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Concise Redox Deracemization of Secondary and Tertiary Amines with a Tetrahydroisoquinoline Core via a Nonenzymatic Process

Yue Ji,[†] Lei Shi,[*,†,‡] Mu-Wang Chen,[†] Guang-Shou Feng,[†] and Yong-Gui Zhou[*,†]

[†]State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China
[‡]State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, P. R. China

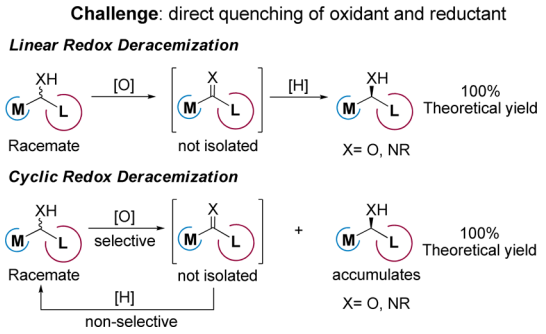
Supporting Information

ABSTRACT: A concise deracemization of racemic secondary and tertiary amines with a tetrahydroisoquinoline core has been successfully realized by orchestrating a redox process consisted of *N*-bromosuccinimide oxidation and iridum-catalyzed asymmetric hydrogenation. This compatible redox combination enables one-pot, single-operation deracemization to generate chiral 1-substituted 1,2,3,4-tetrahydroisoquinolines with up to 98% ee in 93% yield, offering a simple and scalable synthetic technique for chiral amines directly from racemic starting materials.

Classical and kinetic resolution of racemic mixtures are the most widely used methods in large-scale preparation of enantiomerically pure compounds, but they are impeded by the fact that the theoretical yield of the target chiral molecule is only 50% and at least half of the starting material would be discarded.[1] To overcome this restriction, some enantiomerically convergent processes have emerged to obtain single enantiomers from racemates in theoretically 100% yield, including dynamic kinetic resolution (DKR),[2] dynamic kinetic asymmetric transformation (DYKAT),[3] and deracemization.[4] A racemic mixture can be completely converted into a single enantiomer of the same compound through a deracemization process. Deracemization is a highly efficient technology to obtain enantiomerically pure compounds, especially when the substrate and the desired product possess an identical chemical structure. The additional steps to remove the resolving agents from the products are not needed. Thus, deracemization continues to attract considerable research attention because of its obvious atom and step economy.

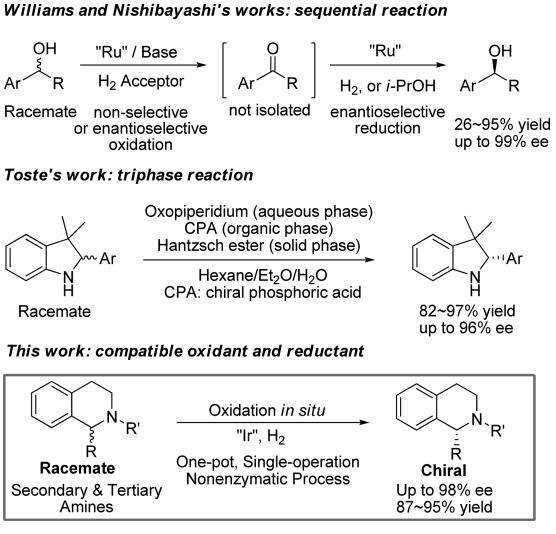
A deracemization reaction comprises two half-reactions that are opposite in reaction direction and have completely distinct mechanistic pathway, at least one of which should operate enantioselectively. Combination of oxidation with reduction is a common practice through destruction and regeneration of the chirality of the stereogenic center. The main challenge of redox-driven deracemization is that oxidants and reductants easily and directly quench each other in single reactor, which usually is thermodynamically and kinetically favorable. Sequential operation or physical isolation of oxidation and reduction has been employed to overcome this problem. Two reaction modes, linear and cyclic redox deracemizations, have been built to achieve deracemization of racemic mixtures of chiral alcohols or amines (Scheme 1).[5,6] However, deracemization techniques to date rely heavily on the utility of biological catalyst systems. As the most representative one, monoamine oxidases (MAOs) coupled with

