Reduction

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Catalytic Biomimetic Asymmetric Reduction of Alkenes and Imines Enabled by Chiral and Regenerable NAD(P)H Models

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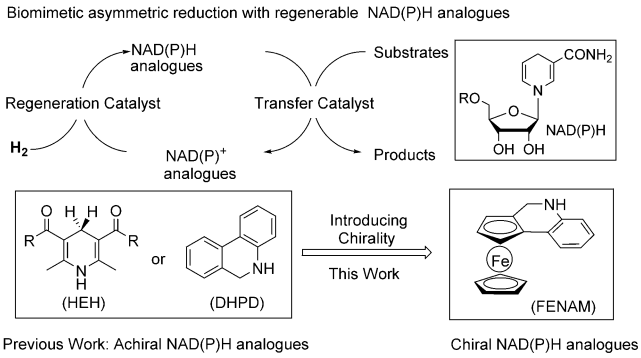
Dedicated to the 70th anniversary of the Dalian Institute of Chemical Physics, Chinese Academy of Sciences

Abstract: *The development of biomimetic chemistry based on the NAD(P)H with hydrogen gas as terminal reductant is a long-standing challenge. Through rational design of the chiral and regenerable NAD(P)H analogues based on planar-chiral ferrocene, a biomimetic asymmetric reduction has been realized using bench-stable Lewis acids as transfer catalysts. A broad set of alkenes and imines could be reduced with up to 98% yield and 98% ee, likely enabled by enzyme-like cooperative bifunctional activation. This reaction represents the first general biomimetic asymmetric reduction (BMAR) process enabled by chiral and regenerable NAD(P)H analogues. This concept demonstrates catalytic utility of a chiral coenzyme NAD(P)H in asymmetric catalysis.*

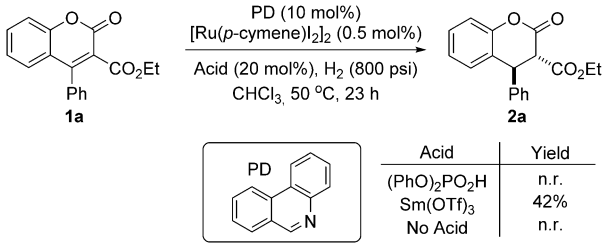
The development of biomimetic approaches plays an important role in agrochemicals, materials, and pharmaceuticals. In the cell, reduced nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) are recognized as a couple of crucial enzymes, and over 400 enzyme redox reactions depend on the interconversion of NAD(P)H and $NAD(P)^+$, reactions such as the citric acid cycle, glycolysis, and amino-acid decomposition.[1] Therefore, efficient methods to realize biomimetic asymmetric reductions (BMAR) have been studied intensively, and the design of NAD(P)H analogues, transfer catalysts, and regeneration catalysts is an important topic[2] (Scheme 1). As the simplest achiral NAD(P)H analogue, Hantzsch esters (HEH)[3] and benzothiazolines[4] have been widely and successfully applied in biomimetic asymmetric reduction of a series of unsaturated compounds in the presence of chiral organocatalysts[5] and metal catalysts.[6] However, these reactions required stoichiometric amounts of the NAD(P)H analogues and suffered from intractable limitations in regeneration.[7] Recently,



Scheme 1. Biomimetic asymmetric reduction (BMAR) based on the coenzyme NAD(P)H.

a catalytic amount of achiral dihydrophenanthridine (DHPD) was employed to realize biomimetic asymmetric hydrogenation of imines and heteroaromatics with chiral phosphoric acid, and is easy to regenerate under hydrogen gas using either a homogeneous ruthenium[8] or iron catalyst.[9] Despite this remarkable progress, the development of a chiral and regenerable NAD(P)H analogues for BMAR is still a long-standing challenge in biomimetic asymmetric catalysis.

For previous work on biomimetic asymmetric reduction based on achiral NAD(P)H analogues, chiral Brønsted acids are used as dominant transfer catalysts to control the enantioselectivity. Owing to the inherent activation pattern (protonation or hydrogen bonding) of chiral Brønsted acids, its substrate scope is mostly confined to the asymmetric reduction of C=N bonds. Obviously, increase in the diversity of the activation pattern will further expand the generality of biomimetic asymmetric reduction. For example, tetrasubstituted alkenes are challenging substrates in asymmetric hydrogenation, especially in the biomimetic asymmetric reductions (Scheme 2).[10] Owing to the inherent activation pattern of Brønsted acids, not surprisingly, no desired



Scheme 2. Initial results about the biomimetic reduction of tetrasubstituted alkenes. n.r. = no reaction.

