*)-ProPhenol enantiomer of ligand **L1** also promoted the reduction without any loss of both reactivity and selectivity (Table 1, entry 11).

To improve the stereoselectivity of the hydrosilylation, further investigations were carried out including the effects of catalyst loading, time and reaction temperature (Table 2). Based on the initial screening performed at room temperature, cooling down to 4 °C increased the *ee* up to 95% of the corresponding product **2a** in case of 5 mol% of the catalyst**,** albeit the efficiency suffered (Table 2, entries 3-4). Although the prolongation of the reaction time had only little effect on the conversion of substrate, the highly promising attempt with chiral zinc-complex encouraged us to pursue further optimizations. A satisfactory yield up to 97% was obtained without any loss of *ee* by employing 10 mol% of the catalyst and prolonged the reaction time up to 48 h (Table 2, entry 7).

Table 1. Initial screening of silanes and solvents in asymmetric hydrosilylation of cyclic imines.[a]



Entry	Silane	Equiv.	Solvent	Yield (%)[b]	*ee* (%)[c]
1	$(EtO)_3SiH$	3.0	THF	73	45
2	$PhSiH_3$	3.0	THF	49	10
3	$PhMe_2SiH$	3.0	THF	trace	–
4	PMHS	3.0	THF	67	64
5	$(EtO)_2MeSiH$	3.0	THF	80	66
6	$(EtO)_2MeSiH$	3.0	MeCN	30	59
7	$(EtO)_2MeSiH$	3.0	Toluene	97	54
8	$(EtO)_2MeSiH$	3.0	DCM	92	55
9	$(EtO)_2MeSiH$	3.4	THF	87	74
10	**$(EtO)_2MeSiH$**	**4.0**	**THF**	**98**	**88**
11[d]	$(EtO)_2MeSiH$	4.0	THF	98	88 (*S*)
12	$(EtO)_2MeSiH$	4.5	THF	98	86

[a] Reactions were carried out by stirring a solution of $ZnEt_2$ (10 mol%, 15 wt. % in toluene) with (*S*,*S*)-ProPhenol **L1**-ligand (5 mol%) in THF (1 mL) at room temperature for 24 h, containing DEMS (1.5-2.3 mmol) and cyclic imine (**1a**) (0.5 mmol) dissolved in THF (0.2 mL) unless otherwise stated. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction performed with (*R*,*R*)-ProPhenol **L1**. The absolute

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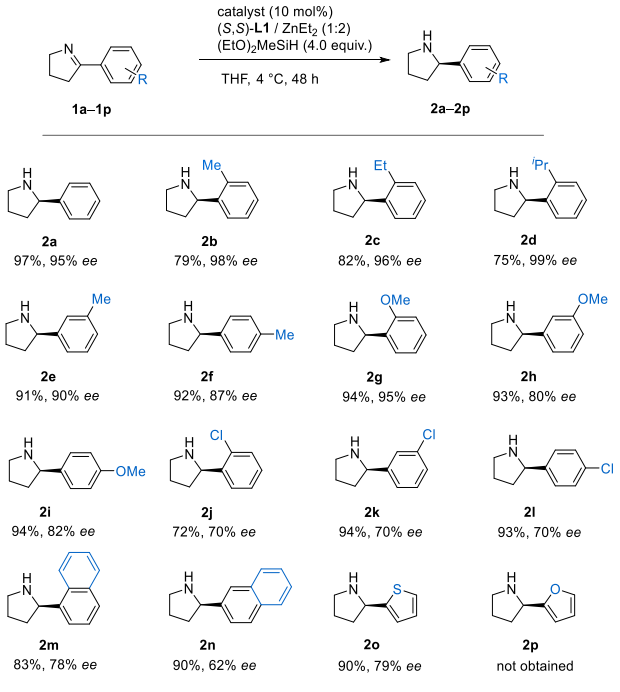
stereochemistry of product (**2a**) was determined by comparison of optical rotation with literature values.

Table 2. Asymmetric hydrosilylation of cyclic imines under various conditions. [a]

Entry	T (°C)	Time (h)	Cat. (mol%)	Yield (%)[b]	*ee* (%)[c]
1	rt	24	5	98	88
2	4	24	5	trace	–
3	4	60	5	42	94
4	4	72	5	53	95
5	4	24	10	45	95
6	4	36	10	80	95
7	**4**	**48**	**10**	**97**	**95**
8[d]	4	48	10	88	82

[a] Reactions were carried out by stirring a solution of $ZnEt_2$ (2x mol%, 15 wt. % in toluene) with (*S*,*S*)-ProPhenol **L1** (x mol%) in THF (1 mL) at the specified time and temperature, containing DEMS (2.0 mmol, 4.0 equiv.) and cyclic imine **1a** (0.5 mmol) dissolved in THF (0.2 mL) unless otherwise stated. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction was carried out in 0.5 mL of THF.

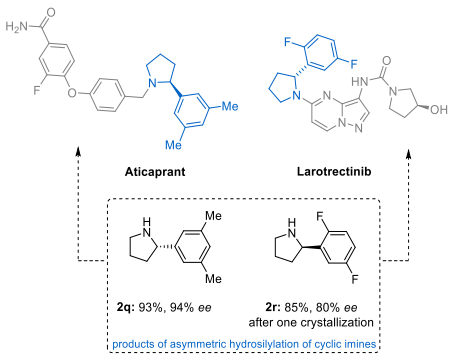
At the established optimal conditions, the scope of the zinc-catalyzed enantioselective hydrosilylation with respect to the 2-aryl-substituted pyrroline substrates was examined, as presented in Scheme 2.