Scheme 1. Linear and Cyclic Redox Deracemization



chemical reduction conditions, such as BH_3−NH_3, metal-catalyzed hydrogenation, etc., can lead to the efficient formation of enantiomerically pure amines in cyclic deracemization mode (Scheme 1).[6] During biocatalyzed processes, the good compatibility between oxidation and reduction is probably due to the fact that the active reacting site is shielded by the protein or cell wall. To the best of our knowledge, pure chemically catalytic deracemization is still very rare (Scheme 2). Williams and Nishibayashi independently developed elegant Ru-catalyzed

Scheme 2. Chemically Catalytic Redox Deracemization



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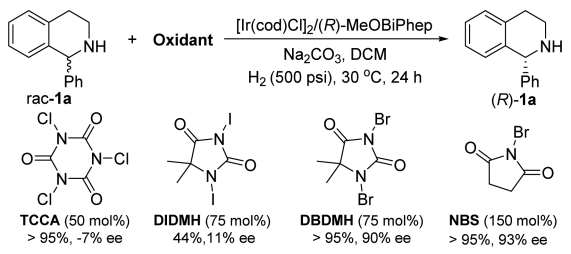
deracemization of secondary alcohols.[7] The reaction operates in discrete sequential nonselective or enantioselective oxidation and enantioselective hydrogenation steps. Recently, a facile organocatalyzed deracemization of amines was reported by the Toste group.[8] Their brilliant strategy of aqueous/organic/solid-phase separation successfully minimizes the direct quenching of the oxidant and reductant, enabling one-pot, single-operation deracemization. As current well-developed catalytic oxidation/reduction reactions can provide a huge number of possibilities of redox combinations for the deracemization technique and the scope of substrates would be further widened under non-enzymatic conditions, pure chemically catalytic deracemization is promising and highly desirable. Herein we report a concise deracemization of secondary and tertiary amines with a tetrahydroisoquinoline (THIQ) core by orchestrating a redox process consisting of oxidation in situ and highly enantioselective hydrogenation.

In previous research work on Ir-catalyzed asymmetric hydrogenation reported by us and other groups,[9] some oxidizing agents containing halogen, such as iodine, trichloroisocyanuric acid (TCCA), and *N*-bromosuccinimide (NBS), can significantly improve the performance of the catalyst by elevating the valence state of the metal center (Ir^{I} to Ir^{III}). Even the use of excess oxidant does not affect the results of hydrogenation. On the other hand, this kind of mild oxidant can also oxidize some racemic secondary amines into prochiral imines.[10] Taking these two facts into consideration, we envisaged that using this rare compatibility of Ir-catalyzed hydrogenation conditions with halogen oxidants would realize a linear redox deracemization of some amines, particularly those important motifs in natural alkaloids and pharmaceutical molecules such as tetrahydroisoquinoline.[11] For this purpose, two conditions must be met: first, the direct quenching between the oxidant and reductant (metal hydride) must be much slower than oxidation of the amine; second, the oxidation should take place with 100% conversion and faster than the asymmetric hydrogenation.

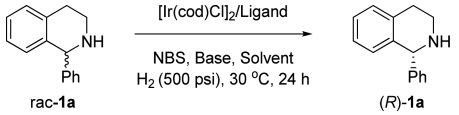
Initially, 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) was selected as a model compound to investigate the deracemization conditions because it can be easily oxidized to the imine by halogen reagents and also be furnished enantioselectively through hydrogenation of the cyclic imine.[12] In the presence of a 2 mol % loading of the chiral Ir complex generated in situ from $[Ir(cod)Cl]_2$ and (*R*)-MeOBiPhep and 0.5 equiv of TCCA as the oxidant, the deracemization of racemic **1a** was conducted in dichloromethane under H_2 at 500 psi (Scheme 3). After 24 h, **1a** was recovered with 7% ee in 95% yield. This positive result confirmed our hypothesis and encouraged us to further investigate the effect of the identity of the oxidant on the enantioselectivity. Surprisingly, when oxidants containing bromine were used, especially NBS, the ee value dramatically increased to 93%. This remarkable improvement is probably due to the dual role of NBS in activating the metal catalyst and the oxidizing substrate.