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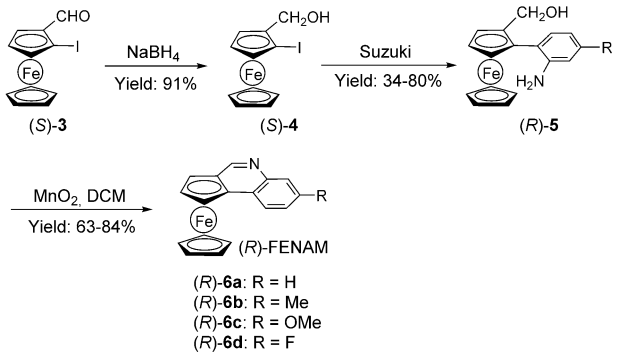
biomimetic reduction was observed using phosphoric acid as a transfer catalyst in the presence of phenanthridine (PD). Gratifyingly, the switch of transfer catalyst to the Lewis acid $Sm(OTf)_3$ delivered the desired product **2a** in 42% yield. Without the transfer catalyst, no reaction occurred. To further increase the diversity of activation pattern, we envisioned that the development of chiral and regenerable NAD(P)H model might provide a general biomimetic asymmetric reduction with other transfer catalysts (Scheme 1). Herein, we report a biomimetic asymmetric reduction based on ferrocene-derived chiral and regenerable NAD(P)H models with readily available Lewis acids as achiral transfer catalysts, alongside wide substrate scope, and excellent activities and enantioselectivities.

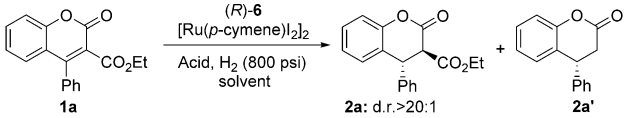
Considering that dihydropyridine is the key structural moiety for regeneration of NAD(P)H analogues under hydrogen gas with ideal atom economy, we sought to explore a chiral NAD(P)H analogue containing dihydropyridine moiety. In addition, the chiral and regenerable NAD(P)H analogue should be conveniently prepared from commercially available materials and must be capable of being finely tuned. Inspired by the application of planar chirality in asymmetric synthesis,[11] we designed a chiral NAD(P)H analogue (**6**) incorporating planar chirality and the phenanthridine structure (Scheme 3). Through three simple operations (reduction, Suzuki coupling, and oxidative cyclization), a series of NAD(P)H analogues, FENAM (*R*)-**6a–d,** was easily synthesized from the readily available chiral (*S*)-2-iodoferrocenecarboxaldehyde (**3**; Scheme 3).[12]



Scheme 3. Synthesis of the NAD(P)H analogues FENAM (*R*)-**6** with planar chirality.

To verify the efficiency of the planar-chiral NAD(P)H analogues, the tetrasubstituted alkene **1a** was chosen as model substrate for biomimetic asymmetric reduction (Table 1). Ruthenium(II) and acid were employed as the regeneration and transfer catalyst, respectively. As with the achiral NAD(P)H model phenanthridine (Scheme 2), the Lewis acid displayed higher reactivity over Brønsted acid and gave the desired product **2a** in high enantioselectivity (87%, entries 1–3). A small amount of the side product **2a′** was detected and results from decarboxylation. According to investigations on solvent effects, better reactivity but lower selectivity was observed in THF (entries 2, 4–6). The evaluation of the transfer catalyst suggests $Yb(OTf)_3$ to be optimal

Table 1: Optimization of reaction conditions.[a]



