Catalytic Reduction of Oximes to Hydroxylamines: Current Methods, Challenges and Opportunities

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Abstract: Catalytic reduction of oximes represents a direct efficient approach to synthesize valuable hydroxylamine derivatives. However, this transformation presents significant challenges: oximes are hard to reduce and, if reactive, reductive cleavage of the weak N–O bond often leads to primary amine side products. The first suitable systems involved the use of platinum-based heterogeneous catalysts with hydrogen as reductant and stoichiometric amounts of a strong Brønsted acid. More recently, metal-free and transition-metal-based homogeneous catalysts have been developed, which display the highest turnovers (up to 4000). In the asymmetric variants, the E/Z-geometry of the oxime double bond affects significantly the stereoselectivity, sometimes requiring extra synthetic efforts in substrate preparation. This minireview provides an overview of the advances and limitations in catalytic oxime to hydroxylamine reduction. Emphasis is put on highlighting and comparing the practical aspects of the existing methods, such as their reaction conditions and substrate scope. Additionally, future directions for improving this young research area are suggested.

1. Introduction

The hydroxylamine motif is present in many active ingredients of pharmaceuticals and agrochemicals, as well as in natural products.$^\text{[1–5]}$ Additionally, hydroxylamine derivatives are versatile intermediates in organic synthesis,$^\text{[6–9]}$ powerful ligands$^\text{[10,11]}$ and catalysts.$^\text{[12]}$ Therefore, having efficient synthetic access to this scaffold is of significant importance. Among the different strategies for producing N-alkyl-N-hydroxylamine derivatives,$^\text{[13]}$ the reduction of unsaturated oxime precursors is particularly attractive in terms of versatility, step- and atom-economy. Transformations involving the reduction C=N double bonds are omnipresent in both academic and industrial settings for accessing nitrogen-containing chemicals.$^\text{[14–16]}$ Conventional methods that allow the conversion of oximes or oxime ethers to hydroxylamines involve largely the use of borohydride stoichiometric reductants,$^\text{[17–22]}$ and also hydrosilanes$^\text{[23]}$ or organotin hydrides.$^\text{[24]}$ These present the disadvantages of large waste generation, toxicity, and elevated cost, which are especially concerning in large-scale industrial processes.

In contrast, catalytic reductions employing cheap environmentally benign reductants, such as hydrogen gas, are ideal from a sustainability perspective.$^\text{[25]}$ Whereas catalytic reductions of unsaturated imines to produce amine products are established,$^\text{[26,27]}$ analogous oxime reductions to hydroxylamine derivatives are scarce. These substrates present additional challenges (Figure 1, top). For instance, they are more resilient to hydride (or other nucleophiles) attack to the C=N bond due to the extra stability provided by resonance with the adjacent oxygen atom lone pairs (likewise oximes show increased resistance to hydrolysis).$^\text{[28]}$ Secondly, the N–O bond is susceptible to reductive cleavage, therefore high chemoselectivity towards reduction of the oxime C=N bond is required to neatly produce hydroxylamine products instead of primary amines. The later can form either via hydroxylamine over-reduction (path A)$^\text{[29]}$ or via oxime N–O bond cleavage followed by imine reduction (path B).$^\text{[30,31]}$ Lastly, significant differences in reactivity and stereoselectivity are generally observed depending on the E- or Z-geometry of the oxime double bond (see below). This often requires reacting pure oxime isomers in order to reach high levels of stereoselectivity in the reduction.

This minireview describes for the first time the few existing methods suitable for the selective catalytic reduction of oximes to N-alkyl-N-hydroxylamine products, from a practical perspective. First, the different competent catalysts are overviewed. Subsequently, the substrate’s stereochemical influence in the reduction is discussed, along with various synthetic approaches.

![Figure 1. Challenges in catalytic reduction of oximes to hydroxylamine products (top), and overview of available methods (bottom).](image-url)
Afterwards different reduction systems are individually commented, highlighting their reaction conditions, substrate scope and functional group compatibility. Some limitations of the methods are also indicated, and finally, possible directions for improvement are discussed.

