Organic LETTERS

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Identification of an Imine Reductase for Asymmetric Reduction of Bulky Dihydroisoquinolines

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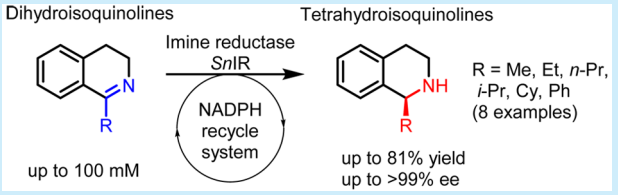
Supporting Information

ABSTRACT: A new imine reductase from *Stackebrandtia nassauensis* (*Sn*IR) was identified, which displayed over 25- to 1400-fold greater catalytic efficiency for 1-methyl-3,4-dihydroisoquinoline (1-Me DHIQ) compared to other imine reductases reported. Subsequently, an efficient *Sn*IR-catalyzed process was developed by simply optimizing the amount of cosolvent, and up to 15 g L^{-1} 1-Me DHIQ was converted completely without a feeding strategy. Furthermore, the reaction proceeded well for a panel of dihydroisoquinolines, affording the corresponding tetrahydroisoquinolines (mostly in *S*-configuration) in good yields (up to 81%) and with moderate to excellent enantioselectivities (up to 99% ee).



Optically pure tetrahydroisoquinolines (THIQs) as an important class of chiral scaffolds exist widely in numerous alkaloids, possessing exquisite biological activity and pharmaceutical properties.[1] The representative examples include 1-methyl-1,2,3,4-tetrahydroisoquinoline (1-Me THIQ) with a parkinsonism-preventing effect,[2] salsolidine with an inhibition effect on monoamine oxidase,[3] and solifenacin for treating overactive bladder syndrome (Figure 1).[4] Therefore,

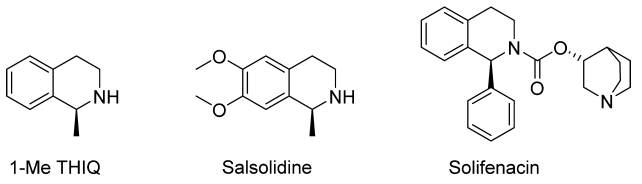


Figure 1. Structures of 1-Me THIQ, salsolidine, and solifenacin.

the highly efficient methods for synthesis of chiral THIQs, especially asymmetric hydrogenation and asymmetric transfer hydrogenation, have attracted increasing interest in recent years.[5] Various metal and organic catalysts have been developed for the asymmetric synthesis of THIQs in good yields.[6] However, despite the high catalytic efficiency of chemical catalysts, their stereoselectivity remains a challenge in these methods. To date, only relatively few examples with excellent enantioselectivity for 1-Me THIQ have been reported by the Xiao group (*S*-configuration),[6a] Zhou group (*S*-configuration),[6e] and Chan group (*R*-configuration).[6h] Recently, artificial imine reductases[7] and a cascade deracemization method combined with monoamine oxidase[8] were also developed for the synthesis of enantiomerically pure THIQs.

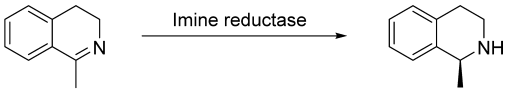
In recent years, with the continuous development of imine reductases (IREDs),[9−12] the enzymatic asymmetric reduction of dihydroisoquinolines (DHIQs) to chiral THIQs has been developed rapidly as an attractive approach owing to its environmental friendliness and 100% theoretical yield.[13] An (*S*)-IRED from *Streptomyces* sp. GF3546[11a] and an (*R*)-IRED from *Streptomyces* sp. GF3587[11e] that are capable of the asymmetric reduction of 1-Me DHIQ were first identified. Although good to high enantioselectivities (>98% ee for (*S*)-IRED and 71% ee for (*R*)-IRED) were achieved, the two enzymes displayed relatively low catalytic efficiency (k_{cat}/K_m = 0.038 s^{-1} mM^{-1} for (*S*)-IRED and 1.22 s^{-1} mM^{-1} for (*R*)-IRED). Recently, another (*S*)-selective IRED named *Ao*IRED from *Amycolatopsis orientalis* and its mutant Y179A were described, which showed the highest catalytic efficiency for 1-Me DHIQ so far (k_{cat}/K_m of 2.03 s^{-1} mM^{-1} for mutant Y179A).[12d]

