REPORT

ORGANIC CHEMISTRY

Iridium-catalyzed acid-assisted asymmetric hydrogenation of oximes to hydroxylamines

Josep Mas-Roselló[1], Tomas Smejkal[2], Nicolai Cramer[1]*

Asymmetric hydrogenations are among the most practical methods for the synthesis of chiral building blocks at industrial scale. The selective reduction of an oxime to the corresponding chiral hydroxylamine derivative remains a challenging variant because of undesired cleavage of the weak nitrogen-oxygen bond. We report a robust cyclometalated iridium(III) complex bearing a chiral cyclopentadienyl ligand as an efficient catalyst for this reaction operating under highly acidic conditions. Valuable *N*-alkoxy amines can be accessed at room temperature with nondetected overreduction of the N–O bond. Catalyst turnover numbers up to 4000 and enantiomeric ratios up to 98:2 are observed. The findings serve as a blueprint for the development of metal-catalyzed enantioselective hydrogenations of challenging substrates.

Asymmetric hydrogenation with homogeneous transition metal catalysts is one of the most efficient methods for the preparation of single enantiomers at industrial scale (*1*, *2*). The enormous progress in highly enantioselective reduction of prochiral olefins and ketones is tightly linked to the development of new chiral ligand architectures (*3*, *4*). In the context of chiral amine synthesis, the catalytic asymmetric hydrogenation of imine or enamine precursors is a well-established method and is frequently used industrially (*5*). In stark contrast, related metal-catalyzed hydrogenations of oximes to produce chiral hydroxylamines have proven elusive (Fig. 1B). These substrates are often inert, and when reactivity is observed, undesired reductive cleavage of the labile N–O bond leads to primary amines (*6*). Therefore, the development of a complementary homogeneous hydrogenation mode is required.

The *N*-alkoxy amine group is an increasingly common motif in agrochemicals and pharmaceuticals, with the N–O bond offering favorable physical and biological properties (*7*). Compared to the related, more abundant, chiral amine moieties in drugs (*8*), current bioactive N–O compounds either lack chirality or are marketed as racemates (Fig. 1A). A practical asymmetric synthesis would facilitate incorporation of chiral three-dimensional hydroxylamine scaffolds as design elements in drug discovery (*9*). So far, only the use of substoichiometric to stoichiometric amounts of chiral oxazaborolidine borane adducts was shown to yield hydroxylamine products in an enantioselective fashion. However, those reactions suffer as well from undesirable primary amine by-products, depending on the oxime structure (*10*, *11*) (Fig. 1C). Moreover, costs and waste build-up make this method difficult to scale. Here, we present cyclometalated chiral iridium(III) complexes bearing a chiral cyclopentadienyl ligand (Fig. 1D, purple) and an achiral aryl imine *C*,*N*-chelate (Fig. 1D, green). We apply them for the enantioselective hydrogenation of protonated oximes to hydroxylamine derivatives, showcasing their potential in asymmetric catalysis. Related *C*,*N*-chelated half-sandwich Ir(III) complexes (*12*) have already found diverse applications in catalysis, including hydrogenation, dehydrogenation, oxidation, and hydrofunctionalization, among other transformations (*13*–*15*).