Up to date, three different catalyst classes have been reported as competent for selective oxime to hydroxylamine reduction: transition-metal based heterogeneous or homogenous catalysts, and purely organic homogeneous catalysts (Figure 1, bottom). Heterogeneous catalysts are generally cost-effective systems since they do not require often-complex supporting ligands. Their facile separation from the product and recovery makes them attractive for large-scale applications. Up to date, the competent ones for oxime reduction contain either platinum or nickel plus cobalt bimetallic mixtures, and all use hydrogen gas as reductant. These systems have only achieved moderate catalytic efficiencies (up to 290 TON), which devaluates their advantages.

Complementary homogeneous catalysts, typically composed of a transition metal bearing specific ligand(s), may be easier to tune in order to reach high activity and selectivity under mild reaction conditions. Of this second class, so far only chiral phosphine-ligated rhodium complexes and cyclometallated iridium complexes have been shown to be suitable catalysts for oxime hydrogenations. The later display the highest catalytic performance (up to 4,000 TON), and can also effect enantioselective reductions if equipped with a chiral cyclopentadienyl ligand. The third class englobes homogenous organocatalysts. Two different methods are available: one uses simple tris(pentafluorophenyl)borane, $\text{B(C}_6\text{F}_5)_3$, as catalyst for oxime ether hydrogenation to access O-substituted hydroxyamine derivatives as racemates. Alternatively, the combination of chiral norephedrine with borane adducts was claimed in a patent to be a suitable system for the catalytic enantioselective reduction of a single substrate. Nevertheless, employing costly and toxic BH$_3$ as reductant should be less preferred than H$_2$, especially in large-scale production. Whereas metal-free catalysts seem ideal sustainable options, they do not reach yet the catalytic efficiency of transition-metal-based systems.

2. Stereochemoal Considerations: Oxime E/Z-Geometry

Oximes bearing different substituents in the carbon atom exist as E- or Z-diastereoisomers provided by the geometry of the C=N double bond. These are generally stable (can be isolated) and show different reactivity and stereoselectivity in their reduction. For example, back in 1992 Williams found totally opposite diastereoselectivity when reacting separately oxime benzyl ethers E-1 and Z-1 with stoichiometric amounts of (Me$_3$N)BH(OAc)$_3$ (Scheme 1A). The corresponding N-benzyloxoyamine epimers 2 and epi-2 were obtained in significantly different yields. Soon after, Chan and co-workers observed different enantioselectivity in the hydrogenation of either E- or Z-isomers of 1-acetonaphthone oxime 3 using a chiral phosphine-ligated rhodium catalyst (Scheme 1B). The optical rotation of the products, presumably the doubly reduced primary amine 4, had opposite signs. In practice, these early observations suggest that to seek for high levels of stereoselectivity in the reduction, the ketoxime substrate should be prepared as a single geometrical isomer.

Scheme 1. Impact of the oxime’s E/Z geometry in the reduction.

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Nicola Cramer earned his PhD in 2005 at the University of Stuttgart under the guidance of Sabine Laschat. After a postdoctoral stint with Barry Trost at Stanford, he completed his habilitation at ETH Zurich from 2007 to 2010 with Erick Carreira. Subsequently, he moved to EPFL as assistant professor, was tenured in 2013 and promoted to full professor in 2015. His research encompasses sustainable enantioselective metal-catalyzed transformations and their implementation in synthesis. A focus is placed on asymmetric C-H functionalizations enabled by novel ligand designs.
Conventional oxime (ether) syntheses involve ketone condensation with hydroxylamine (or an O-substituted analogue) (5→7), or the tautomerization of nitroso compounds 6 formed by carbanion nitrosation or reduction of nitro precursors (Scheme 2A). These two synthetic approaches typically afford E/Z-diastereomeric mixtures (E/Z-7), with the ratio depending on the stereoelectronic properties of the oxime substituents. Few selected examples of mixtures (7a-f, synthesized from ketones) are shown in Scheme 2A. The diastereoisomers may be separated by means of column chromatography or (re)crystallization. These are long-term configurationally stable either neat or in solution with exceptions. In the presence of a strong acid, isomerization occurs via nucleophilic addition/elimination of the conjugate base or solvent to the Csp² center of the N-protonated oxime (oximes have pKa lower than 2). Additionally, elevated heating of mixtures has been utilized to enrich the content of the thermodynamically-favored E-isomer. Whereas photoexcitation under light irradiation typically favors the Z-isomer.

