Communication

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

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

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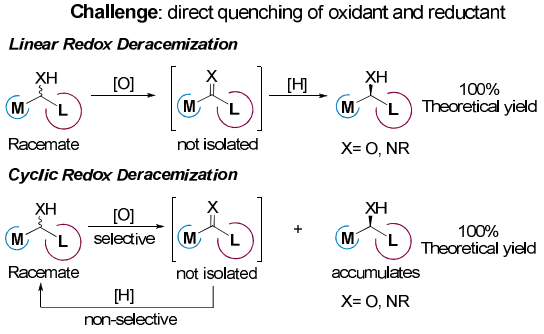
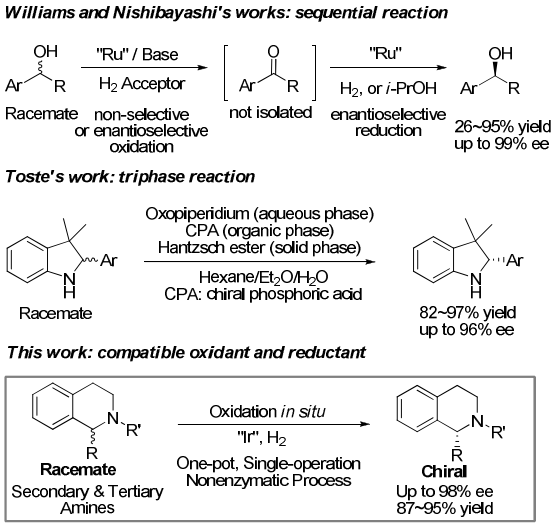
ABSTRACT: A concise deracemization of racemic secondary and tertiary amines with tetrahydroisoquinoline core has been successfully realized by orchestrating a redox process consisted of *N*-bromosuccinimide oxidation and iridum-catalyzed asymmetric hydrogenation. This compatible redox combination enables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

Classical and kinetic resolution of a racemic mixture are the widest methods used 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 a half of starting material would be discarded.[1] To overcome this restriction, some enantiomerically convergent processes have emerged to obtain single enantiomer from a racemate in theoretically 100% yield, including dynamic kinetic resolution,[2] dynamic kinetic asymmetric transformation[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 obvious atom- and step-economy.

Scheme 1. Linear and Cyclic Redox Deracemization



Scheme 2. Chemically Catalytic Redox Deracemization

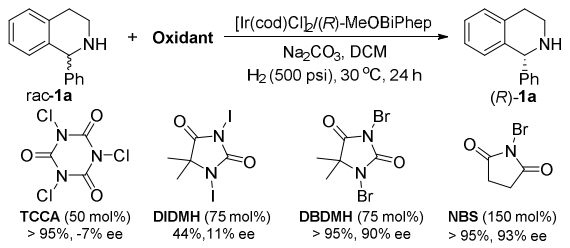


Deracemization reaction is comprised of two half-reactions that are opposite in reacting direction and completely distinct in mechanistic pathways, at least one should operate enantioselectively. Combination of oxidation with reduction is a common practice through destroying and regenerating of the chirality of 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 a racemic mixture of chiral alcohols or amines (Scheme 1).[5,6] However, deracemization technique relies heavily on the utility of biological catalyst systems till now. As the most representative one, monoamine oxidases (MAO) coupled with chemical reduction condition, 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, good compatibility between oxidation and reduction is probably due to the active reacting site is shielded by 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 deracemization of secondary alcohols.[7] The reaction operated in discrete sequential non-selective or enantionselective oxidation and enantioselective hydrogenation steps. Recently, a facile organocatalyzed deracemization of amines was reported by Toste group.[8] Their brilliant strategy of aqueous/organic /solid phase separation successfully minimized the direct quenching of oxidant and reductant, which enabled a one-pot single-operation deracemization. Given current well-developed catalytic oxidation/reduction reactions can provide a huge number of possibilities of redox combinations for deracemization technique, as well as the scope of substrates would be further widened under non-enzyme conditions, pure chemically catalytic deracemization is promising and highly desirable. Herein, we wish to report a concise deracemization of secondary and tertiary amines with tetrahydroisoquinoline core by orchestrating a redox process consisted of oxidation *in situ* and highly enantioselective hydrogenation.

In previous research work on iridium-catalyzed asymmetric hydrogenation reported by us and other groups, [9] some oxidizing agents containing halogen, such as iodine, TCCA (trichloroisocyanuric acid) and NBS (*N*-bromosuccinimide), can significantly improve the performance of catalyst by elevating the valence state of the center metal (Ir(I) to Ir(III)). Even using excess oxidants would not affect the results of hydrogenation. On the other hand, this kind of mild oxidants can also oxidize some racemic secondary amines into prochiral imines.[10] Taking two facts together into consideration, we envisaged that using this rare compatibility of Ir-catalyzed hydrogenation condition 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 have to be met. First, the direct quenching between oxidant and reductant (metal-hydride) has to be much slower than oxidation of amines; second, the oxidation should take place in 100% conversion and faster than asymmetric hydrogenation.