[a] Reactions were performed with $ZnEt_2$ (20 mol%, 15 wt. % in toluene) and (*S*,*S*)-ProPhenol **L1** (10 mol%) in THF (1 mL) at 4 °C for 48 h, containing DEMS (2.0 mmol) and specified imines **1a-p** (0.5 mmol) dissolved in THF (0.2 mL). [b] Isolated yield after silica gel chromatography. [c] *Ee* values were determined by chiral HPLC analysis.

Scheme 2. Asymmetric zinc-catalyzed hydrosilylation of various 2-aryl-substituted pyrrolidines.[a,b,c]

In the range of substrate studies, a variety of cyclic imines participated successfully in the asymmetric reduction and gave access to optically pure pyrrolidines with high yields and excellent enantioselectivities. These compounds are mostly pivotal components in pharmaceutical drugs or drug candidates. The investigations revealed that the electronic properties and the position of the substituent attached to the phenyl ring have a decisive influence, mainly on the reaction enantioselectivity. Cyclic imines possessing electron-donating groups (**2b–2i**) gave products with a high level of enantioselectivity (80-99%), whereas replacing by the substrates bearing electron-withdrawing groups (**2j–2l**) decreased the selectivity in each case. Interestingly, cyclic amines containing electron-donating groups placed in the *ortho* position were formed with higher *ee* (95-99%), while the *meta*- and *para*-substituted imines provided slightly lower enantioselectivities up to 90% *ee*. Moreover, the presence of alkyl substituents in the *ortho* position attached to the phenyl ring afforded the desired products **2b–2d** with very good yields and the highest enantioselective control up to 99% *ee*. In contrast to the above-mentioned substrates, 2-aryl pyrroline halogen derivatives resulted in a formation of the corresponding products **2j–2l** with good yields and the same level of enantioselectivity up to 70%, regardless of the substituent positions. The replacement of the aryl substituent by the heterocyclic groups led to slightly lower selectivity (79% *ee*) for cyclic amine **2o** containing thiophene rings. Similar investigation made for the reduction of furan-based pyrroline **2p** was unsuccessful, probably due to additional coordination of the Lewis acid by the heteroatom. Application of elaborated methodology to the six-membered cyclic imines was also not successful and led to racemic amines, unfortunately.



Scheme 3. Synthesis of pharmaceutical drug precursors *via* zinc-catalyzed enantioselective reduction of cyclic imines.

Finally, we demonstrated the utility of the developed methodology and the potential for the further functionalization of chiral cyclic amines in the synthesis of biologically active molecular skeletons (Scheme 3). Zinc-catalyzed asymmetric hydrosilylation of the corresponding cyclic imines under elaborated conditions provided 2-aryl pyrrolidines (**2q–2r**) with high yields and enantioselectivity up to 94% *ee* (for **2q**). Asymmetric hydrosilylation of difluoro- substituted Larotrectinib precursor was however less selective (68% *ee*). Improvement of the purity of product **2r** to 80% *ee* was achieved by additional recrystallization with D-malic acid.[4a] Thus, the afforded cyclic amines **2q–2r** may represent valuable pharmaceutical key intermediates for drugs such as: Aticaprant and Larotrectinib.

In conclusion, we have developed a new strategy for enantioselective hydrosilylation of cyclic imines promoted by the chiral zinc catalyst. This is also the first successful application of zinc-based catalyst in a stereoselective reduction of cyclic imines, which provides new insight into further extent of the synthetic scope. The elaborated system is based on cost-effective and easily accessible zinc-complex prepared from commercially available ProPhenol ligand enantiomers. Furthermore, the presented method provides a facile access to a diverse range of enantioenriched 2-aryl-substituted pyrrolidines with very good yields and excellent enantioselectivities. The chiral products accessible using this methodology are versatile scaffolds for further functionalization, and can be rapidly transformed into biologically active compounds or pharmaceutical drugs.

Experimental Section

General procedure for Zinc-Catalyzed Asymmetric Hydrosilylation of Cyclic Imines

Under an argon atmosphere at room temperature $ZnEt_2$ solution (15 wt. % in toluene, 0.1 mL, 0.1 mmol) and (*S*,*S*)-ProPhenol **L1** (32 mg, 0.05 mmol) were dissolved in anhydrous THF (1 mL) and stirred for 60 min. $(EtO)_2MeSiH$ (0.32 mL, 2.0 mmol, 4.0 equiv.) was then added and the mixture was cooled down to 4 °C, and stirred for additional 5 min. The corresponding cyclic imine (0.5 mmol, 1.0 equiv.) was dissolved in anhydrous THF (0.2 mL) and subsequently added to the reaction. The resulting mixture was stirred at 4 °C for 48 h. After this time, the reaction mixture was directly poured onto a silica gel column and eluted with a mixture of ethyl acetate-methanol (10:1 + 1% Et_3N, v/v). The *ee* values were determined by HPLC method.

Acknowledgements

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COMMUNICATION

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