Preliminary studies revealed that cyclometalated Cp*-iridium complex **Ir1** (Fig. 2) engages in highly efficient homogeneous oxime hydrogenations in the presence of stoichiometric amounts of a strong Brønsted acid (*16*). The reaction is fully chemoselective toward reduction of the C=N bond of oxime, showing no reductive cleavage of the N–O bond. The required acid assistance in the reaction suggests an ionic hydrogenation mechanism (fig. S1), whereby a protonated substrate receives a hydride from a metal complex via an outer-sphere mechanism (*17*). The enantiodetermining facial-selective hydride delivery to the non-coordinated substrate is often the slowest step (*18*). This is distinct from classical homogeneous hydrogenation, where the substrate is bound to a metal center and subsequently receives the two hydrogen atoms from the same catalyst entity (*19*). The strong Brønsted acid fulfils a triple role: (i) The oxime substrate (~5 orders of magnitude less basic than an imine) is protonated, activating it toward hydride addition; (ii) the conjugated base dissociates from iridium, facilitating dihydrogen coordination and its subsequent heterolytic cleavage into a proton and a hydride source (*20*); and (iii) *N*-protonation of the basic hydroxyl amine product prevents catalyst poisoning (Fig. 1D). The need for stoichiometric amounts of a strong acid severely complicates the use of chiral proton sources (e.g., chiral phosphoric acids). We hypothesized that chiral cyclopentadienyl (Cp^x) ligands, which have emerged as powerful ligands for transition metal–catalyzed C-H functionalizations (*21*), constitute a potential entry point for enantioselective oxime hydrogenation. Although transient cyclometalated species of Cp^x metal complexes are frequent intermediates in C-H functionalizations (*22*), their use as stable cyclometalated complexes for catalytic purposes has been far less explored.

Oxime substrates **1** were typically obtained as *E*/*Z*-diastereomeric mixtures. When required (see below), separation by silica gel column chromatography delivered the pure benchstable *E* and *Z* isomers. Air- and moisture-stable iridium(III) complexes **Ir1** to **Ir4** were accessed in a straightforward two-step sequence. Their subsequent evaluation as selective catalysts in the reduction of oxime *E*-**1a** to *N*-*tert*-butoxylamine **2a** is summarized in Fig. 2 and fig. S2. The hydrogenation tests were conducted with 1 mol % of the iridium complex, 1.5 equivalents of methanesulfonic acid (MsOH), and 50 bar of H_2 at 23°C in 2-propanol (*16*). Exposure of *E*-**1a** to achiral complex **Ir1**, bearing an acetophenone imine as the lower chelate portion, resulted in quantitative formation of **2a** with no detected overreduction by nuclear magnetic resonance (NMR) analysis. Using (*S*)-**Ir2** where the Cp* unit was replaced by our chiral binaphthyl-derived Cp^x ligand (*23*) gave (*S*)-**2a** in 41% yield and 70:30 enantiomeric ratio (e.r.). Encouraged by this proof of principle, we tailored the lower chelating *C*,*N*-ligand architecture for the transformation resulting in **Ir3**. Additional 3,5-dimethyl groups of the aniline unit and a cyclic rigid tetralone backbone with an ethylene glycol ether adjacent to the iridium boosted the catalyst performance, giving **2a** in >99% yield and improved 89:11 e.r. In particular, the proximal (2-methoxyethyl) ether substituent rendered the complex more robust toward deactivation. In addition, the oxygen atoms of the tail might engage in hydrogen-bonding interactions with the substrate (*24*). The enantioselectivity of the hydrogenation was further improved by retaining the optimal *C*,*N*-ligand and tuning the capping chiral Cp^x ligand, resulting in **Ir4**, which has the Cp^x methoxy units replaced by phenyl groups (*25*). Using **Ir4** as the precatalyst produced **2a** in >99% yield and