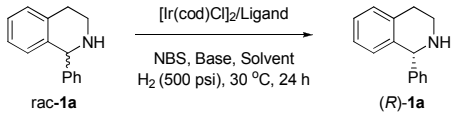
Scheme 3. Effect of Oxidants on Deracemization of 1-Phenyl-1,2,3,4-tetrahydroisoquinoline



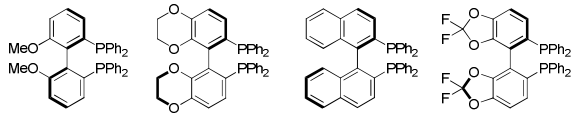
Initially, 1-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** was selected as model compound to investigate deracemization condition because it can be easily oxidized into imine by halogen reagents and also be enantioselectively furnished through hydrogenation of cyclic imine.[12] In the presence of 2 mol%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

Next, a survey of solvent revealed that 1,2-dichloroethane is more suitable than others (Table 1, entries 1-5). Deracemization of **1a** performed well and offered high values of ee with most of inorganic base (entries 5-8), while organic base triethylamine showed a negative effect on enantioselectivity. A slight improvement in enantioselectivity was provided by reducing amount of sodium carbonate (entry 9). Diverse arrays of commercially available ligands depicted in table 1 were tested to investigate the effect of the nature of ligand on 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 condition for deracemization of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **1a**: using $[Ir(cod)Cl]_2$/(*R*)-SynPhos as catalyst, 1.5 equiv. of NBS as oxidant, 0.55 equiv. of sodium carbonate as base and 1,2-dichloroethane as solvent to perform reaction at 30 °C and at a hydrogen of 500 psi.

Table 1. Optimization of 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

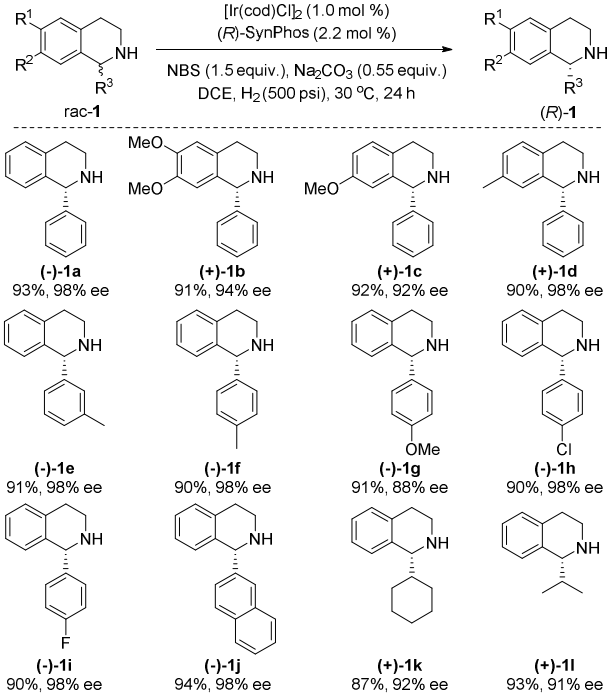


[a] Reaction conditions: **1a** (0.2 mmol), $[Ir(cod)Cl]_2$ (1 mol%), ligand (2.2 mol%), NBS (1.5 equiv.), base (0.55 equiv.), solvents 3 mL; [b] Determined by ^1H NMR; [c] Determined by HPLC for the corresponding benzamide. cod = 1,5-cyclooctadiene.

The scope of this deracemization reaction was examined under the optimized condition 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* and good yields (> 90%). Notably, it was found that the electronic property of substrates affects the enantioselectivity to a certain extent. Introduction of electron-donating methoxy group on isoquinoline core or 1-phenyl resulted relatively lower *ee*s (**1b**, **1c** and **1g**), because some possible side reactions might consume a part of oxidants. Those substrates containing an electron-deficient phenyl (**1h**, **1i** and **1j**) were deracemized with excellent enantioselectivity (98% *ee*). With alkyl substituent at 1-

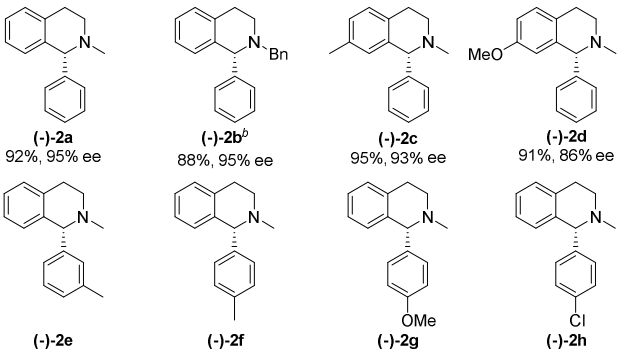
position (**1l**, **1k**), high yields and good enantioselectivities can still be obtained, albeit *ee* values somewhat decreased.

