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Base-free Asymmetric Transfer Hydrogenation of 1,2-Di- and Monoketones Catalyzed by a Chiral Iron(II) Hydride

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§SCS-DSM Award for best poster presentation in Inorganic & Coordination Chemistry

Abstract: The chiral iron(II) hydride complex [FeH(CNCEt$_3$)(**1a**)](BF$_4$) (**3**, **1a** is a chiral macrocycle with an (NH)$_2$ P$_2$ donor set) catalyzes the base-free transfer hydrogenation (ATH) of prochiral ketones and the hemireduction of benzils to the corresponding benzoins using ^{i}PrOH as hydrogen donor. Ketones give the same excellent enantioselectivity (up to 99% ee) as the parent catalyst [Fe(CNCEt$_3$)$_2$(**1a**)](BF$_4$)$_2$ (**2**), which is only active upon treatment with NaO^{t}Bu. Benzoins, whose labile stereocenter is known to undergo racemization under basic conditions, are formed in up to 83% isolated yield with enantioselectivity as high as 95%.

Keywords: Asymmetric transfer hydrogenation · Base-free · Benzoin · Hydride complexes · Iron catalysis

Lorena De Luca was born in Conegliano (Italy) in December 1991. She studied industrial chemistry with a focus on homogeneous catalysis applied to organic synthesis at the Ca'Foscari University in Venice, where she received her MA in July 2015 in the field of new chiral aminobisphosphonates as potential anti-resorption bone drugs under the supervision of Prof. Giorgio Strukul. In August 2015, she joined Prof. Antonio Mezzetti's group at ETH Zürich to pursue her PhD in the field of chiral hydride complexes of iron(II) as catalysts for the base-free asymmetric hydrogenation of polar double bonds.

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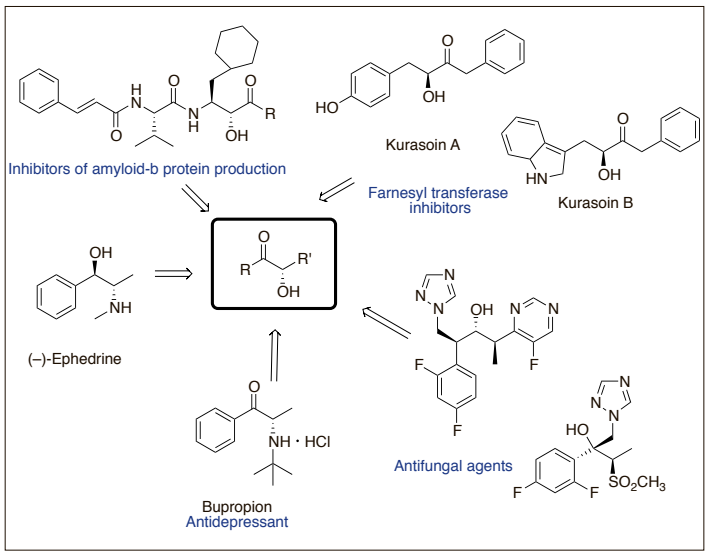
Introduction

Enantiopure alcohols represent important building blocks for a broad variety of molecules[1,2] that find application in pharmaceutical, agrochemical, and fragrance chemistry.[3] Thus, the asymmetric reduction of cheap and readily available prochiral ketones to the corresponding enantiopure alcohols has been largely exploited in synthetic organic chemistry. The approaches used for the enantioselective reduction of C=O double bonds are direct hydrogenation (AH), transfer hydrogenation (ATH), and hydrosilylation (AHS), which differ according to the hydrogen donor employed. AH uses dihydrogen as reducing agent, is perfectly atom economic, and is hence the method of choice in industry[4] despite the use of molecular hydrogen. As for AHS, silanes are attractive reductants since they are easy to handle, commercially available, stable, and only mildly hydridic.[5] Moreover, AHS operates under mild conditions, which is ideal for late stage functionalization of complex molecules.[1] Drawbacks are the hydrolysis of the silyl ether and the silicon waste. Asymmetric transfer hydrogenation (ATH) with ^{i}PrOH as hydrogen donor is operationally simple and thermoneutral, but is reversible and can be hence applied only when the equilibrium favors the optically active alcohol. The use of ^{i}PrOH as solvent and high substrate dilution maximizes the reaction yield. However, as the enantiomeric excess (ee) erodes as equilibrium is approached,[6] the reaction must be monitored closely. Alternatively, formic acid can be used as H_2 donor, as CO_2 evolution is irreversible, but the reaction is quite exothermic, and formic acid can inhibit the catalyst.