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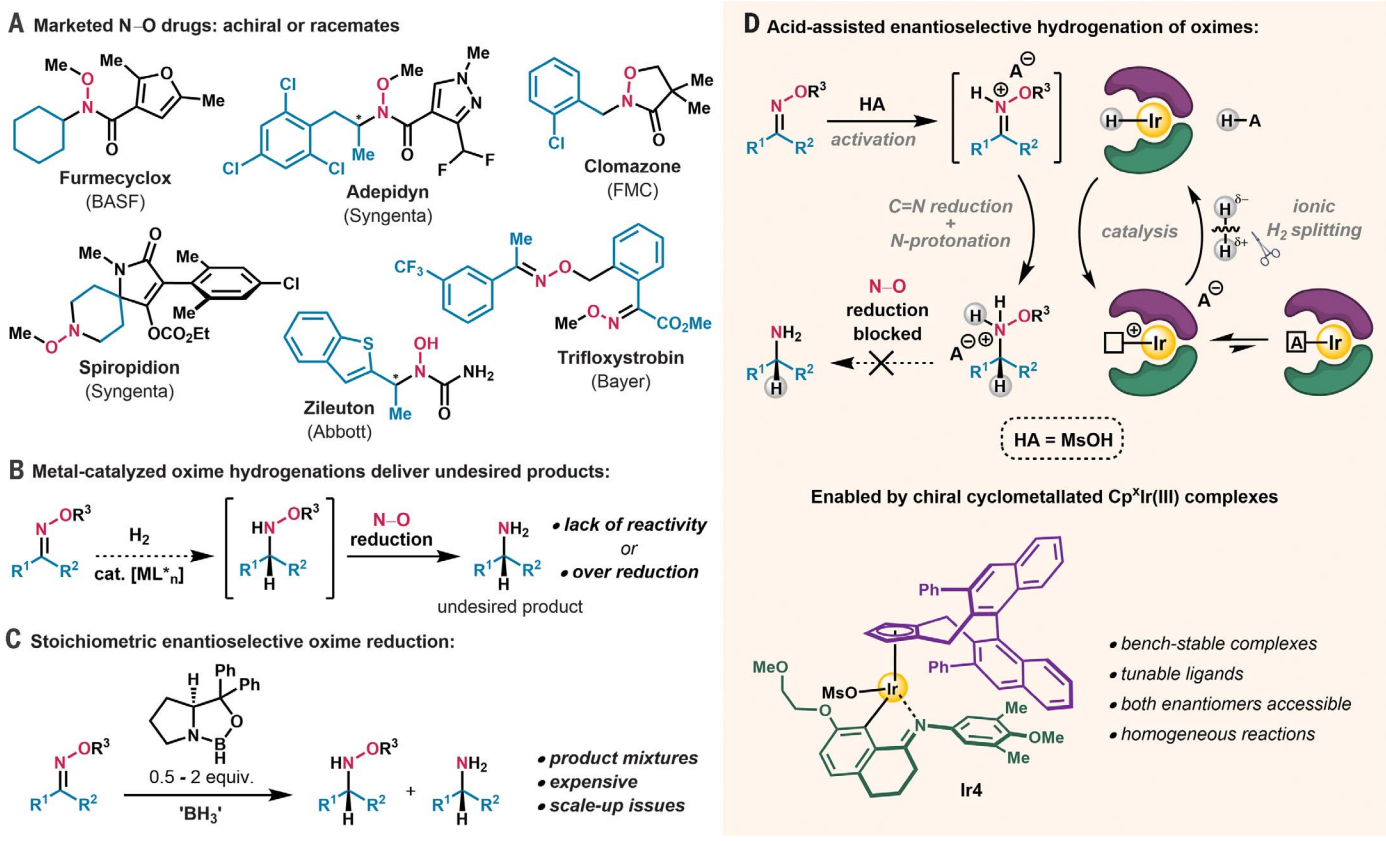
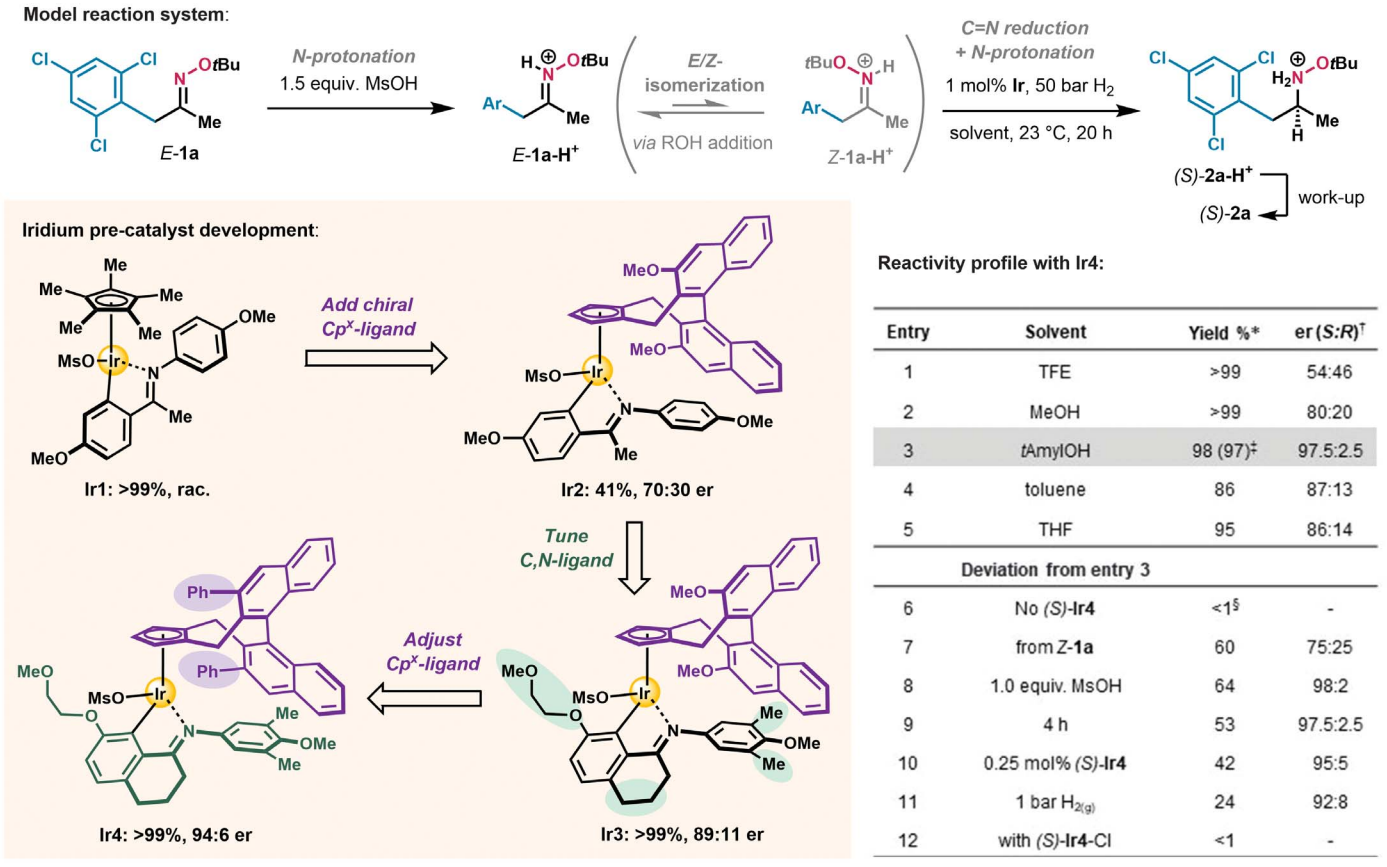