However, to date, the reported IREDs rarely possess sufficient activity for preparative synthesis of chiral THIQs at high concentrations. Although asymmetric reduction of 10 g/L of 1-Me DHIQ (69 mM) had been carried out by an (*R*)-IRED, the reaction had to be performed using a substrate feeding strategy (twice) to avoid possible substrate inhibition.[11f] Furthermore, to the best of our knowledge, reported IREDs were mainly employed for asymmetric reduction of model substrates, such as 1-Me DHIQs **1a** and **1g**. For more bulky 1-substituted DHIQs, particularly the pharmaceutically relevant imines, such as 1-phenyl-3,4-DHIQ, an important scaffold for the pharmaceutical solifenacin (Figure 1), have not been tested. Therefore, the exploration of new IREDs that allow efficient synthesis of valuable chiral THIQs remains highly desirable.

Received: April 27, 2017

DOI: 10.1021/acs.orglett.7b01274
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening of IREDs



1a 2a

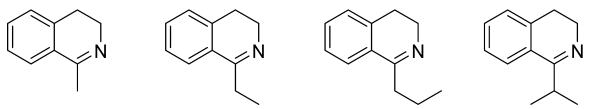
entry	IRED	source	accession no.	specific activity (U/mg)[a]	ee (%)[b]
1	*Sn*IR	*S. nassauensis*	WP_013019548.1	2.9	99 (*S*)
2	*Se*IR	*S. espanaensis*	WP_015105194.1	1.9	98 (*S*)
3	*Ad*IR	*A. decaplanina*	WP_007032738.1	1.6	99 (*S*)

[a]Specific activity was determined at pH 7.0 and 30 °C using purified enzyme. [b]Enantiomeric excess was determined by chiral HPLC.

As part of our ongoing research on IREDs-catalyzed asymmetric reduction of cyclic imines,[14] herein we report an *S*-preferential IRED (designated as *Sn*IR) from *Stackebrandtia nassauensi*, which possesses the highest catalytic efficiency (up to 54.0 and 79.7 s^{-1} mM^{-1} for **1a** and **1b**) compared to other IREDs reported so far in the literature. Up to 100 mM (15 g/L) of **1a** was converted completely by *Sn*IR to the corresponding 1-Me THIQ, with >99% ee under the optimized reaction conditions. Moreover, for other 1-substituted-DHIQs, even bulky 1-phenyl-3,4-DHIQ (**1f**), *Sn*IR was also able to reduce.

Initially, an IRED library constructed previously in our lab[14a] was explored for the asymmetric reduction of the model substrate **1a**. As a result, three (*S*)-IREDs exhibited good activities and excellent enantioselectivities (Table 1). Among them, *Sn*IR from *Stackebrandtia nassauensis* displayed the highest specific activity (2.9 U/mg) and enantioselectivity (>99% ee). Subsequently, to further assess their catalytic efficiency, the kinetic parameters of these three IREDs toward **1a** were determined. As shown in Table 2 (entries 1−3), *Sn*IR showed the highest catalytic efficiency (k_{cat}/K_m = 54.0 s^{-1} mM^{-1}), which is over 1400-, 40-, and 25-fold greater than (*S*)-IRED from *Streptomyces* sp. GF3546,[11a] (*R*)-IRED from *Streptomyces* sp. GF3587,[11e] and *Ao*IRED from *Amycolatopsis orientalis*,[12d] respectively. The kinetic parameters of *Sn*IR toward other substrates **1b**−**1d** were also investigated. The highest turnover number (k_{cat}) and catalytic efficiency (k_{cat}/K_m) were observed for **1b**, after which the k_{cat}/K_m significantly decreased with the increase of steric hindrance of substrates (Table 2, entries 4−6). However, different extents of substrate inhibition (K_i) were observed in all cases.