Based on the above considerations, ATH with ^{i}PrOH is the method of choice in academia.[7] However, a severe limitation is that most of the precatalysts developed for this transformation require base activation, which excludes base-sensitive substrates from the substrate scope. An eminent example are benzoins, whose labile stereocenter readily racemizes under basic conditions, making the asymmetric hemihydrogenation of the corresponding 1,2-diketones a formidable challenge. The resulting α-hydroxyketones (acyloins) contain a highly directing hydroxyl group and an easily functionalizable prostereogenic carbonyl moiety. Therefore, enantiomerically pure acyloins have found application as chiral templates in asymmetric reactions and as valuable building blocks in the synthesis of natural products and bioactive molecules (Scheme 1).[8]

Enantiopure benzoins have been prepared by Friedel-Craft,[9] cross-benzoin condensation,[10] oxidative kinetic resolution of diols,[11] α-hydroxylation of ketones,[12] alkene ketohydroxylation, oxidation of enolates or enol ethers,[13] and AHS with chiral frustrated Lewis pairs (Scheme 2).[14] The enantioselective hemireduction of benzils is scarcely documented with transition metal catalysts[15,16] and has been largely entrusted to enzymatic transformations.[8] Various microorganisms catalyze

Scheme 1. Bioactive compounds containing the α-hydroxyketone scaffold.



the asymmetric reduction of benzils to enantiomerically enriched benzoins, with the usual restriction of biocatalytic methods that only one single enantiomer can be obtained. Therefore, a reliable, broadly applicable, purely chemical method for benzil hemireduction would mark a major milestone.

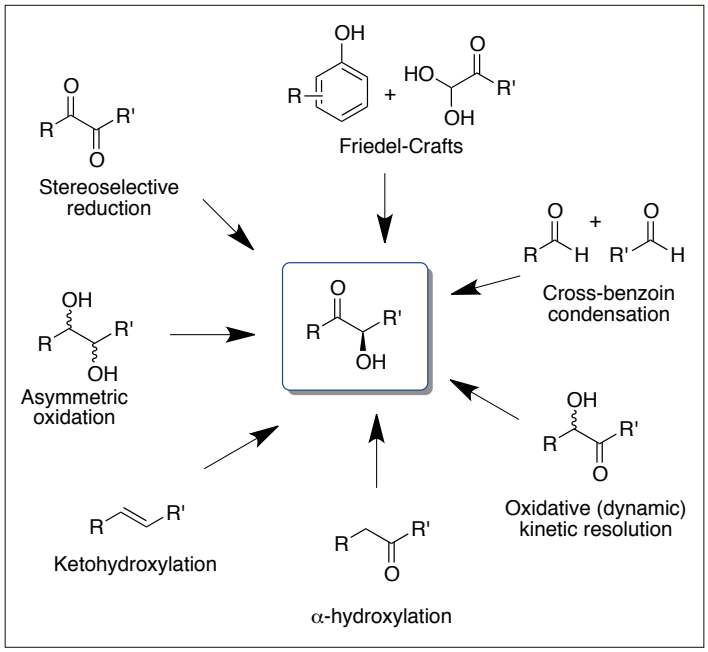
In a seminal work on benzil hemihydrogenation, Ohgo reported the asymmetric direct hydrogenation of benzil to (*S*)-benzoin in high yield (98%) and 62% ee under mild conditions. The catalytic system employs achiral bis(dimethylglyoximato)cobalt(II) and a cinchona alkaloid (such as quinine or quinidine) as chiral auxiliary (Scheme 3a).[15] More recently, Ikariya reported a well-defined *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine ruthenium(II) complex as catalyst for the ATH of 1,2-diketones in quantitative yield and excellent enantioselectivity (up to 99% ee, Scheme 3b). Notably, the catalyst reduces 1,2-arylalkyl diketones at the less hindered carbonyl group. However, the reaction conditions have to be strictly controlled in order to avoid the formation of the diol, and symmetric benzils have not been studied (Scheme 3b).[16]