Methods for the stereoselective production of ketoximes are scarce in the literature. A selection are shown in Scheme 2B. In 1974, Kaiser reported the synthesis of aryl alkyl Z-ketoximes 11 from α-bromoacetophenones Z-8. Those slowly degrade into electrophilic 1-nitrosostyrene compounds 9, and were trapped by hydride or different heteroatom (N, O, S) nucleophiles affording the corresponding oximes Z-10 with excellent diastereoselectivity. Others showed that O-alkylation of 10 can provide ether derivatives Z-11 without detectable isomerization. In 2013, Dolliver and co-workers disclosed a complementary approach to synthesize stereo-defined ketoximes 14. Starting from benzoic acids 12, a 3 step sequence delivered aryl-iodooximes 13 as single Z-isomers. Subsequently, a Suzuki-type cross-coupling allowed the insertion of aryl, vinyl or alkynyl substituents in a stereospecific manner to yield 14 as single geometrical isomers. Recently, Song et al. described a versatile stereoselective method whereby E/Z-mixtures of chloro-oximes 15 were directly functionalized with aryl boronic acids. A base-promoted 1,4-boronate shift afforded ketoximes 16 in excellent diastereoselectivity. All three strategies are limited to having at least one aryl C-substituent. Clearly the development of new methods with extended or complementary substrate scope (e.g. bis-alkyl ketoximes) and stereoselectivity is of high interest.

3. Heterogeneous Transition-Metal Catalysts

To the best of our knowledge, the first selective catalytic oxime hydrogenations were performed by Vavon in the 1920s using Adams’ catalyst (PtO₂), 3 bar of hydrogen pressure, stoichiometric hydrochloric acid in ethanol at room temperature (Scheme 3). Others adopted later this protocol to hydrogenate different protonated E/Z-oximes 17 yielding N-alkyl-N-hydroxylamine derivatives 18 as racemates. These were

Scheme 2. Different approaches for oxime (ether) synthesis.
liberated from the corresponding hydroxylammonium chloride salts upon basification (typically with aqueous sodium bicarbonate). Regarding the collective substrate scope, aryl-acetone oximes 17 a–f with or without O-alkyl substitution were reduced to afford N-hydroxy/alkoxy derivatives of amphetamines 18 a–f. In the particular case of 18f, an alternative set of conditions (b), involving Pt on charcoal (Pt/C) as catalyst and sulfuric acid was described in a patent. Longer alkyl ketoximes, such as 17 g, h were also tolerated. In contrast, acetonophene oxime 17 i was little reactive, benzophenone oxime 17 j was inert and aldokimes 19 dimerized to N,N-dialkyl products 20.

In the 1960s, Rosen & Green investigated the performance of different heterogeneous catalysts in the hydrogenation of 2-indanone oxime 21 (Scheme 4A). Palladium on charcoal (Pd/C) or Pearlman’s catalyst (Pd(OH)₂) were inactive under standard hydrogenation conditions of 3 bar of H₂ pressure, room temperature in methanol (conditions a). In stark contrast, using Pd/C in highly acidic media (stoichiometric amounts of sulfuric acid in acetic acid as solvent) gave the doubly reduced amine product 23 in 93% yield (conditions b). Remarkably, employing Pt/C as catalyst switched the selectivity towards the hydroxylamine product 22, which was obtained in 54% yield under otherwise identical conditions (conditions c). Using elemental Nickel favored the formation of primary amine 23, with higher yields when operating under basic conditions and mild heating (conditions d). A control experiment revealed the sluggish formation of ammonium salt 23-H⁺ from pre-formed hydroxylamine 22 using Pd/C catalyst and acid (Scheme 4B). Based on this, the authors proposed the following reaction paths in strongly acidic media (Scheme 4C): from the protonated oxime 21-H⁺, palladium favours N–O bond scission leading to iminium / enamine species 24-H⁺/25-H⁺, which are further reduced to 23-H⁺. Alternatively, platinum reduces chemoselectively the C=N bond of 21-H⁺ giving hydroxylammonium species 22-H⁺, which can be liberated to 22 upon basic work-up.