Scheme 3. Effect of Oxidants on Deracemization of 1-Phenyl-1,2,3,4-tetrahydroisoquinoline

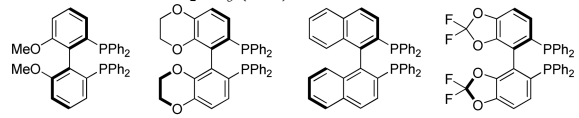


Next, a survey of solvents revealed that 1,2-dichloroethane is more suitable than others (Table 1, entries 1−5). The

Table 1. Optimization of the Deracemization Conditions[a]



entry	solvent	base (equiv)	ligand	recovery (%)[b]	ee (%)[c]
1	DCM	Na_2CO_3 (0.75)	**L1**	>95	93
2	toluene	Na_2CO_3 (0.75)	**L1**	86	−55
3	dioxane	Na_2CO_3 (0.75)	**L1**	92	−48
4	MeOH	Na_2CO_3 (0.75)	**L1**	>95	−19
5	DCE	Na_2CO_3 (0.75)	**L1**	>95	96
6	DCE	Cs_2CO_3 (0.75)	**L1**	>95	95
7	DCE	K_3PO_4 (0.50)	**L1**	>95	95
8	DCE	Et_3N (1.50)	**L1**	>95	−14
9	DCE	Na_2CO_3 (0.55)	**L1**	>95	97
10	DCE	Na_2CO_3 (0.55)	**L2**	>95	98
11	DCE	Na_2CO_3 (0.55)	**L3**	>95	95
12	DCE	Na_2CO_3 (0.55)	**L4**	94	85



[a]Reaction conditions: **1a** (0.2 mmol), $[Ir(cod)Cl]_2$ (1 mol %), ligand (2.2 mol %), NBS (1.5 equiv), base (0.55 equiv), solvent (3 mL). cod = 1,5-cyclooctadiene. [b]Determined by ^1H NMR analysis [c]Determined by HPLC for the corresponding benzamide.

deracemization of **1a** performed well and offered high ee values with several inorganic bases, while the organic base triethylamine showed a negative effect on the enantioselectivity (entries 5−8). A slight improvement in enantioselectivity was provided by reducing the amount of sodium carbonate (entry 9). The diverse array of commercially available ligands depicted in Table 1 were tested to investigate the effect of the nature of the ligand on the deracemerization process. (*R*)-SynPhos (**L2**), an electron-rich diphosphine ligand with axial chirality, afforded the highest selectivity of 98% ee (entry 10). Thus, we established the optimal conditions for deracemization of **1a** to employ $[Ir(cod)Cl]_2$/(*R*)-SynPhos as the catalyst, 1.5 equiv of NBS as the oxidant, 0.55 equiv of sodium carbonate as the base, and 1,2-dichloroethane as the solvent at 30 °C with a hydrogen pressure of 500 psi.

The scope of this deracemization reaction was examined under the optimized conditions identified above. As depicted in Scheme 4, a series of 1-aryl-substituted tetrahydroisoquinolines could be effectively deracemized into enantiomerically enriched forms with up to 98% ee in good yields (>90%). Notably, it was found that the electronic properties of the substrates affect the enantioselectivity to a certain extent. Introducing an electron-donating methoxy group on the isoquinoline core or the 1-phenyl group resulted in relatively lower ee values (**1b**, **1c**, and **1g**), possibly because side reactions consume some of the oxidant. Those substrates containing an electron-deficient 1-phenyl group (**1h**, **1i** and **1j**) were deracemized with excellent enantioselectivity (98% ee). With an alkyl substituent at the 1-