Our group has recently prepared chiral 14- (**1a**) or 15-membered (**1b**) macrocyclic ligands with a N_2P_2 donor set (Scheme 4) and has studied their application in the iron-catalyzed ATH of ketones.[17]

In combination with bulky isonitrile ligands, such N_2P_2 macrocycles stabilize iron(II) in the low spin state and give air- and moisture-stable precatalysts that display excellent facial recognition – and hence enantioselectivity – in the ATH of prochiral aromatic ketones.[17] Upon base activation, complexes $[Fe(CNCEt_3)_2(\mathbf{1})](BF_4)_2$ reduce alkylaryl ketones with high activity (TOF up to 6650 h^{-1}) and excellent enantioselectivity (up to 99.6% ee).[17a,d] Notably, these macrocyclic complexes are the first example of iron(II) catalysts that give high enantioselectivity with a broad substrate scope.[17d]

In view of the great potential of these ligands, we set out to develop an ATH catalyst that does not require basic activation and might be suitable for base-sensitive substrates, with particular attention to the problem of the enantioselective hemireduction of benzils to benzoins. We reasoned that the base is most probably required to convert precatalyst $[Fe(CNCEt_3)_2(\mathbf{1a})](BF_4)_2$ (**2**) to a hydride species containing the H–N–Fe–H motif that is held responsible for hydrogen transfer to the carbonyl group of ketones in the putative ATH catalytic cycle shown in Scheme 5.[18,19] Therefore, we prepared the hydride complex $[FeH(CNCEt_3)(\mathbf{1a})](BF_4)$ (**3**) as the ideal drop-in catalyst for the base-free ATH of polar double bonds.[20]

Scheme 2. Synthesis of α-hydroxyketones.