Table 2. Kinetics Parameters of *Sn*IR and Other IREDs[a]



1a 1b 1c 1d

entry	IRED-substrate	K_m [mM]	K_i [mM]	k_{cat} [s^{-1}]	k_{cat}/K_m [s^{-1} mM^{-1}]
1	*Sn*IR-**1a**	0.056	1.5	3.02	54.0
2	*Se*IR-**1a**	0.048	8.6	1.22	25.5
3	*Ad*IR-**1a**	0.113	2.0	1.26	11.1
4	*Sn*IR-**1b**	0.041	1.9	3.27	79.7
5	*Sn*IR-**1c**	0.045	3.4	1.37	30.4
6	*Sn*IR-**1d**	0.068	2.7	0.21	3.07

[a]Kinetic parameters were determined at pH 7.0 and 30 °C using purified enzyme.

To evaluate the synthetic capability of *Sn*IR, preparative asymmetric reduction of 100 mM **1a** was performed in a 10 mL reaction system. However, only 18% of **1a** was converted within 24 h when 5% DMSO was added, which might be attributed to severe substrate inhibition, thus significantly decreasing the conversion. Interestingly, 10 mM **1a** could be reduced efficiently into **2a** with >99% conversion when 1% DMSO was utilized. We presumed that lower concentration of DMSO probably led to the drop of soluble substrate in aqueous solution, alleviating substrate inhibition of *Sn*IR. Therefore, the reactions with varied amounts of DMSO were systematically investigated at a substrate concentration of 20 mM. The results summarized in Table 3 clearly show that the reaction is dramatically affected by the amount of cosolvent DMSO. The reduction of DMSO amount could remarkably shorten the reaction time. When the amount of DMSO was reduced to 1% from 5%, the time required for a full conversion dropped from 12 to 0.5 h. Nevertheless, when no DMSO was added, the reaction proceeded at a slightly slow rate, which may be due to the limitation of mass transfer of substrate. Hence, 1% DMSO was chosen for reactions with a higher substrate loading and the reduction of even 100 mM **1a** could proceed well in 1% DMSO, thereby providing a simple and efficient procedure for preparative synthesis of THIQs.

Table 3. Optimization of Reaction Conditions for the Asymmetric Reduction of 1a[a]

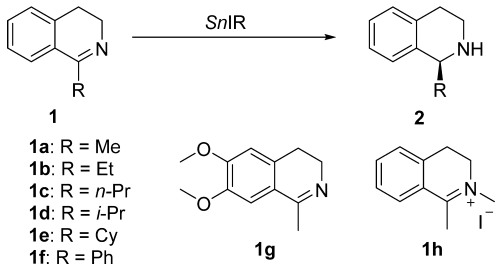
entry	concn [mM]	DMSO [%]	time [h]	conversion [%][b]
1	100	5	24	18
2	10	1	0.5	>99
3	20	5	12	>99
4	20	2	1	>99
5	20	1	0.5	>99
6	20	0	2	>99
7	50	1	2	>99
8	100	1	4	>99

[a]The reaction mixture (10 mL) contains 0.1−1 mmol substrate, 100 mg of *Sn*IR (cell-free extract), 10 mg of *Bm*GDH (cell-free extract), 1.5 mmol of glucose, 5 μmol of $NADP^+$, 0−0.5 mL of DMSO, and 9.5−10 mL of potassium phosphate buffer (100 mM, pH 7.0) shaken at 30 °C, 200 rpm. [b]Conversion was determined by HPLC.