Fig. 1. Relevance of hydroxylamines and strategies for their enantioselective production by oxime reductions. (**A**) Marketed biologically active compounds containing N–O bonds either lack chirality or are sold as racemates. (**B**) Metal-catalyzed asymmetric oxime hydrogenations lead to undesired primary amine products. (**C**) Asymmetric reductions with stoichiometric chiral oxazaborolidine reagents proceed with partial cleavage of the N–O bond, are expensive, and are difficult to scale up. (**D**) Iridium(III) complexes enable the enantioselective hydroxylamine synthesis via the developed asymmetric hydrogenation platform.

94:6 e.r. ^{1}H-NMR analysis of **Ir4** in tetrahydrofuran (THF)–d_8 revealed a 70:30 diastereomeric mixture provided by the iridium stereogenic center. Upon in situ hydride incorporation, complex **Ir4-H** was detected in 96:4 diastereomeric ratio (d.r.) (fig. S3). This likely represents the ceiling of achievable selectivity. X-ray crystallographic analysis of related complex **Ir3b-I** provided additional structural insights of the complex in the solid state (fig. S4).

The hydrogenation proceeds in a variety of solvents. However, the catalyst reactivity and selectivity were lower in aprotic solvents such as toluene and THF (Fig. 2, entries 4 and 5). Among alcoholic solvents, *tert*-amyl alcohol (*t*AmylOH) was superior, giving excellent levels of enantioselectivity (97.5:2.5 e.r.) and conversion (98%) for the reduction of *E*-**1a** to **2a** (entry 3), whereas the reduction of *Z*-**1a** under otherwise identical conditions resulted in a modest conversion and modest enantioselectivity (entry 7). In line with previous reports (*26*), this indicates a strong impact of the oxime *E*/*Z* stereochemistry on the reaction outcome, with *E*-**1a** providing superior reactivity and selectivity. Because protonated oximes can isomerize by nucleophilic addition/elimination to the C=N double bond, the choice of the alcoholic solvent and the Brønsted acid is key to achieving high selectivity by tuning the substrate *E*/*Z* equilibration rate versus the hydrogenation rate. Pure *E*-**1a** isomer equilibrates to an 80:20 *E*/*Z*-mixture in the absence of **Ir4** (entry 6). Using the catalyst in *t*AmylOH produced **2a** in 97.5:2.5 e.r., irrespective of the reaction time (4 or 20 hours); this indicates that the hydrogenation is faster than oxime isomerization (entries 3 and 9). Performing the reduction in methanol (MeOH), which triggers a faster oxime isomerization, caused a drop in selectivity to 80:20 e.r. (entry 2). In contrast, 1.0 equivalents of MsOH, the minimum required amount of acid, in *t*AmylOH afforded **2a** in 98:2 e.r., although this was accompanied by incomplete conversion of *E*-**1a** (entry 8). 2,2,2-Trifluoroethanol disrupted essential interactions for stereocontrol and yielded **2a** in modest 54:46 e.r. (entry 1). Additional experiments showing the impact of the acid strength and stoichiometry on the reaction outcome are summarized in fig. S4. A high enantioselectivity was maintained at 0.25 mol % catalyst loading (entry 10) or with lower hydrogen pressure (1 bar H_2) (entry 11). With lower loadings, the risk of catalyst deactivation by chloride anion contamination increases. The chloride analog of (*S*)-**Ir4** was completely catalytically incompetent as a result of the high Cl-Ir binding affinity (entry 12). The absolute configuration of **2a** was confirmed by single-crystal x-ray analysis of its 4-nitrobenzenesulfonic acid salt.

Using the optimized conditions with a slow *E*/*Z*-oxime equilibration regime, the acid-assisted enantioselective reduction was applicable to a variety of oximes **1**, producing the corresponding alkoxy amines **2** in excellent yields and enantioselectivity (Fig. 3). Contrasting the reported racemic $B(C_6F_5)_3$-catalyzed oxime hydrogenation (*27*), the bulky *tert*-butoxy group of **1a** is not mandatory. Substrates with *O*-methyl as well as other primary and secondary *O*-alkyl substituents were quantitatively hydrogenated in high enantioselectivities, up to 97:3 e.r. Even free oximes were smoothly reduced to the corresponding hydroxylamine products without any detectable N–O bond



