A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201706261
Angew. Chem. 10.1002/ange.201706261

Link to VoR: http://dx.doi.org/10.1002/anie.201706261
http://dx.doi.org/10.1002/ange.201706261

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10.1002/anie.201706261

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Base-Free Asymmetric Transfer Hydrogenation of 1,2-Di- and Monoketones Catalyzed by a $(NH)_2P_2$-Macrocyclic Fe^{II} Hydride**

Lorena De Luca and Antonio Mezzetti*

Abstract: The hydride isonitrile complex [FeH($CNCEt_3$)(**1a**)]BF_4 (**2**) containing a chiral $P_2(NH)_2$ macrocycle (**1a**), in the presence of 2-propanol as hydrogen donor, catalyzes the base-free asymmetric transfer hydrogenation (ATH) of prostereogenic ketones to alcohols and the hemihydrogenation of benzils to benzoins, which contain a base-labile stereocenter. Benzoins are formed in up to 83% isolated yield with enantioselectivity reaching 95% ee. Ketones give the same enantioselectivity observed with the parent catalytic system [$Fe(CNCEt_3)_2$(**1a**)] (**3a**) that operates with added NaO^tBu.

Asymmetric transfer hydrogenation (ATH) is experiencing a golden age[1] also thanks to the development of earth-abundant, nontoxic catalysts of base metals.[2] However, the base additives that are required to activate the precatalyst[3] tend to limit the reaction scope. An eminent example are α-hydroxy ketones, *e.g.* benzoin (**A**) or, more generically, acyloins (Chart 1), whose base-labile stereocenter easily racemizes upon heating or in basic media,[4] making the asymmetric hemihydrogenation of 1,2-diketones a formidable challenge.[5]

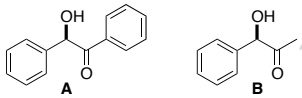

Chart 1. Acycloins (such as **A** and **B**) contain a base-labile stereocenter.

Enantiomerically pure acyloins are frequent structural subunits in natural products[6] and bioactive molecules,[7] and act as chiral templates and building blocks[8] thanks to the combination of the highly directing hydroxyl group with the easily functionalized prostereogenic carbonyl.[9] Their synthesis has been accomplished by a number of chemical and biocatalytic[7] methods such as the stoichiometric[10] and catalytic[11] oxidation of enolates or enol ethers, alkene ketohydroxylation,[9] oxidative kinetic resolution,[12] dynamic kinetic resolution,[13] monooxidation of 1,2-diols,[14] benzoin condensation,[15] Friedel-Crafts reactions,[16] enzymatic reductions,[17] and asymmetric hydrosilylation with chiral frustrated Leiws pairs.[18] Enantiopure propargylic alcohols can be converted to *O*-acylated α-hydroxyketones without racemization/epimerization.[19] However, most of the above methods have drawbacks in terms of catalyst loading, substrate scope, enantioselectivity, or atom economy, which might be overcome by an approach based on asymmetric hydrogenation. After Ohgo's pioneering cobalt-catalyzed H_2 hydrogenation of benzil to benzoin with modest enantioselectivity (62% ee),[20] advances have been slow. Asymmetric transfer hydrogenation (ATH) has been used to reduce 1-phenyl-1,2-propanedione to the enantiopure α-hydroxy ketone **B** (Chart 1).[5a] To the best of our knowledge, however, no highly enantioselective hydrogenation catalyst has been reported for the hydrogenation of benzils to benzoins (**A**).

Therefore, we set out to develop a catalyst for the asymmetric hydrogenation of base-sensitve carbonyl compounds, in particular benzil, starting from our recently reported bis(isonitrile) iron(II) complexes [$Fe(CNR)_2$(**1**)]$(BF_4)_2$ (**3**) containing the chiral $(NH)_2P_2$ macrocycles **1a** and **1b** (Chart 2), which catalyze the ATH of a broad spectrum of ketones upon activation with NaO^tBu.[21]