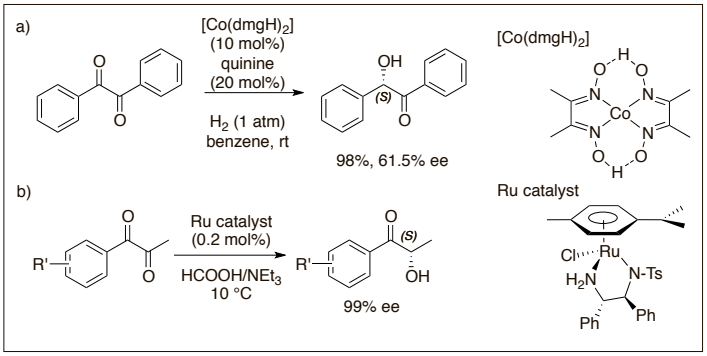
Results and Discussion

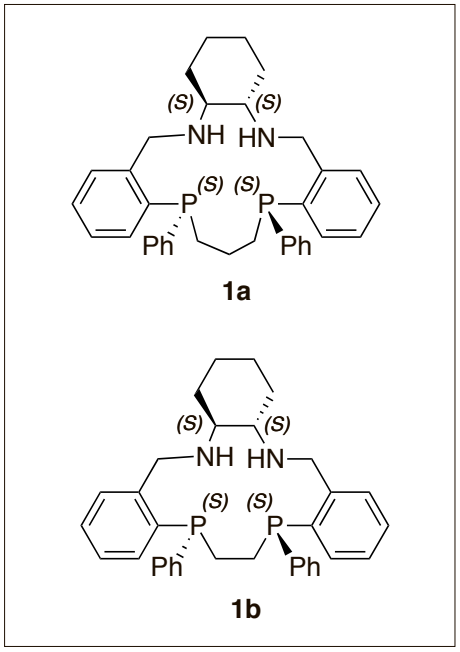
Synthesis of Hydride 3

The hydride complex **3** was prepared stepwise from the previously reported[17a] bis(acetonitrile) complex $[Fe(NCCH_3)_2(\mathbf{1a})](BF_4)_2$ (**4**) (Scheme 6).[20] In the first step, complex **4** was treated with isonitrile $CNCEt_3$ (1 equiv) and an excess of KBr in dichloromethane at 50 °C for 16 h. The bromoisonitrile complex $[FeBr(CNCEt_3)(\mathbf{1a})]BF_4$ (**5**) was isolated in good yield (80%) as an orange solid after filtering off the salts and precipitation with hexane. The ^{31}P NMR spectrum of **5** showed a tight AX system at δ 54.3 and 49.0 ($^2J_{P,P'}$= 59.5 Hz in THF-d_8) for the two inequivalent P atoms, suggesting that both the phosphines are in *trans* position to the amines ($^2J_{P,P'}$= 59.5 Hz in THF-d_8).[20]

The bromoisonitrile complex **5** reacts with $NaBHEt_3$ (1 equiv) in THF solution to give $[FeH(CNCEt_3)(\mathbf{1a})](BF_4)$ (**3**). Hydride **3** decomposes upon isolation, but is stable in THF solution under argon and was fully characterized by NMR spectroscopy. In the ^1H NMR spectrum, the hydride ligand appears as a doublet of doublets at δ –5.45 with two very similar $^2J_{P,H}$ coupling constants of 64.6 and 57.5 Hz. The large difference in the chemical shift of the phosphines (δ 65.5 and 37.7) indicates that the macrocyclic ligand is bent in the *cis*-β configuration. In a preliminary communication, we have proposed that the hydride ligand is *cis* to both phosphines on the basis of the significantly different $^2J_{P,C}$ values (27.0 and 14.6 Hz) in the labeled ^{13}C-labeled derivative $[FeH(^{13}CNCEt_3)$

Scheme 3. Hemireduction of α-diketones.





Scheme 4. Chiral macrocyclic ligands with a $P_2(NH)_2$ donor set.

(**1a**)](BF$_4$).[20] However, ongoing spectroscopic 2D NMR studies suggest that the hydride is located in *trans* position to the phosphine resonating at high field (Scheme 6).[21]

Hydride 3 in the ATH of Aromatic Ketones

The hydride complex **3** was tested in the base-free ATH of selected ketones with ^{i}PrOH as hydrogen donor under the same conditions used with the bis(isonitrile) complex **2**, with the sole remarkable difference that no base was added (Scheme 7).[20]

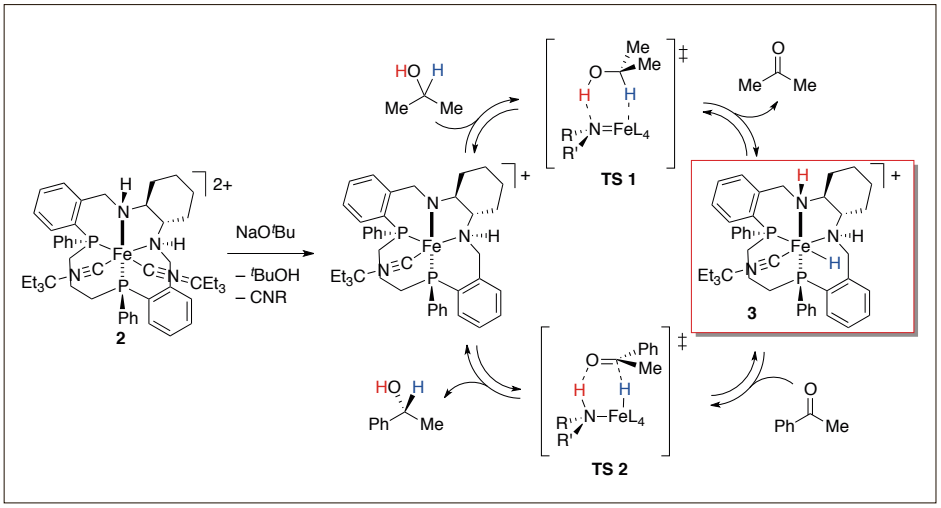
As compared to the system formed by **2** and base, catalyst **3** is on average less active, but maintains the same excellent enantioselectivity (up to 99%). Interestingly, when NaO^{t}Bu (10 equiv) is added, hydride **3** catalyzes the ATH of acetophenone with the same activity observed for **2**/NaO^{t}Bu, which suggests that the base is not only needed for the formation of the active species, but may also play a role in catalyst turnover.