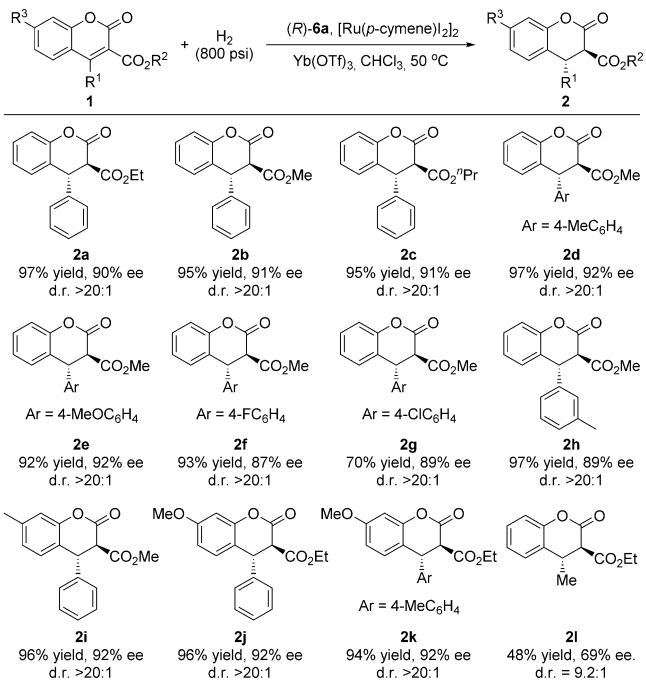
Entry	Acid	Slovent	Model	Conv. [%][b]	**2a**/**2a′**[b]	*ee* [%][c]
1	$(PhO)_2PO_2H$	$CHCl_3$	(*R*)-**6a**	<5	–	–
2	$Sm(OTf)_3$	$CHCl_3$	(*R*)-**6a**	11	10:1	87
3	–	$CHCl_3$	(*R*)-**6a**	<5	–	–
4	$Sm(OTf)_3$	CH_2Cl_2	(*R*)-**6a**	11	4.5:1	85
5	$Sm(OTf)_3$	toluene	(*R*)-**6a**	31	5.2:1	86
6	$Sm(OTf)_3$	THF	(*R*)-**6a**	>95	4.5:1	83
7	$Cu(OTf)_2$	$CHCl_3$	(*R*)-**6a**	<5	–	–
8	$La(OTf)_3$	$CHCl_3$	(*R*)-**6a**	41	>20:1	92
9	$Sc(OTf)_3$	$CHCl_3$	(*R*)-**6a**	<5	–	–
10	$Yb(OTf)_3$	$CHCl_3$	(*R*)-**6a**	88	>20:1	90
11	$Yb(OTf)_3$	$CHCl_3$	(*R*)-**6b**	80	>20:1	89
12	$Yb(OTf)_3$	$CHCl_3$	(*R*)-**6c**	63	>20:1	87
13	$Yb(OTf)_3$	$CHCl_3$	(*R*)-**6d**	17	>20:1	89
14	$Yb(OTf)_3$	$CHCl_3$	(*R*)-**6a**	97[d]	>20:1	90

[a] Reactions were carried out with **1a** (0.10 mmol), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol%), **6** (10 mol%), acid (20 mol%), and solvent (2 mL) under H_2 (800 psi) at 50°C for 23 h. [b] Conversion and selectivity were measured by analysis of the ^1H NMR spectra. [c] Determined by chiral-phase HPLC. [d] Yield of isolated product for the reaction run on a 0.15 mmol scale for 80 h.

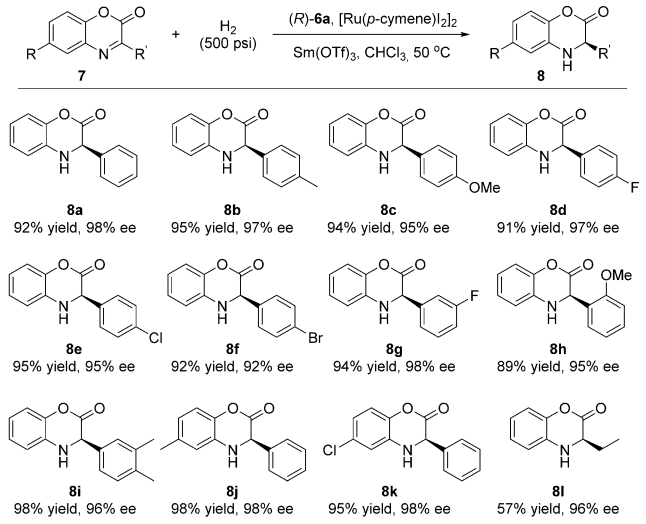
with regard to reactivity and enantioselectivity (entries 7–10). No improvement of enantioselectivity was observed using (*R*)-**6b–d**, having different steric and electronic properties (entries 11–13). Excellent yield of isolated **2a** was achieved by prolonging the reaction time (97% yield; entry 14). Thus, the optimal reaction conditions were identified as: alkenes **1** (1.0 equiv), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol%), FENAM (*R*)-**6a** (10 mol%), and achiral transfer catalyst Lewis acid $Yb(OTf)_3$ (20 mol%) under H_2 (800 psi) in $CHCl_3$ at 50°C.