Finally, to investigate the substrate scope of *Sn*IR, the specific activities of *Sn*IR toward other DHIQs were also measured (Table S1). The results showed that the activity decreased relatively along with the increase of substituent size on the 1-position of the DHIQ ring. Then asymmetric reductions of a panel of DHIQs were performed on a preparative scale (1.0 mmol) under the optimized conditions (Table 4). For **1a**, **1b**, and **1g**, a 100 mM substrate could be converted totally within

DOI: 10.1021/acs.orglett.7b01274
Org. Lett. XXXX, XXX, XXX−XXX

Table 4. Asymmetric Reduction of 3,4-DHIQ Derivatives by *Sn*IR[a]



entry	substrate	concn [mM]	volume [mL]	time [h]	conv [%][c]	yield [%][d]	ee [%][c]
1	**1a**	100	10	4	>99	72	>99 (*S*)
2	**1b**	100	10	2	>99	81	93 (*S*)
3	**1c**	50	20	3	>99	77	8 (*R*)
4	**1d**	50	20	12	>99	76	98 (*S*)
5	**1e**	10	100	12	>99	73	80 (*R*)
6	**1f**	5	200	12	>99	81	51 (*S*)
7	**1g**	100	10	4	>99	76	>99 (*S*)
8[b]	**1h**	10	50	12	>99	75	87 (*R*)

[a]The reaction mixture contained 5−100 mM substrate, 100 mg of *Sn*IR (cell-free extract), 10 mg of *Bm*GDH (cell-free extract), 50−150 mM glucose, 0.5 mM $NADP^+$, 1% (v/v) DMSO and potassium phosphate buffer (100 mM, pH 7.0) shaken at 30 °C, 200 rpm. [b]No DMSO was added. [c]Conversion and enantiomeric excess were determined by chiral HPLC or GC. The absolute configurations of the products were assigned by comparing the sign of the optical rotation with literature data. [d]Isolated yields.

2−4 h, affording the corresponding products in good yields (72−81%) and with good to excellent enantioselectivities (93−99% ee). Moreover, the corresponding *N*-methyl iminium salt **1h** was also reduced in full conversion on a 0.5 mmol scale (10 mM in 50 mL), giving **2h** in 75% yield and with 87% ee within 12 h. For other substrates (**1c−1f**), >99% conversions were achieved at 5−50 mM substrate loading within 3−12 h. However, the enantioselectivity decreased with the increase of steric hindrance of 1-substituents except **1d**, indicating the stereoselectivity of *Sn*IR is particularly sensitive to substrate size. It is interesting to note that product **2e** was obtained with *R*-configuration, which may probably be attributed to the change of substrate binding mode. In addition, *Sn*IR exhibited good activity toward monocyclic imine 6-methyl-2,3,4,5-tetrahydropyridine (**3**), affording the corresponding amine (*S*)-2-methylpiperidine (**4**) with 97% ee (Figure S3).

In summary, a new *S*-preferential IRED from *Stackebrandtia nassauensis* with high catalytic efficiency and excellent enantioselectivity toward 1-Me DHIQ was identified. By simple optimization of cosolvent content, we developed a highly efficient imine reductase-catalyzed asymmetric reduction process for 1-substituted DHIQs. Under the optimized conditions, up to 100 mM (15 g/L) of 1-Me DHIQ could be reduced completely in 4 h without a batch-feeding strategy. Various DHIQs, including bulky substrate **1f**, were converted rapidly into the corresponding chiral THIQs by *Sn*IR in good yields (up to 81%) and with moderate to excellent enantioselectivity (up to 99% ee), indicating that *Sn*IR is promising for reducing sterically hindered cyclic imines. Protein engineering of *Sn*IR is currently underway in our laboratory to improve its enantioselectivity and activity toward bulky DHIQs, particularly those of pharmaceutical relevance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01274.

Experimental procedures; characterization of *Sn*IR; characterization data of the products; copies of NMR, HPLC, GC spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (Nos. 31200050, 21472045, and 21536004), the Fundamental Research Funds for the Central Universities (22A201514043) and Shanghai Pujiang Program (15PJ1401200).

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DOI: 10.1021/acs.orglett.7b01274
Org. Lett. XXXX, XXX, XXX−XXX