Hydride 3 in the ATH of 1,2-Diketones

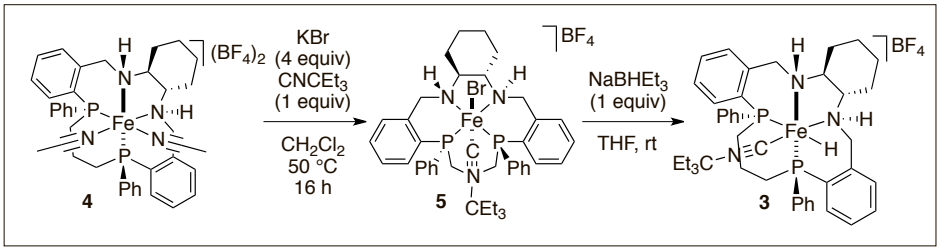
With a catalyst for the base-free ATH of standard ketones in hand, we explored its application in the base-free hemireduction of benzil **8a** to benzoin **9a**. Preliminary experiments showed that the reaction proceeded sluggishly under the standard conditions used for the reduction of monoketones. However, upon increasing the catalyst loading to 1 mol% and lowering the substrate concentration to 0.05 M, (*S*)-benzoin (**9a**) was obtained in 75% yield and 95% ee after 75 min of reaction time (Scheme 8a). Recrystallization from ^{i}PrOH gave (*S*)-**9a** as single enantiomer (>99.95% ee) in 61% overall yield.[20] Under the conditions in Scheme 8a, only traces of *meso*-hydrobenzoin (*meso*-**10a**) were formed. Longer reaction times gave substantial amounts of *meso*-**10a** and an increased enantiomeric excess for (*S*)-**9a**, which indicates that benzoin **9a** undergoes kinetic resolution (that is, (*R*)-**9a**, the minor enantiomer, is hydrogenated to *meso*-**10** faster than (*S*)-**9a**). This implies that the second reduction operates under substrate control, as often observed in the reduction of α-hydroxyketones.[22]

Under analogous conditions (Scheme 8b), the catalytic system formed by the bis(isonitrile) complex **2** after activation with NaO^{t}Bu (10 equiv *vs.* 2) reduced **8a** to racemic benzoin *rac*-**9a** in 22% yield and a significant amount of *meso*-**10a** (54%) after 15 min of reaction time. After 30 min, only *meso*-hydrobenzoin (*meso*-**10a**) was detected.[20] Overall, these results suggest that, in the presence of base, benzoin **9a** rapidly racemizes and that (*R*)-**9a** is then rapidly reduced to *meso*-**10a** (Scheme 9). The latter reaction is highly favored because the catalyst preference for the formation of the *S* enantiomer reinforces the substrate control that favors the *meso* product. When the reaction is carried out under base-free conditions, the reduction of the major product (*S*)-**9a** to *meso*-**10a** is slow as it goes against the catalyst native sense of induction of forming an *S* stereocenter, which allows the reaction to stop at the benzoin intermediate. At the same time, the fast reduction of the minor product (*R*)-**9a** to *meso*-**10a** leads to the observed kinetic resolution.