Entry	Solvent	Yield %*	er (S:R)†
1	TFE	>99	54:46
2	MeOH	>99	80:20
3	*t*AmylOH	98 (97)‡	97.5:2.5
4	toluene	86	87:13
5	THF	95	86:14
	Deviation from entry 3		
6	No (*S*)-**Ir4**	<1§	-
7	from *Z*-**1a**	60	75:25
8	1.0 equiv. MsOH	64	98:2
9	4 h	53	97.5:2.5
10	0.25 mol% (*S*)-**Ir4**	42	95:5
11	1 bar $H_{2(g)}$	24	92:8
12	with (*S*)-**Ir4**-Cl	<1	-

Fig. 2. Development of the iridium precatalyst and reaction optimization. Conditions: *E*-**1a**, 1 mol % **Ir**, 50 bar H_2, 1.5 equiv MsOH, 0.5 M in *i*PrOH, 23°C, 20 hours, basic work-up to free **2a**. *Determined by ^{1}H-NMR with internal standard; yield of **2a** virtually identical to the consumption of **1a**. †e.r. determined by chiral HPLC. ‡Isolated yield. §>99% of **1a** recovered (4:1 *E*:*Z*).

scission, as exemplified by **2b**. Despite the acidic reaction conditions, an acid labile acetal moiety (**2c**) and *O*-benzyl group susceptible to hydrogenolysis (**2d**, **2e**) did not interfere and remained intact. Substrate selectivity control by existing stereocenters at the ether oxygen atom, as exemplified by **1e** with the (*S*)-α-methylbenzyl group, could be overridden by the iridium catalyst. Product **2e** was obtained either in a 4:1 d.r. for the mismatched case with (*S*)-**Ir4** or in a 7:93 d.r. using the matched catalyst isomer (*R*)-**Ir4**. In general, the enantiomeric purity of products **2** could be upgraded by simple recrystallization of their salts, as shown for compound (*S*)-**2g** (from 93:7 e.r. to 99:1 e.r. with 81% recovery). When starting from pure *Z*-**1g** isomer, the antipode (*R*)-**2g** was formed in 20:80 e.r. Dialkyl oximes **1l** and **1m** bearing 2° and 3° alkyl substituents were equally well reduced, giving for instance *N*-**2m**, the *N*-methoxy derivative of rimantadine (*28*) in 93:7 e.r. Related substrates with adjacent hydroxyl or tosylate groups at the α-carbon atom were compatible, affording reduced products **2n** and **2o** in excellent yields and high selectivities. Another salient application is the access to *N*-alkoxy amino acid derivatives, as shown for valine analog **2p** formed in 98% yield and 90:10 e.r. The protocol works with D_2 generated by Skrydstrup's two-chamber setup, thus qualifying for practical deuterium isotopic labeling of valuable hydroxylamine scaffolds. Accordingly, benzoxazine **2q**-d_1 was synthesized in 80% yield and 97:3 e.r. with 92% deuterium incorporation.

We next targeted the synthesis of *N*-alkoxy derivatives of valuable chiral α-branched benzylamines (*29*). No stereocontrol was achieved with 4-methoxy acetophenone derived oxime *E*-**1j**, which equilibrates to a 9:1 *E*:*Z* isomeric mixture under the reaction conditions. Sterically more demanding *Z*-**1k**, with a locked Z-configuration due to the *tert*-butyl substituent, gave **2k** in 92:8 e.r. To further investigate the impact of the aryl oxime stereochemistry on the reaction, we individually subjected the separated isomers *Z*-**1rc** and *E*-**1rc** to conditions for fast hydrogenation (3 mol % **Ir4**) and slow isomerization (*i*PrOH, 1.0 equiv of MsOH, 2 hours) (Fig. 3B). The diastereoisomer having the *N*-OR moiety trans to the large substituent (here *Z*-**1rc**) reacted much faster and more selectively to **2rc** (99%, 97:3 e.r.) than did *E*-**1rc** (22%, 70:30 e.r.), which suggests that actually only ~7% of isomer *E*-**1rc** was reduced. Given this behavior, we hypothesized that using conditions with a fast *E*/*Z* equilibration regime would be most beneficial. Indeed, hydrogenation of a 1:1 *E*:*Z* mixture of **1rc** under equilibrating conditions [ethanol (EtOH), 1.5 equiv of MsOH] formed **2rc** in quantitative yield and 92:8 e.r.