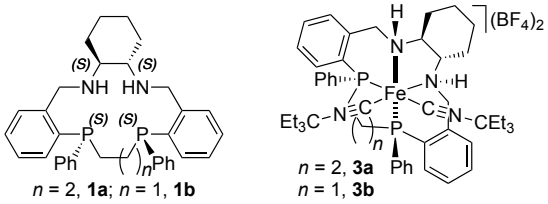

Chart 2. Macrocyclic iron(II)/$(NH)_2P_2$ complexes

The base-free ATH of carbonyl functions has been pioneered with iridium,[22] and several achiral catalysts have been reported.[23] Yet, the base issue does not affect only transfer hydrogenation,[1,3] as also catalysts for the direct (H_2) hydrogenation (AH) of ketones require basic activation. In the case of iron(II), achiral BH_4 adducts catalyze the H_2 hydrogenation of ketones without the addition of base.[24] However, due to the formation of alkoxide from BH_4^- in the alcoholic medium, this system may be unsuitable for base-sensitive substrates. A notable exception is Noyori's base-free AH ruthenium(II) catalyst, which, however, as not been tested with 1,2-diphenylethane-1,2-diones (benzils).[25] We report here the first base-free Fe^{II} catalyst for the ATH of ketones, the hydride complex [FeH(CNR)(**1a**)]BF_4 (**2**), which promotes the asymme-

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[**] We thank Prof. Dr. Kilian Muñiz for the useful discussion and the ETH Zürich for financial support to L. D. L. (grant no. ETH-0914-2).

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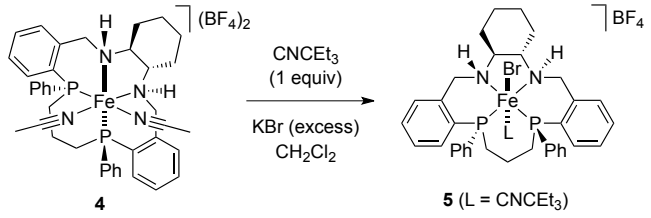
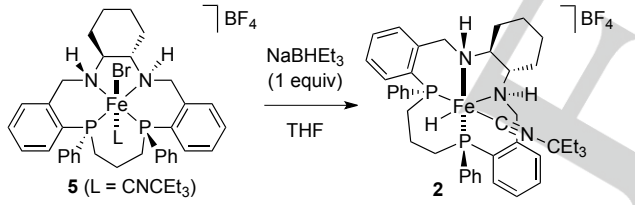
tric hemireduction of benzils to the corresponding benzoins with up to 95% ee, and of monoketones with up to 99% ee.

Hydride **2** was prepared stepwise from [Fe(MeCN)$_2$(**1a**)] (**4a**)[21f] by reaction with CNCEt$_3$ (1 equiv) and an excess of KBr in dichloromethane at 50°C for 16 h (Scheme 1). The resulting bromoisonitrile complex *trans*-[FeBr(CNCEt$_3$)]BF$_4$ (**5**) was isolated as orange solid after filtering off the salts and precipitation with hexane (80% yield, see Supporting Information).[26] The inequivalent P atoms give a tight AX system in the ^{31}P{^{1}H} NMR spectrum (δ 54.3 and 49.0, $^2J_{P,P'}$=59.5 Hz, THF-d_8), suggesting that both phosphines are *trans* to amine. The *trans* configuration is further supported by the similar $^2J_{P,C}$ coupling constants (27.9 and 23.0 Hz) observed in the ^{31}P{^{1}H} NMR spectrum of the ^{13}C-labeled isonitrile derivative [FeBr(^{13}CNCEt$_3$)(**1a**)]BF$_4$ (**5'**), which shows that the isonitrile ligand is *cis* to both phosphines.



Scheme 1. Synthesis of bromoisonitrile complex **5**

The bromoisonitrile complex **5** reacts with NaBHEt$_3$ (1 equiv) in THF to give *cis*-β-[FeH(CNCEt$_3$)(**1a**)]BF$_4$ (**2**) (Scheme 2).