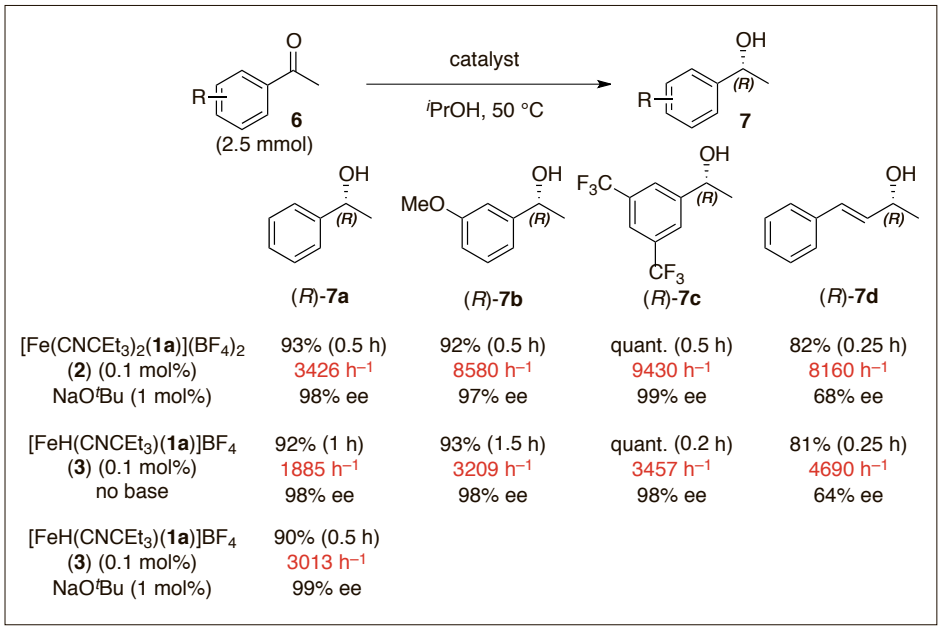
The excellent and unprecedented result achieved in the hemireduction of unsubstituted benzil **8a** prompted us to enlarge the



Scheme 5. Speculative mechanism for the ATH of ketones with catalyst **2**.



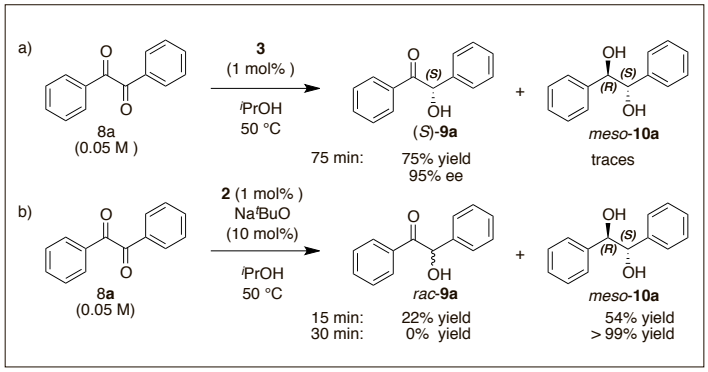
Scheme 6. Synthesis of hydride complex **3**.



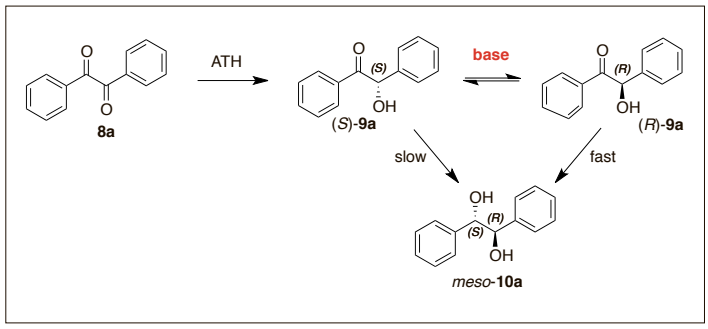
[Fe(CNCEt$_3$)$_2$(**1a**)](BF$_4$)$_2$ (**2**) (0.1 mol%) NaO^{t}Bu (1 mol%)	93% (0.5 h) 3426 h^{-1} 98% ee	92% (0.5 h) 8580 h^{-1} 97% ee	quant. (0.5 h) 9430 h^{-1} 99% ee	82% (0.25 h) 8160 h^{-1} 68% ee
[FeH(CNCEt$_3$)(**1a**)]BF$_4$ (**3**) (0.1 mol%) no base	92% (1 h) 1885 h^{-1} 98% ee	93% (1.5 h) 3209 h^{-1} 98% ee	quant. (0.2 h) 3457 h^{-1} 98% ee	81% (0.25 h) 4690 h^{-1} 64% ee
[FeH(CNCEt$_3$)(**1a**)]BF$_4$ (**3**) (0.1 mol%) NaO^{t}Bu (1 mol%)	90% (0.5 h) 3013 h^{-1} 99% ee			

Scheme 7. Comparison of **2** and **3** under basic and base-free conditions (GC yields, TOF (in red) calculated after 15 min).

Scheme 8. Catalytic performance of **3** (a) and **2** (b) in the hemireduction of benzil **8a**.