Recently in 2020, Ciotonea et al. developed a heterogeneous catalyst based on bimetallic Ni/Co nanoparticles highly dispersed onto mesoporous SBA-15 silica (Scheme 5). The catalyst was prepared in one step with the optimal Ni to Co weight ratios being 1:1. It showed excellent chemoselectivity and good performance in the hydrogenation of three differently substituted ketoximes 17 i-k, including arylketoximes 17 j that are problematic to reduce with Pt-catalysts. Here, the presence of strong Brønsted acid in the reaction is not needed, offering an alternative for reducing substrates containing acid-labile moieties. The slightly bigger catalyst loading (2.5 mol%) compared to the Pt-based system (0.35–1 mol%) is compensated by the greater earth-abundance and reduced cost of Ni and Co. However, recycling of the catalyst must be performed under the strict exclusion of air, and a significant gradual loss of activity was observed in the reduction of 2-methylquinoline after each cycle (from 72% yield at cycle 1 to 21% at cycle 5). Additionally, elevated temperature and long reaction time seem to be required for high product yields. Perhaps reactivity could be improved by addition of equimolar amounts of a strong acid as activator, as shown by the authors in the hydrogenation of an indole substrate.

### 4. Homogeneous Transition-Metal Complexes

In 2007, Kadyrov and co-workers claimed in a patent the heterogeneous hydrogenation of β-oxime esters 26 (Scheme 6). Loading 1 mol% of an in situ formed phosphine-ligated rhodium catalyst, equimolar amounts of HBF₄ under 20 bar of hydrogen, four substrates were reduced to the corresponding N-methoxyamines 27 in high yields. Excellent enantioselectivity was reported for two examples (27 a; absolute configuration unknown), and the rest (27 c, d) were not determined. From a practical standpoint, the commercial availability of the Josiphos-type ligand and the rhodium source, added to the room-temperature reaction conditions make this catalytic system attractive. Mechanistically, β-oxime esters can easily tautomerize to 2,3-unsaturated esters 28, so the

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**Scheme 4.** Studies by Rosen & Green (1963) on heterogeneous oxime hydrogenation.

**Scheme 5.** Bimetallic Ni/Co-catalyzed heterogeneous oxime hydrogenation.
described transformation is likely to proceed via reduction of the C=C double bond of the enamine tautomer. This methodology is likely limited to α-acidic tautomerizing substrates. Recently, the Cramer group and Syngenta Crop Protection AG jointly developed novel cyclometalated cyclopentadienyl iridium(III) complexes Ir1 and Ir2 and applied them as catalysts for homogeneous oxime hydrogenation (Scheme 7). These are air- and moisture-stable, and can be prepared in 3 or 5 steps (Ir1 and Ir2, respectively) from commercial materials. Both enantiomers of the chiral Cp ligand of Ir2 are available. The standard reaction conditions involve 50 bar of hydrogen pressure, 1.5 equivalents of methanesulfonic acid, and alcohol solvents at room temperature. The reduction proceeds with full chemoselectivity towards the oxime C=O bond, obtaining chiral N-hydroxy and N-alkoxyamines in enantiomeric ratios up to 98:2 and catalyst turnover numbers up to 4000. Based on the nature of the catalyst and experimental evidence, the authors proposed an ionic hydrogenation mechanism whereby the acid plays multiple roles: i) activates the oxime substrate by N-protonation; ii) the conjugate base mediates heterolytic H2 splitting; iii) quenches the hydroxylamine basic product, preventing catalyst poisoning.

Up to date, this is the most general method regarding substrate scope. Using 1 mol% of Ir1, both aldoximes and ketoximes bearing C-alkyl and aryl substituents were well-reduced, leading to the corresponding linear or branched N-alkyl-N-hydroxylamine products 30a–d in excellent yields as racemates. A diaryl ketoxime was also hydrogenated to α,α-diarylamine 30c, albeit in reduced yield. Free oximes and oxime ethers reacted equally well, and remarkably benzyl ethers (30d) were stable towards hydrogenolysis. Moreover, the protocol is highly diastereoselective when additional stereogenic centers are present in the substrate, such as showcased with N-hydroxy-norephedrine 30e and exocyclic methoxamine (R,R)-30f.