Scheme 2. Synthesis of hydride complex **2**

Hydride **2** decomposes upon isolation, but is stable in THF solution under argon for at least 15 days and was characterized in solution. In the ^{1}H NMR spectrum in THF-d_8, the hydride ligand gives a doublet of doublets at δ –5.45 with similar coupling constants ($^2J_{P,H}$=64.6 Hz, $^2J_{P',H}$=57.5 Hz), indicating that it is *cis* to both phosphines. In the ^{31}P{^{1}H} NMR spectrum, the high-frequency shift of one of the AX signals (δ 65.5 and 37.7, $^2J_{P,P'}$=27.6 Hz) suggests that one phosphine is *trans* to isonitrile. Accordingly, in the ^{31}P{^{1}H} NMR spectrum of the ^{13}C-labeled analogue, the P,C-coupling constants to the isonitrile ligand differ widely between the phosphine resonating at δ 65.5 ($^2J_{P,C}$=27.0 Hz) and the one at δ 37.7 ($^2J_{P,C}$=14.6 Hz).

The hydride complex *cis*-β-[FeH(CNCEt$_3$)(**1a**)]BF$_4$ (**2**) was tested in the base-free asymmetric transfer hydrogenation of standard substrates (Chart 3) with 2-propanol as hydrogen donor to benchmark it against the base-activated precatalyst [Fe(CNR)$_2$(**1a**)](BF$_4$)$_2$ (**3a**).[21a] Therefore, the same substrate amount, concentration, and catalyst loading were used. Beside the absence of base, the only difference was the small amount of THF deriving from the preparation of **2**. In fact, the hydride complex **2** was prepared before each catalytic run by treating **5** with NaBHEt$_3$ (1 equiv) in THF (0.4 mL) at room temperature. After stirring for 5 min, the solution was diluted with 2-propanol (12.5 mL) and heated to 50°C. After stirring for 10 min, the reaction was started by adding one of the ketones **6** (2.5 mmol). The resulting light orange solution was stirred at 50°C and sampled at regular intervals to determine the conversion to the corresponding alcohols (*R*)-**7** and the enantioselectivity (by chiral GC or HPLC depending on the substrate). The reaction times reported in Table 1 are those at which the ATH reaction has just reached equilibrium.

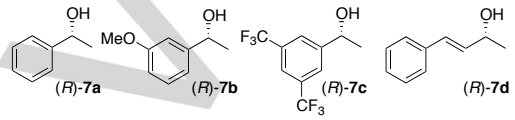


Chart 3. Scope of the ATH of ketones

With acetophenone (**6a**), the hydride complex **2** is less active than the previously reported, closely related system that uses the bis(isonitrile) complex **3a** and NaO^{t}Bu as added base (Table 1, entries 1, 3). However, the enantioselectivity is the same (98% ee). When base (NaO^{t}Bu, 1 mol%) is added to the reaction catalyzed by hydride **2**, acetophenone is reduced at the same rate observed with **3a**/NaO^{t}Bu, indicating that the base plays a role in catalytic turnover, while the enantioselectivity is slightly improved.

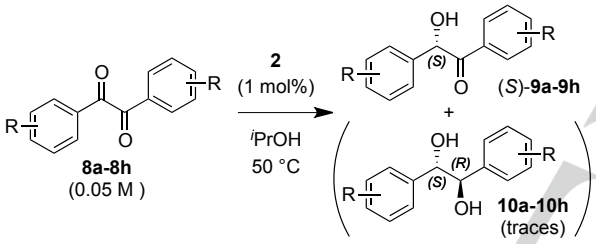
Table 1. Asymmetric Transfer Hydrogenation of **6** to **7** with **2** and **3a**.[a]

entry[a]	Substr.	Cat.	Base (mol%)	*t* (h)	TOF[b] (h^{-1})	Yield (%)	ee (%)
1	**6a**	**2**	0	1.0	1885	92	98
2	**6a**	**2**	1	0.5	3013	90	99
3	**6a**	**3a**	1	0.5	3426	93	98
4	**6b**	**2**	0	1.5	3209	93	98
5	**6b**	**3a**	1	0.5	8580	92	97
6	**6c**	**2**	0	0.2	3457	quant	98
7	**6c**	**3a**	1	0.5	9430	quant	99
8	**6d**	**2**	0	0.25	4690	81	64
9	**6d**	**3a**	1	0.25	8160	82	68

[a] Reaction conditions: Substrate **6** (2.5 mmol), catalyst **2** or **3a** (2.5 μmol, 0.1 mol%), 2-propanol, *T*=50°C. Results with catalyst **3a** were obtained with added NaO^{t}Bu (0.025 mmol, 1 mol%) (data from ref. 21a). Conversion and enantiomeric excess were determined by GC and HPLC, respectively (see Supporting Information for details). [b] TOF at 15 min.