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



Considering tertiary amines are widely popular in natural alkaloids, we also explored the deracemization of *N*-methyl and *N*-benzyl 1-aryl substituted tetrahydroisoquinolines (Scheme 5, **2a**-**2h**). To our delight, racemic tertiary amines with THIQ core can be recovered in 87~95% yields with high *ee*s (86~95%) after the similar deracemization treatment. It is noteworthy that *N*-benzyl group could be removed as temporary protected group. This is very practical in multistep total synthesis of complex compound. In contract with secondary amines, the enantioselectivity of deracemization of these substrates is more sensitive with electronic property of the chiral ligand used (see supporting information), strong electron-deficient **L4** only give <50% ee. This phenomenon should be resulted by two different reacting intermediates, imine and iminium, produced by NBS oxidation of two kinds of amines.[10, 13]

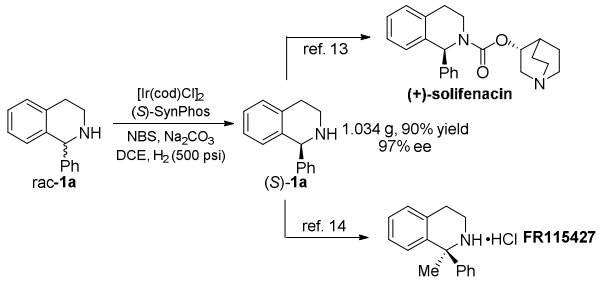
Scheme 5. Deracemization of *N*-methyl and *N*-benzyl 1-Substituted 1,2,3,4-Tetrahydroisoquinolines[a]



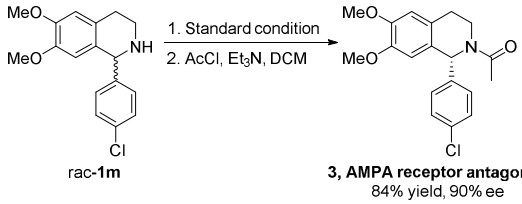
[a] under standard condition depicted in scheme 4. [b] 2.0 equiv. NBS.

To demonstrate the practical utility, deracemization of compound **1a** was performed under the optimal condition in gram scale, employing (*S*) instead of (*R*)-SynPhos as ligand. (*S*)-**1a** was prepared in 90% isolated yield and 97% *ee* (Scheme 6), which is key intermediate for the synthesis of some drug molecules, such as (+)-Solifenacin[14] and (+)-FR115427.[15] Besides, compound **3**, a potent noncompetitive AMPA receptor antagonist,[12b,16] was efficiently synthesized *via* deracemization of **1m** followed by acylation with 90% ee and 84% overall yield (Scheme 7).

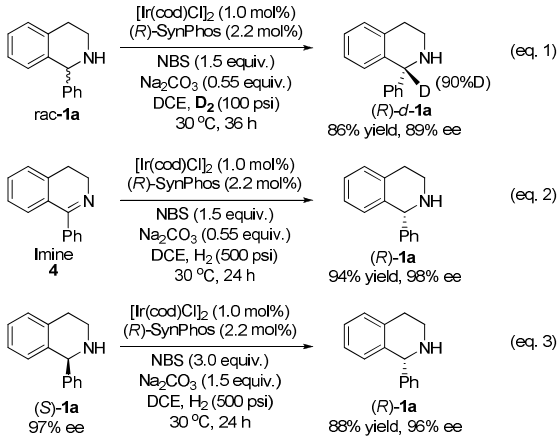
Scheme 6. Deracemization at Gram Scale and Applications



Scheme 7. Synthesis of AMPA Receptor Antagonist



Next, to gain insight into the reaction mechanism, 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 the racemic substrate was oxidized to imines firstly and C1 stereogenic center regenerated by Ir-catalyzed enantioselective hydrogenation. When imine **4** was subjected to the optimized reaction condition, **1a** was obtained with 94% yield and 98% ee (eq. 2), which is almost identical to the result of deracemization of **1a**. This result further confirmed the deracemization pathway involving an imine intermediate. In addition, an interesting reaction of configuration switch was carried out, and (*S*)-**1a** (97% ee) was able to be transformed into (*R*)-**1a** (96% ee) with 88% yield after being treated under deracemization condition (eq. 3).



By using an orchestrated redox process consisted of NBS oxidation and iridium-catalyzed asymmetric hydrogenation, we have realized one-pot one-operation deracemization of secondary and

tertiary amines with tetrahydroisoquinoline core under pure chemical condition. This methodology provides a concise access to chiral tetrahydroisoquinolines in 98% ee directly from the racemic substrates with 100% theoretical yield, which is valuable for preparation of some important drugs, including (+)-solifenacin, (+)-FR115427 and AMPA receptor antagonist. Further studies to expand the scope to other amines or alcohols are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Procedures and spectral (NMR, HRMS, HPLC) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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