In the asymmetric version, oxime ethers generally provided higher enantioselectivity than free oximes (7a vs. 7b). As usual, different oxime geometrical isomers reacted differently: whereas E-29f favored the (R)-enantiomer of N-methoxyamphetamine analogue 30i in 86% ee, the Z-isomer led to the antipode (S)-30i in 60% ee. While no stereocontrol was achieved with ρ-methoxy acetophenone oxime E-7c, the bigger tert-butyl analogue Z-7e gave 30j in 92:8 er and 90% yield. In this case, chiral catalyst Ir2 displayed a much higher activity than Ir1 which was inactive. N-alkoxy amino acid derivatives could be prepared, such as valine analogue 30l, and the method allowed for isotopic labelling via in situ generation of Scheme 6. Rhodium-catalyzed homogeneous (asymmetric) hydrogenation of β-oxime esters.

Scheme 7. Iridium-catalyzed homogeneous (asymmetric) hydrogenation of oximes.
deuterium gas as reductant (30k). Notably, substrates bearing similar-in-size C-substituents, such as 29m–o, were reduced as E/Z-mixtures. Under fast-isomerizing reaction conditions (over-stoichiometric amounts of methanesulfonic acid combined with nucleophilic alcohol solvents), a kinetically favorable hydrogenation of the Z isomer over the E isomer led to high product yields and enantioselectivities. A 25 g batch of E/Z-29m was fully converted to (R)-30m using as low as 0.05 mol% of Ir2, which demonstrates the scalability of the method. Several functional groups that are frequently problematic in hydrogenations, such as sulfur heteroarenes 30n and nitro groups 30o, were compatible.

5. Homogeneous Organocatalysts

While several metal-free systems exist that promote ketone and imine reductions, the choice for oximes is rather limited. In a seminal work, in 2014 the group of Oestreich used B(C$_5$F$_5$)$_3$ as catalyst to hydrogenate ketoxime ethers 31 (R$^2$ $\neq$ H) to racemic hydroxylamine derivatives 32a–g without scission of the N–O bond (Scheme 8). The reactions were performed under high pressure of hydrogen (100 bar), at room temperature or moderate heating in toluene (conditions a). The presence of bulky silyl or 8BuO-substituents in the oximes was mandatory for reactivity leading to high product yields. If desired, the products could be desilylated to afford free hydroxyl derivatives 32h in excellent yields. A benzophenone oxime ether 32a was unreactive.

Mechanistically, the authors proposed the formation of a frustrated Lewis pair (FLP) between the highly acidic B(C$_5$F$_5$)$_3$ and the weakly basic oxime substrate. FLPs are known to mediate heterolytic dihydrogen splitting, generating in this case HB(C$_5$F$_5$)$_3$ and protonated oximes as hydride receiving electrophiles. In a follow-up publication, the scope of the transformation was extended to aldoxime ethers 31 (R$^2$–H) by using 1,4-dioxane as solvent (conditions b). Given the reduced basicity of aldoximes compared to ketoximes, the ethereal solvent was needed presumably acting as the base in the FLP adduct. With the modified reaction conditions, different linear N-alkyl N-silyloxylamine products such as 32i–k were synthesized in high yields and chemoselectivity.

Clearly an attractive feature of this method is the simplicity of the borane catalyst. On the other hand, its high electrophilicity and oxophilicity may cause poisoning in the presence of other basic functionalities (e.g., amines, carbonyls), alcohols, or even moisture. Glove-box set up and relatively high catalyst loadings seem to be required (5–10 mol%), which can hamper its application in big-scale processes.