With optimal reaction conditions in hand, the substrate scope of biomimetic asymmetric reduction of the tetrasubstituted alkenes **1** using a catalytic amount of (*R*)-**6a** was explored (Scheme 4). It is noteworthy that the thermodynamically preferred product, 3,4-*trans*-disubstituted dihydrocoumarins, could be obtained for the aryl-substituted substrates **1a–k** in a highly diastereoselective manner (d.r. >20:1) with high enantioselectivities and activities (**2a–k**).[13] The absolute configuration of **2e** was assigned as (3*R*,4*R*) by X-ray diffraction analysis (for details, see the Supporting Information). As for the methyl-substituted substrate, moderate diastereo- and enantioselectivity could be obtained (**2l**).

Because of the Lewis acid's ability to activate imines, this strategy might be suitable for biomimetic asymmetric reduction of C=N bonds. Substituted benzoxazinones (**7**) were chosen as model substrates[14] to validate our hypothesis (Scheme 5). Through optimization (see the Supporting Information) of the reaction conditions, $Sm(OTf)_3$ emerged as the best transfer catalyst in terms of reactivity and enantioselectivity. Generally, excellent yields (89–98%) and enantioselectivities (92–98%) were obtained in this biomimetic asymmetric hydrogenation system regardless of the electronic



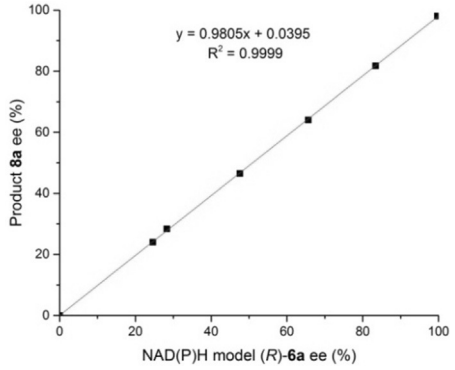
Scheme 4. Substrate scope for Lewis acid promoted BMAR of tetra-substituted alkenes.



Scheme 5. Substrate scope for Lewis acid promoted BMAR of benzoxazinones.

properties of the substituent on **7** (**7a**–**k**). As for the alkyl-substituted substrate, moderate yield and high enantioselectivity (96%) could be obtained (**8l**).

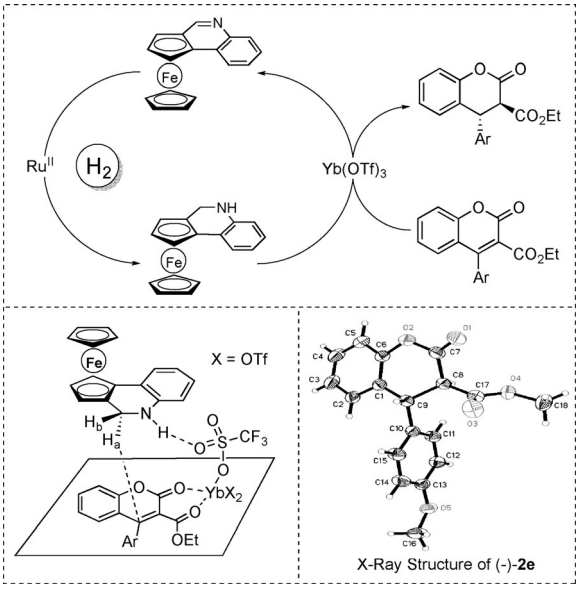
Configuration stability of (*R*)-**6a** was obtained by heating it in THF (at 60°C), $ClCH_2CH_2Cl$ (at 80°C), and toluene (at 100°C) for 4 hours, respectively, and the HPLC analysis showed the *ee* values were retained.[15] Thus, the planar-chiral NAD(P)H analogue could have potential applications under harsh reaction conditions. Furthermore, the enantioselectivity of the product was proportional to the enantiomeric excess of (*R*)-**6a** (Scheme 6). The observed linear dependence indicates



Scheme 6. Dependence of enantioselectivity of the product **8a** on the *ee* value of (*R*)-**6a**.

that only a monomeric chiral catalyst, rather than an aggregate of two or more catalysts, is catalyzing the reaction.