Scheme 9. Base effect on the reaction and stereochemical considerations



scope and explore the functional group tolerance of catalyst **3** under optimized reaction conditions (Scheme 10).

Para-substituted benzils are reduced in good yield and excellent enantioselectivity regardless of the electronic properties of the substituents. Thus, (*S*)-2-hydroxy-1,2-bis(4-methoxyphenyl)ethan-1-one (*S*)-**9b** was obtained with 65% overall yield and 93% ee (after recrystallization from ^{i}PrOH). In contrast, *meta*-substituted 1,2-diketones are sensitive to the electronic nature of the substituents. Electron-rich 1,2-bis(3-methoxyphenyl)ethane-1,2-dione (**8c**) was hemihydrogenated to the corresponding benzoin (*S*)-**9c** in good yield (67%) and high enantioselectivity (87%) after 2 h of reaction time. The reduction of 3-fluorobenzil **8d** was faster, yielding 58% of the monoreduced product (*S*)-**9d** after 60 min, but gave lower enantioselectivity (49% ee). The *ortho*-substituted 1,2-bis(2-fluorophenyl)ethane-1,2-dione **8e** was reduced in lower yield (39%) and moderate enantioselectivity (62% ee).

Conclusions

In summary, the chiral iron(II) hydride [FeH(CNCEt$_3$)(**1a**)](BF$_4$) (**3**) is the first base-free iron(II) catalyst for the ATH of ketones, and in particular for base-sensitive substrates. Catalyst **3** displays the same enantioselectivity and, when base is added, the same activity of the benchmark bis(isonitrile) complex [Fe(CNCEt$_3$)$_2$(**1a**)](BF$_4$)$_2$ (**2**) that operates under basic conditions. We have exploited the base-free nature of catalyst **3** for the hemireduction of benzils, which gives highly enantiomerically enriched α-hydroxyketones that would rapidly racemize in basic media. Thus, catalyst **3** is the first highly enantioselective catalyst for the reduction of symmetrically substituted, diaromatic α-diketones and represents a viable, broadly applicable, and purely chemical method for the highly enantioselective synthesis of acyloins. Therefore, **3** nicely complements Ikariya's catalyst for the hemireduction of alkylaryl α-diketones, which exploits the preferential reduction of the less hindered position.[16] Our next goals are to improve the catalyst activity and expand the substrate scope. To this end, we are carrying out extensive NMR spectroscopic studies to better understand the nature of the active species and to disclose the role of the base.