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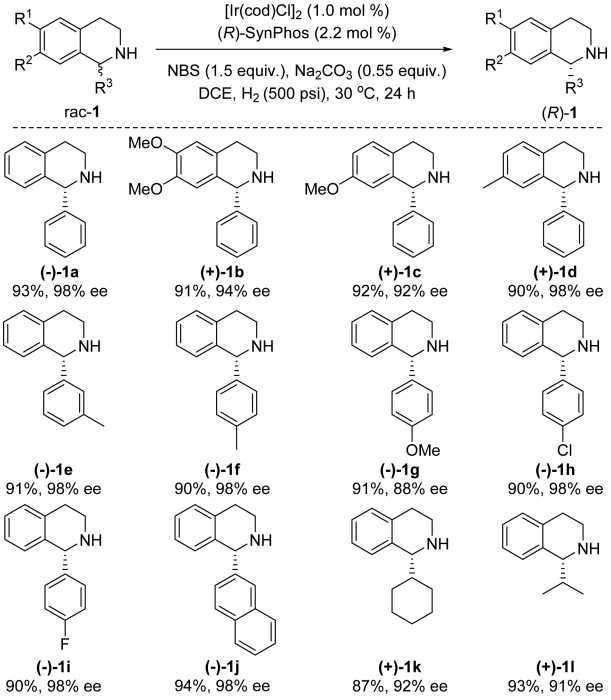
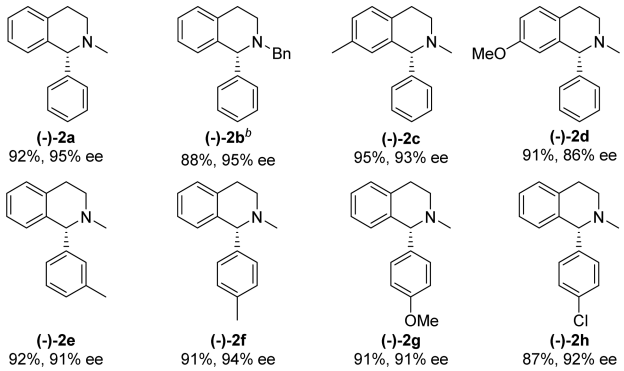
Scheme 4. Deracemization of 1-Substituted 1,2,3,4-Tetrahydroisoquinolines



position (**1l**, **1k**), high yields and good enantioselectivities were still obtained, although the ee values were somewhat decreased.

Considering that tertiary amines are widely found in natural alkaloids, we also explored the deracemization of *N*-methyl- and *N*-benzyl-1-aryl-substituted tetrahydroisoquinolines (**2a**–**h**; Scheme 5). To our delight, racemic tertiary amines with a

Scheme 5. Deracemization of *N*-Methyl- and *N*-Benzyl-1-Aryl-Substituted 1,2,3,4-Tetrahydroisoquinolines[a]

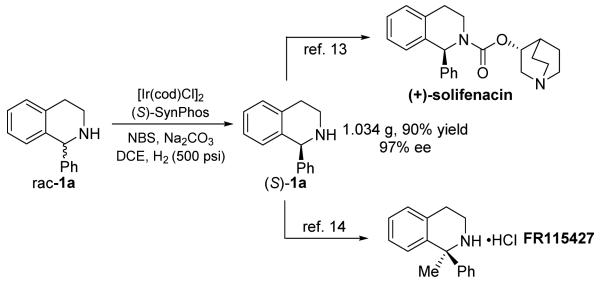


[a]Under the standard conditions depicted in Scheme 4, unless otherwise noted. [b]2.0 equiv of NBS was used.