Based on the experimental results and the putative mechanism of NAD(P)H-analogue-promoted biomimetic asymmetric reduction,[8a] a plausible mechanism for our biomimetic asymmetric reduction of C=N and C=C unsaturated bonds is illustrated (Scheme 7). Just like the NAD(P)H-



Scheme 7. Proposed mechanism and transition state. For the X-ray structure the thermal ellipsoids are shown at 50% probability.

mediated reduction, this catalytic biomimetic asymmetric reduction comprises two cascade redox cycles promoted by two achiral catalysts. For the Lewis acid catalyzed reaction, coordination for activation plays a major role in the biomimetic asymmetric reduction process.

In summary, through rational design of chiral regenerable NAD(P)H analogues based on planar-chiral ferrocene, we have successfully developed a new biomimetic asymmetric reduction with hydrogen gas as the terminal reductant. Using either the readily available and bench-stable achiral Lewis acid ytterbium or samarium triflate as the transfer catalyst, the substrate scope was significantly extended. A broad set of

electron-deficient tetrasubstituted alkenes and imines could be reduced with up to 98% yield and 98% *ee*. It is worth mentioning that this is the first successful chiral and regenerable NAD(P)H analogue enabling a general biomimetic asymmetric reduction. From the point of view of organic synthesis, the above biomimetic reactions provide direct access to a variety of chiral amines and dihydrocoumarins which are prevalent in natural products, synthetic intermediates, and pharmaceuticals. We anticipate that this concept will open a new horizon for the development of asymmetric biomimetic chemistry of coenzyme NAD(P)H in other fields.

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Conflict of interest

The authors declare no conflict of interest.

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[1] a) J. Gébicki, A. Marcinek, J. Zielonka, *Acc. Chem. Res.* **2004**, *37*, 379; b) R. H. Houtkooper, C. Cantó, R. J. Wanders, J. Auwerx, *Endocr. Rev.* **2010**, *31*, 194; c) H. Wu, C. Tian, X. Song, C. Liu, D. Yang, Z. Jiang, *Green Chem.* **2013**, *15*, 1773; d) H. Lin, *Org. Biomol. Chem.* **2007**, *5*, 2541.

[2] For the selected reviews and papers on chiral NAD(P)H models, see: a) Y. Ohnishi, M. Kagami, A. Ohno, *J. Am. Chem. Soc.* **1975**, *97*, 4766; b) N. Kanomata, T. Nakata, *J. Am. Chem. Soc.* **2000**, *122*, 4563; c) N.-X. Wang, J. Zhao, *Synlett* **2007**, *18*, 2785; d) C.-B. Bai, N.-X. Wang, Y. Xing, X.-W. Lan, *Synlett* **2017**, *28*, 402.

[3] For selected reviews on Hantzsch-ester-mediated biomimetic asymmetric reduction, see: a) S. G. Ouellet, A. M. Walji, D. W. C. Macmillan, *Acc. Chem. Res.* **2007**, *40*, 1327; b) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084; c) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498; d) A. M. F. Phillips, A. J. L. Pombeiro, *Org. Biomol. Chem.* **2017**, *15*, 2307.

[4] For selected reviews and papers on benzothiazoline-mediated biomimetic asymmetric reduction, see: a) C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388; b) C. Zhu, T. Akiyama, *Org. Lett.* **2009**, *11*, 4180; c) C. Zhu, T. Akiyama, *Adv. Synth. Catal.* **2010**, *352*, 1846; d) A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180; *Angew. Chem.* **2011**, *123*, 8330; e) T. Sakamoto, K. Mori, T. Akiyama, *Org. Lett.* **2012**, *14*, 3312.

[5] For selected papers on organocatalytic asymmetric reactions, see: a) S. Singh, U. K. Batra, *Indian J. Chem. Sect. B* **1989**, *28*, 1; b) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2004**, *44*, 108; *Angew. Chem.* **2004**, *117*, 110; c) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *Angew. Chem. Int. Ed.* **2004**, *43*, 6660; *Angew. Chem.* **2004**, *116*, 6829; d) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; e) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32; f) S. Mayer, B. List, *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; *Angew. Chem.* **2006**, *118*, 4299; g) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368; h) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; *Angew. Chem.* **2006**, *118*, 3765; i) N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976; j) Q.-S. Guo, D.-M. Du, J.-X. Xu, *Angew. Chem. Int. Ed.* **2008**, *47*, 759; *Angew. Chem.* **2008**, *120*, 771; k) N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 13862; l) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; m) L. Ren, T. Lei, J.-X. Ye, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 771; *Angew. Chem.* **2012**, *124*, 795; n) Q. Yin, S.-G. Wang, S.-L. You, *Org. Lett.* **2013**, *15*, 2688; o) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383; p) Z.-L. Xia, C. Zheng, S.-G. Wang, S.-L. You, *Angew. Chem. Int. Ed.* **2018**, *57*, 2653; *Angew. Chem.* **2018**, *130*, 2683.