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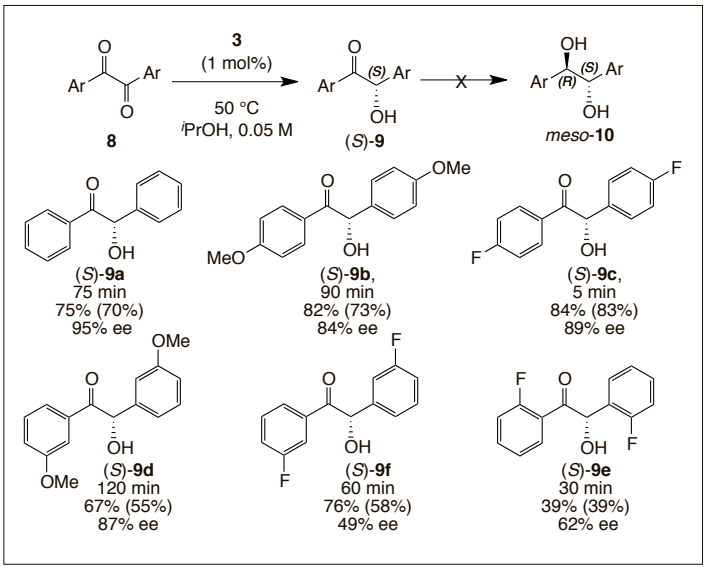
[1] 'Comprehensive Asymmetric Catalysis', Vol. I, Eds. E. N. Jacobsen, A. Pfaltz, H. Imamoto, Springer, Berlin, **1999**, chapter 6.
[2] J. G. de Vries, C. J. Elsevier, in 'The Handbook of Homogeneous Hydrogenation', Wiley-VCH, Weinheim, **2007**.
[3] H. U. Blaser, B. Pugin, F. Spindler, *Top. Organomet. Chem.* **2012**, *42*, 65.
[4] H. U. Blaser, F. Spindler, M. Studer, *Appl. Catal. A: General* **2001**, *221*, 119.
[5] S. Rendler, M. Oestreich, in 'Modern Reduction Methods', Eds. P. G. Andersson, I. J. Munslow, Wiley-VCH, Weinheim, **2008**, p. 183.
[6] S. Gladiali, R. Taras, 'Reduction of Carbonyl Compounds by Hydrogen Transfer', in 'Modern Reduction Methods', Eds. P. G. Andersson, I. J. Munslow, Wiley-VCH, Weinheim, **2008**.
[7] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621.
[8] P. Hoyos, J. V. Sinisterra, F. Molinari, A. S. R Alcantara, P. Dominguez de María, *Acc. Chem. Res*. **2009**, *43*, 288.
[9] C. Vila, L. Quintero, G. Blay, M. C Muñoz, J. R. Pedro, *Org. Lett*. **2016**, *18*, 5652.
[10] D. Enders, U. Kallfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; *Angew. Chem.* **2002**, *114*, 1822.
[11] a) B. Plietker, *Org. Lett.* **2004**, *6*, 289; b) O. Onomura, H. Arimoto, Y. Matsumura, Y. Demizu, *Tetrahedron Lett.* **2007**, *48*, 8668.
[12] a) P. Muthupandi, S. K. Alamsetti, G. Sekar, *Chem. Commun.* **2009**, 3288; b) S. K. Alamsetti, P. Muthupandi, G. Sekar, *Chem. Eur. J.* **2009**, *15*, 5424; c) P. Muthupandi, G. Sekar, *Tetrahedron: Asymm.* **2011**, *22*, 512; d) C. T. Chen, J. Q. Kao, S. B. Salunke, Y. H. Lin, *Org. Lett.* **2011**, *13*, 26; e) S. Agrawal, E. Martinez-Castro, R. Marcos, B. Martin-Matute, *Org. Lett.* **2014**, *16*, 2256.

Scheme 10. Benzoin scope and reaction time. Isolated yields are given in parenthesis.



[13] a) F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919; b) T. Hashiyama, K. Morikawa, K. B. Sharpless, *J. Org. Chem.* **1992**, *57*, 5067; c) K. Morikawa, J. Park, P. H. Andersson, T. Hashiyama, K. B. Sharpless, *J. Am. Chem. Soc*. **1993**, *115*, 8463; d) W. Adam, R. T. Fell, V. R. Stegmann, C. R. Saha-Möller, *J. Am. Chem. Soc.* **1998**, *120*, 708.

[14] X. Y. Ren, H. F. Du, *J. Am. Chem. Soc.* **2016**, *138*, 810

[15] a) Y. Ohgo, S. Takeuchi, Y. Natori, J. Yoshimura, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2124; b) Y. Ogho, Y. Tashiro, S. Takeuchi, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1549.

[16] T. Koike, K. Murata, T. Ikariya, *Org. Lett*. **2000**, *2*, 3833.

[17] a) R. Bigler, R. Huber, M. Stöckli, A. Mezzetti, *ACS Catal*. **2016**, *6*, 6455; b) R. Bigler, A. Mezzetti, *Org. Process Res. Dev.* **2016**, *20*, 253; c) R. Bigler, R. Huber, A. Mezzetti, *Synlett* **2016**, *27*, 831; d) R. Bigler, R.Huber, A. Mezzetti, *Angew. Chem. Int. Ed.* **2015**, *54*, 5171; e) R. Bigler, A. Mezzetti, *Org. Lett.* **2014**, *16*, 6460; f) R. Bigler, E. Otth, A. Mezzetti, *Organometallics* **2014**, *33*, 4086.

[18] J. S. M. Samec, J. E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237.

[19] R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49.

[20] L. De Luca, A. Mezzetti, *Angew. Chem. Int. Ed.* **2017**, *56*, 11949.

[21] L. De Luca, A. Mezzetti, manuscript in preparation.

[22] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc*. **1988**, *110*, 629.