The reaction of the electron-rich **6b** is significantly slower with catalyst **2** than with **3a**/NaO^{t}Bu, but the enantioselectivity reaches 98% ee at reaction completeness (entries 4, 5). Interestingly, the industrially relevant, electron-poor **6c** was converted quantitatively in a shorter time (15 min) with catalyst **2** than with **3a** (30 min, entries 6, 7), albeit at the cost of marginally lower enantioselectivity (98 and 99% ee, respectively). Both catalysts reduce benzylideneacetone (**6d**) chemoselectively at the carbonyl function with comparable enantioselectivity (64 and 68% ee, entries 8, 9).

Then, to take advantage of the base-free nature of ATH catalyzed by hydride **2**, benzils (**8**) were studied as substrates, as their hemireduction gives α-hydroxyketones (Scheme 3), which undergo rapid stereomutation in the presence of base.[4] Preliminary experiments showed that 1,2-diphenylethane-1,2-dione (**8a**) is reduced sluggishly to benzoin (**9a**) under the conditions used for ketones **6** (Scheme 3, Table 1). However, upon increasing the catalyst loading to 1 mol% and lowering the substrate concentration to 0.05 M, benzoin (**9a**) was obtained with 75% yield and 95% ee after 75 min (Table 2, entry 1). Only traces of hydrobenzoin (**10a**) were detected after this reaction time. Recrystallization from ^{i}PrOH gave (*S*)-benzoin (**9a**) as a single enantiomer (ee > 99.95%) with 61% overall yield.



Scheme 3. ATH of benzils with catalyst **2**

For the sake of comparison, **8a** was hydrogenated with catalyst **3a** in the presence of base (NaO^{t}Bu, 10 equiv). After a reaction time of 15 min, racemic benzoin (**9a**) was formed (22%) along with a conspicuous amount of *meso*-hydrobenzoin (**10a**) (54% GC yield). After 30 min of reaction time, benzil conversion to (*R,S*)-**10a** was quantitative (by GC). Thus, the base strongly accelerates the ATH reaction as expected,[3,27] and the second hydrogenation step occurs under substrate control (see Supporting Information).[28]

The excellent and unprecedented result achieved with **8a** prompted us to broaden the scope to the substituted benzoins **9b-9h** in Chart 4. The reaction times were optimized for each substrate **8a**-**8h** by monitoring the ATH reaction by GC in preliminary runs, after which the reaction was repeated and stopped just before the appearance of hydrobenzoins **10a-10h**. The isolated yields and ee values of benzoins **9a-9h** are given in Table 2. The enantiopurity of **9a** and **9b** was enhanced by recrystallization, whereas **9c-9h** recrystallized only on standing and hence without enantioenrichment. The absolute configuration of **9a-9h** was determined to be *S* by the sign of the optical rotation (see Supporting Information).

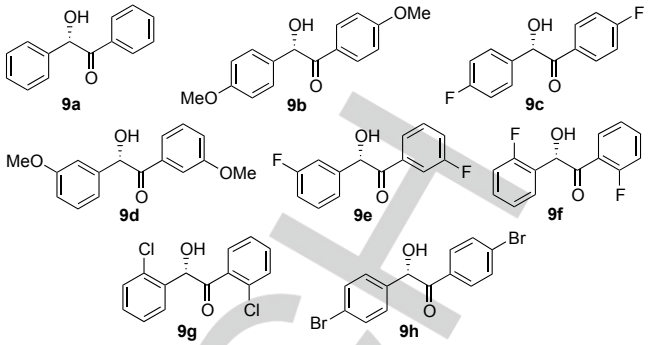


Chart 4. Scope of the base-free ATH of 1,2-diketones **8** to benzoins (*S*)-**9**.