[6] For selected papers on metal-catalyzed asymmetric reactions, see: a) S. Zehani, G. Gelbard, *J. Chem. Soc. Chem. Commun.* **1985**, 1162; b) J. W. Yang, B. List, *Org. Lett.* **2006**, *8*, 5653; c) D.-W. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron: Asymmetry* **2007**, *18*, 1103; d) M. Terada, F. Li, Y. Toda, *Angew. Chem. Int. Ed.* **2014**, *53*, 235; *Angew. Chem.* **2014**, *126*, 239; e) Y.-L. Du, Y. Hu, Y.-F. Zhu, X.-F. Tu, Z.-Y. Han, L.-Z. Gong, *J. Org. Chem.* **2015**, *80*, 4754; f) X.-F. Tu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 11346; *Angew. Chem.* **2012**, *124*, 11508.

[7] For selected papers on regeneration of NAD(P)H analogues, see: a) H. C. Lo, R. H. Fish, *Angew. Chem. Int. Ed.* **2002**, *41*, 478; *Angew. Chem.* **2002**, *114*, 496; b) H.-J. Xu, Y.-C. Liu, Y. Fu, Y.-D. Wu, *Org. Lett.* **2006**, *8*, 3449; c) B. Procuranti, S. J. Connon, *Chem. Commun.* **2007**, 1421; d) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 16432; e) L. Zhao, J. Wei, J. Lu, C. He, C. Duan, *Angew. Chem. Int. Ed.* **2017**, *56*, 8692; *Angew. Chem.* **2017**, *129*, 8818.

[8] a) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 2442; b) Z.-P. Chen, M.-W. Chen, R.-N. Guo, Y.-G. Zhou, *Org. Lett.* **2014**, *16*, 1406; c) M.-W. Chen, B. Wu, Z.-P. Chen, L. Shi, Y.-G. Zhou, *Org. Lett.* **2016**, *18*, 4650.

[9] a) L.-Q. Lu, Y. Li, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 8382; *Angew. Chem.* **2013**, *125*, 8540; b) L.-Q. Lu, Y. Li, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 2763.

[10] For selected reviews and papers on asymmetric hydrogenation of alkenes, see: a) S. Kraft, K. Ryan, R. B. Kargbo, *J. Am. Chem. Soc.* **2017**, *139*, 11630; b) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272; c) M. V. Troutman, D. H. Appella, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4916; d) M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem. Int. Ed.* **2007**, *46*, 8274; *Angew. Chem.* **2007**, *119*, 8422; e) Y.-T. Liu, J.-Q. Chen, L.-P. Li, X.-Y. Shao, J.-H. Xie, Q.-L. Zhou, *Org. Lett.* **2017**, *19*, 3231; f) Y.-T. Liu, L.-P. Li, J.-H. Xie, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 12708; *Angew. Chem.* **2017**, *129*, 12882; g) Q. Wang, W. Huang, H. Yuan, Q. Cai, L. Chen, H. Lv, X. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 16120.

[11] a) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, X.-L. Hou, *Acc. Chem. Res.* **2003**, *36*, 659; b) R. Gómez Arrayás, J. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 7674; *Angew. Chem.* **2006**, *118*, 7836.

[12] O. Riant, O. Samuel, H. B. Kagan, *J. Am. Chem. Soc.* **1993**, *115*, 5835.

[13] CCDC 1831948 contain supplementary crystallographic data of (−)-**2e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] a) F. A. Macías, D. Marín, A. Oliveros-Bastidas, J. M. G. Molinillo, *Nat. Prod. Rep.* **2009**, *26*, 478; b) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 6751; *Angew. Chem.* **2006**, *118*, 6903; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; d) Z.-Y. Xue, Y. Jiang, X.-Z. Peng, W.-C. Yuan, X.-M. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 2132.

[15] The stability experiments and the linear effect experiments are described in detail in the Supporting Information.

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