A variety of substrates **1ra** to **1rk** were conveniently hydrogenated as the unresolved 1:1 *E*/*Z* mixtures, forming the corresponding *N*-methoxy amines in excellent yields and comparably high enantioselectivities. This substrate type allowed the demonstration of the unique chemoselectivity and functional group tolerance of the acid-assisted reduction method. Whereas most transition metal–catalyzed hydrogenation methods frequently reduce aromatic bromo, vinyl, and nitro as well as azido groups, these remarkably remained untouched under our reaction conditions. Moreover, the pinacol boronate group of **2rk** survived, serving as a potential handle for subsequent cross-coupling reactions. Nitrogen and sulfur heteroarenes **2re** and **2rf** were also compatible. (See fig. S6 for tests of additional functional

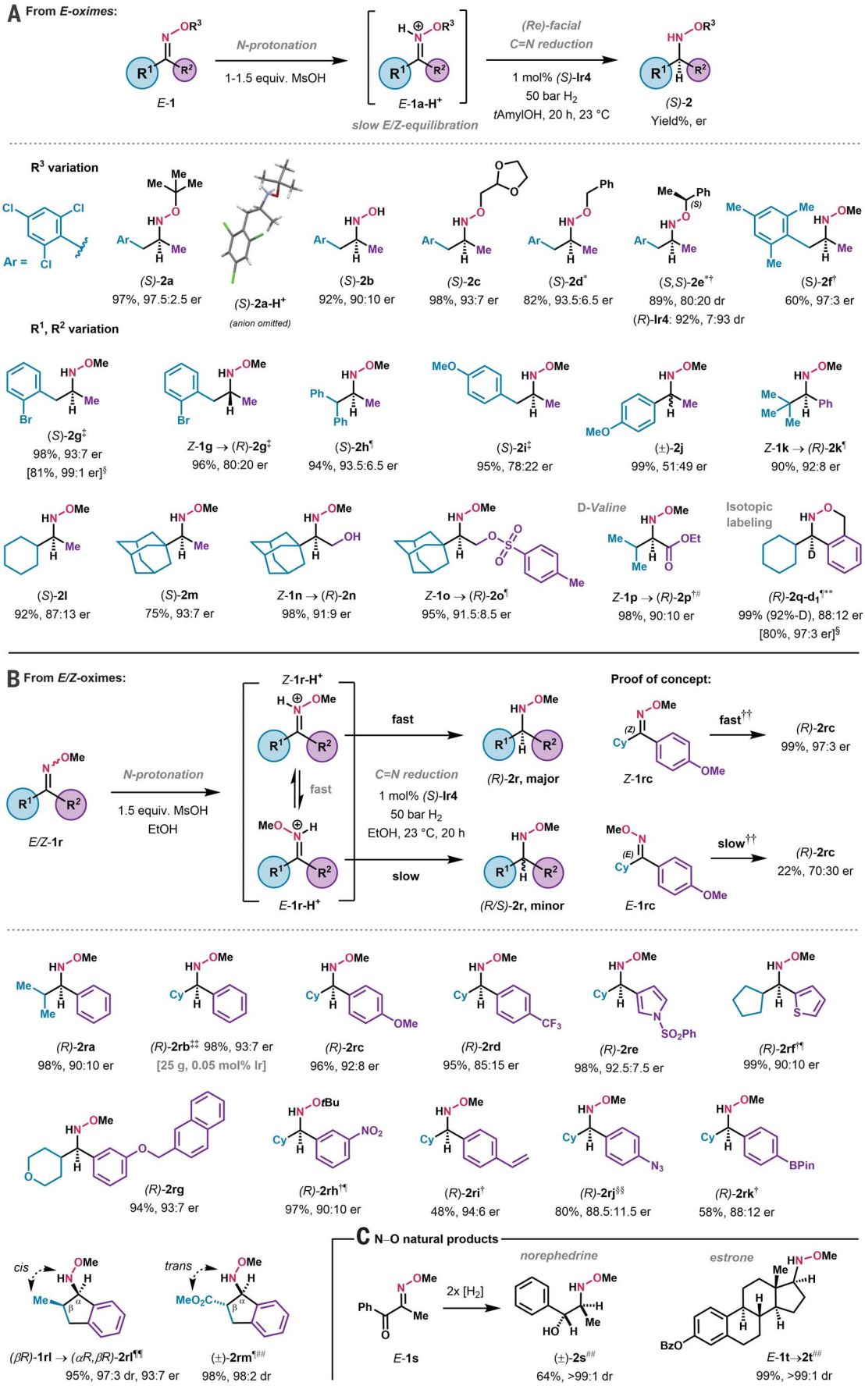


Fig. 3. Substrate scope of the oxime hydrogenation. Isolated yields; e.r. determined by chiral HPLC. (**A**) Hydrogenation of pure *E*-oximes. (**B**) Hydrogenation of *E*/*Z* oxime mixtures. (**C**) Natural product hydroxylamine derivatives. *In *i*PrOH. †2 mol % **Ir4**. ‡5.0 equiv of TFA instead of MsOH. §Recrystallized as its *p*-nitrobenzenesulfonate. ¶In MeOH. #In EtOH. **Ex situ generation of D_2 using COware. ††3 mol % **Ir4**, 1.0 equiv MsOH, *i*PrOH, 23°C, 2 hours. ‡‡94:6 e.r. at 1 mol % **Ir4**. §§20 bar H_2, 5 hours. ¶¶From (βS)-**1rl**: (αS,βS)-**2rl** 99%, 77:23 d.r. ##1 mol % **Ir1**.

groups.) Enzyme inhibitor **1rg** (*30*) could be reduced in quantitative yield and 93:7 e.r., illustrating the applicability of the method for late-stage derivatization. Existing stereogenic centers adjacent to the C=N bond exhibit a strong substrate control. For instance, (*R*)-**1rl** possessing