The *para*-substituted benzils **8b** and **8c** gave the corresponding benzoins **9b** and **9c** with high yields and good enantioselectivity regardless of the electronic properties of the substituents. The bromo analogue **8h** apparently deviates from this trend as it gives only 56% ee, probably because of its poor solubility (the reaction was never homogeneous in ^{i}PrOH at 50 °C). Instead, the *meta*-substituted analogues are sensitive to electronic factors. Thus, 1,2-bis(3-methoxyphenyl)ethane-1,2-dione (**8d**) gave the corresponding α-hydroxyketone **9d** in good yield (67%) and high enantioselectivity (87% ee) after 2 h of reaction time, whereas the reduction of its fluoro analogue **8e** proceeded faster, but at the price of a lower enantioselectivity (49% ee). The *ortho* substituted 1,2-bis(2-fluorophenyl)ethane-1,2-dione (**8f**) gave benzoin **9f** with lower yield and with 62% ee, whereas bulkier *ortho* substituents such as in **8g** significantly decrease the enantioselectivity (41% ee).

Table 2. Asymmetric Transfer Hydrogenation with **2** under Base-free conditions[a]

entry[a]	Substr.	*t* (min)	Yield of **9** (%)	ee of **9** (%)
1	**8a**	75	70 (61)	95 (>99.95)[b]
2	**8b**	90	73 (65)	84 (93)[b]
3	**8c**	45	83	89
4	**8d**	120	55	87
5	**8e**	60	58	49
6	**8f**	30	39	62
7	**8g**	75	51	41
8	**8h**	45	56	56

[a] Reaction conditions: Substrate (0.625 mmol), catalyst **2** (6.25 μmol, 1 mol%), 2-propanol 0.05 M, *T*=50°C. Yields are isolated, data in parentheses are after recrystallization. The enantiomeric excess was determined by chiral HPLC (see Supporting Information for details). [b] After single recrystallization from hot ^{i}PrOH.

The lability of the stereocenter of benzoins **9** in the presence of base has been exploited in highly enantioselective dynamic kinetic resolution (DKR) of benzils to hydrobenzoins for the enantioselective transfer hydrogenation of benzil **8a** to hydrobenzoin **10a** with HCOOH/NEt$_3$ catalyzed by [RuCl(Tsdpen)(η^6-

arene)].[4] However, to the best of our knowledge, hydride **2** is the first example of catalyst for the asymmetric hemihydrogenation of benzils to benzoins. The use of a hydride complex such **2**, which neither needs base activation nor releases an internal base during the reaction, is pivotal in order to perform the asymmetric transfer hydrogenation of base-sensitive substrates. Although mechanistic speculations are beyond the scope of this paper, the similar performance of **2** and **3a**/NaO^{t}Bu, in particular after addition of base to hydride **2**, is striking and may hint to the involvement of hydride **2**, or of a closely related species, in the catalytic cycle with both systems. A mechanistic investigation is under way, and its results will be reported in due time.

Keywords: Acyloins • Iron • Base-free • Asymmetric transfer hydrogenation• Macrocyclic ligands

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[28] a) During reaction optimization, we observed that kinetic resolution occurred in the second hydrogenation step. The increasing ee of the residual benzoin (**9a**) over time implies that the second reduction step is faster for the *R* enantiomer, which suggests that the reduction of the second C=O bond is substrate-controlled, see: b) 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.

10.1002/anie.201706261

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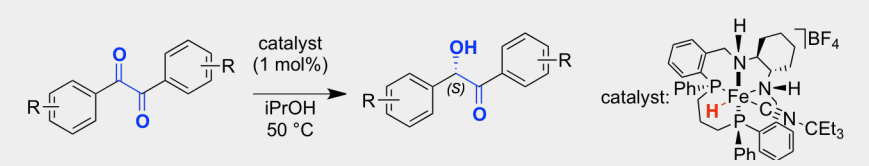

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Base-Free Asymmetric Transfer Hydrogenation of 1,2-Di- and Monoketones Catalyzed by a $(NH)_2P_2$-Macrocyclic Fe^{II} Hydride

Base? No Thanks! A hydride isonitrile iron(II) complex bearing a C_2-symmetric di-amino $(NH)_2P_2$ macrocyclic ligand catalyzes the asymmetric transfer hydrogenation of ketones under base-free conditions with excellent enantioselectivity (up to 99% ee). Base-labile benzoins are formed from the corresponding benzils with up to 95% ee.