THIQ core were recovered in 87–95% yield with high enantioselectivity (86–95% ee) after the similar deracemization treatment. It is noteworthy that the *N*-benzyl group could be removed as a temporary protecting group. This is very practical in multistep total syntheses of complex compounds. In contrast to secondary amines, the enantioselectivity of deracemization of these substrates is more sensitive to the electronic properties of the chiral ligand used (see the Supporting Information), as strongly electron-deficient **L4** gave only <50% ee. This phenomenon should result from two different reacting intermediates, imine and iminium, produced by NBS oxidation of two kinds of amines.[10,13]

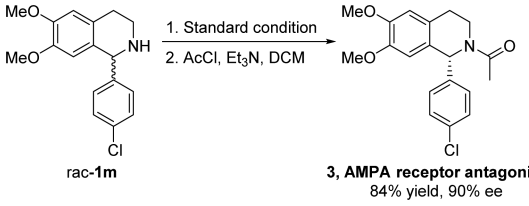
To demonstrate the practical utility of this method, deracemization of compound **1a** was performed under the optimal conditions on a gram scale, employing (*S*)- instead of (*R*)-SynPhos as the ligand. (*S*)-**1a**, which is a key intermediate for the synthesis of some drug molecules, such as (+)-solifenacin[14] and (+)-FR115427,[15] was prepared in 90% isolated yield with 97% ee (Scheme 6). In addition, compound **3**, a potent

Scheme 6. Deracemization on a Gram Scale and Applications

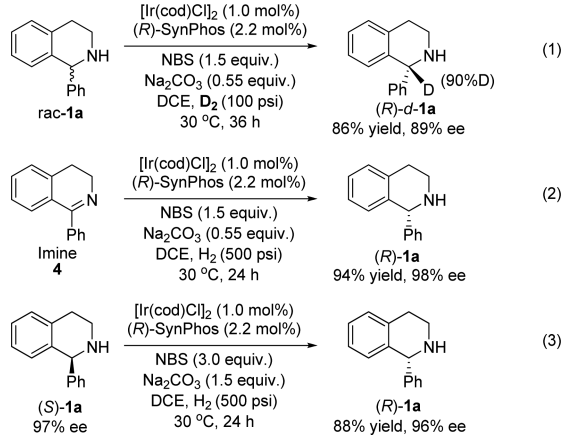


noncompetitive AMPA receptor antagonist,[12b,16] was efficiently synthesized via deracemization of **1m** followed by acylation with 90% ee in 84% overall yield (Scheme 7).

Scheme 7. Synthesis of AMPA Receptor Antagonist 3



Next, to gain insight into the reaction mechanism, an isotopic labeling experiment was conducted under D_2 gas (eq 1). 1-



Deuterio-1-phenyl-1,2,3,4-tetrahydroisoquinoline was formed with 90% deuterium incorporation, which suggests that initially the racemic substrate was oxidized to the imine and then the C1 stereogenic center regenerated by Ir-catalyzed enantioselective hydrogenation. When imine **4** was subjected to the optimized reaction conditions, **1a** was obtained in 94% yield with 98% ee (eq 2), which is almost identical to the result of deracemization of **1a**. This result further confirmed the deracemization pathway

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involving an imine intermediate. In addition, an interesting reaction involving a configuration switch was carried out, and (*S*)-**1a** (97% ee) was transformed into (*R*)-**1a** (96% ee) in 88% yield under the deracemization conditions (eq 3).

By using an orchestrated redox process consisting of NBS oxidation and Ir-catalyzed asymmetric hydrogenation, we have realized one-pot, single-operation deracemization of secondary and tertiary amines with a tetrahydroisoquinoline core under pure chemical conditions. This methodology provides concise access to chiral tetrahydroisoquinolines with 98% ee directly from the racemic substrates in 100% theoretical yield, which is valuable for the preparation of some important drugs, including (+)-solifenacin, (+)-FR115427, and an AMPA receptor antagonist. Further studies to expand the scope to other amines or alcohols are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06659.

Procedures and NMR, HRMS, and HPLC data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*shileichem@dicp.ac.cn

*ygzhou@dicp.ac.cn

Notes

The authors declare no competing financial interest.

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