a β-methyl stereogenic center yielded cis-isomer (*R*,*R*)-**2rl** in 97:3 d.r. and 93:7 e.r. In contrast, β-ester analog (±)-**1rm** gave trans-isomer **2rm** in 98:2 d.r., likely by cis-hydrogenation followed by acid-promoted epimerization of the ester to the thermodynamically more stable product. *N*-methoxy derivatives of norephedrine **2s** and estrone **2t** were formed in highly diastereoselective fashion, the former after double hydrogenation of **1s**. Finally, a 25-g batch of *E*/*Z*-**1rb** was hydrogenated with a reduced 0.05 mol % catalyst loading to (*R*)-**2rb** in a quantitative manner (turnover number 4000) in 93:7 e.r., supporting the scalability of the method. Overall, our findings serve as a blueprint for further asymmetric transition metal–catalyzed ionic hydrogenations of challenging substrates, and highlight the yet untapped potential of cyclometalated chiral Cp^x metal complexes in catalysis.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S6
HPLC Traces
NMR Spectra
References (*31*–*54*)

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Hydrogenations that tolerate N–O bonds

Catalysts that add hydrogen to carbon-carbon, carbon-nitrogen, and carbon-oxygen double bonds are among the most widely used in synthetic chemistry. They are particularly adept at delivering just one of two mirror-image products. However, they may also target adjacent bonds in the compound that would be better left intact. Mas-Roselló *et al.* report that an iridium catalyst paired with a strong acid can hydrogenate C=N bonds without disturbing a weak N–O bond on the same nitrogen center. The reactions proceed at room temperature with high enantioselectivity.

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