Up to date, the only metal-free method available for enantioselective ketoxime reduction employs Core-Itsuno-type chiral oxazaborolidinium borohydride complexes 37 as stoichiometric reductants (Scheme 9A). In multiple reports, these were commonly prepared in situ from norephedrine and two equivalents of borane-tetrahydrofuran adduct (BH$_3$·THF). Typically mixtures of hydroxylamine 34 and primary amines 35 were obtained, with their ratio being strongly dependent on the substrate. Also the choice of amino-alcohol ligand had an influence, with norephedrine complexes displaying highest chemoselectivity over 34. The optical purity of both products is typically identical, which indicates that 35 are generated by

![Image](image-url)
over-reduction of 34 (path A in Figure 1), instead of oxime N–O bond cleavage followed by imine reduction (path B in Figure 1). Opposite enantioselectivity was observed depending on the E/Z-ketoxime geometry.[29]

A collective selection of N-alkoxamines products 34, obtained after reduction of isomerically pure ketoximes precursors E-33, is shown in Scheme 9A. Benzyl ethers 34b performed better than the methyl analogues 34a, and bulky ethers 33c,d did not react. Different aryl and alkyl C-substituents led to variable enantioselectivities with no clear trend (45–91 % ee). Very interestingly, the first single example of a substoichiometric transformation was documented in 2014[30] as described, aryl-acetone oxime E-38 was reduced using 0.5 equivalents of norphenidine and 1 equivalent of borane-N,N-diethylaniline adduct, affording N-methoxyamine (S)-39 in 82% yield (1.6 catalyst turnover) and 92% enantio- metric excess (Scheme 9B). According to the authors, using borane-N,N-diethylaniline adduct enables turnover while preventing the formation of primary amine byproducts. This finding may inspire the development of more active variants.

6. Summary and Outlook

The catalytic reduction of oximes represents an attractive strategy for the efficient synthesis of valuable N-alkyl-N-hydroxylamine derivatives. However, this transformation remains underdeveloped compared to imine or enamine hydrogenations because of several additional challenges. For example, a fine balance in reactivity is needed to selectively reduce the C–N bond of oximes without breaking their sensitive N–O bond. The first competent system was developed nearly a century ago, combining Adam’s catalyst (PtO₂) with hydrogen gas as reductant. As well as the presence of stoichiometric quantities of hydrochloric acid proved key to activate the substrate by N-protonation, and prevent N–O bond over-reduction. Over the last decade, few different alternatives have been developed. These span from heterogeneous Ni/Co bimetallic systems to homogeneous iridium complexes or boron-based organocatalysts. Each of them present different strengths and weaknesses, providing many opportunities for improvement.

Probably the most general and efficient catalyst class are cyclometallated CpIr complexes. These can provide high enantioselectivity, and operate under mild reaction conditions in the presence of acid, allowing for the selective activation of the oxime moiety against a broad range of other functional groups. Nevertheless, the development of more sustainable and cost-effective catalysts is highly desirable, for instance, replacing precious metals by more earth-abundant ones (e.g. Co, Ni, Mn, Fe), as well as designing simpler ligands. Heterogeneous systems capable of maintaining similar activities upon recycling should be targeted. More efforts should be directed to the creation of chiral organocatalysts, for instance capitalizing on the FLP technology, but with increased activity and stability to the environment. Related to this, biocatalytic oxime to hydroxylamine mono-reductions are yet to be developed,[32] despite preliminary studies suggest their feasibility.[33]

From a practical perspective, the holy grail in asymmetric reductions would be overriding the E/Z-oxime geometry bias by means of catalyst control. So far only the above-described chiral iridium catalyst has been capable of reducing a limited set of E/Z-oximes in high yields and enantioselectivities through an acid-promoted dynamic isomerization/hydrogenation process. Alternative ways of inducing oxime isomerization involve heating or photo-irradiation. However little is known about the influence of these factors in asymmetric reductions. Meanwhile, developing new stereoselective oxime syntheses with extensive substrate scope is still of high interest. Whereas already a broad spectra of oximes have been reduced, examples containing ubiquitous functional groups such as primary amines, phosphines, aikyls, or alkynes have not been realized yet. O-acetyl oximes have not been yet catalytically reduced to the corresponding N-acetoxyamines, so far requiring the use of stoichiometric borohydride[21] or hydroxylane[20] reductants. Additionally, performing one-pot reductive hydroxyaminations would give access to N-alkylated products in one step from ketones and hydroxylamine precursors.[34] Likewise, electrophilic activation of the oximes by N-acylation (instead of N-protonation) may lead directly to biologically relevant hydroxamic acids upon reduction. We hope this minireview facilitates better understanding of catalytic oxime reductions, and inspires future advances in the field.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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