solid: mp 204–206 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.41 (d, H_1, $J_{1,2}$ = 7.1), 8.15–7.95 (m, 4), 7.80–7.70 (m, 3), 5.02 (d, H_{12}, $J_{11,12}$ = 4.5), 4.65 (dd, H_9, $J_{9,10}$ = 9.6, $J_{9,11}$ = 1.1), 3.92 (dd, H_{10}), 3.81 (m, H_{11}, $J_{10,11}$ = 1.1); ^{13}C-NMR (DMSO-d_6) δ 141.15, 138.45, 138.01, 135.83, 130.04, 128.76, 128.61, 128.50, 127.50, 127.29, 125.26, 124.16, 121.56, 120.75, 71.39, 69.95, 56.28, 50.50; mass spectrum, *m/e* (relative abundance) 302 (M^+, 57), 284 (74), 256 (99), 255 (98), 244 (70), 226 (64), 215 (100), 202 (50); exact mass calcd for $C_{20}H_{14}O_3$ 302.09432, observed 302.09419.

***r*-11-Bromo-*t*-9,*c*-10,*t*-12-trihydroxy-9,10,11,12-tetrahydrobenzo[*j*]fluoranthene (18).** Prepared as described above from 32 mg of **2** (0.5 h, 0 °C) to give **18**, 42 mg (98% yield). Recrystallization from THF–hexanes gave colorless needles: mp 136 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.32 (d, 1, J = 7.2), 8.11–8.03 (m, 2), 7.94 (d, 2, J = 8.3), 7.76–7.65 (m, 3), 5.83 (dd, 1, J = 5.9, J = 2.9), 5.33 (d, 1, J = 6.2), 4.91–4.79 (m, 3), 4.72 (dd, 1, J = 4.6, J = 1.6), 4.32 (m, 1); ^{13}C-NMR (acetone-d_6) δ 140.57, 139.82, 139.69, 137.60, 137.45, 131.59, 131.29, 129.64, 129.19, 128.63, 128.20, 128.16, 127.62, 126.24, 122.78, 121.40, 73.43, 72.68, 70.78, 60.58. Anal. Calcd for $C_{20}H_{15}BrO_3$: C, 62.66; H, 3.92. Found: C, 62.26; H, 4.44.

***trans*-9,10-Dihydroxy-*syn*-11,12-epoxy-9,10,11,12-tetrahydrobenzo[*j*]fluoranthene (19).** Prepared as described above from **18** (59 mg, 1 h, room temperature) to give **19** (38.4 mg, 83% yield); recrystallization from THF–hexanes afforded colorless needles: mp 209–212 °C dec; ^{1}H-NMR (acetone-d_6) δ 8.37 (d, H_1, $J_{1,2}$ = 7.0), 8.14 (d, 1, J = 6.9), 8.07 (d, 1, J = 7.7), 8.01 (d, 1, J = 8.3), 7.99 (d, 1, J = 8.1), 7.80–7.70 (m, 2), 7.53 (d, 1, J = 7.7), 4.90 (d, H_{12}, $J_{11,12}$ = 4.1), 4.66 (d, H_9, $J_{9,10}$ = 4.8), 4.22 (dd, H_{10}, $J_{10,11}$ = 2.1), 3.90 (m, H_{11}); ^{13}C-NMR (DMSO-d_6) δ 139.35, 138.63, 138.46, 135.78, 135.64, 132.04, 129.89, 128.72, 128.58, 128.43, 127.84, 127.53, 127.31, 123.88, 122.29, 121.05, 71.73, 70.18, 58.27, 47.94; mass spectrum, *m/e* (relative abundance) 284 ($M - H_2O$, 100), 255 (12), 238 (17), 237 (25). A molecular ion peak for **19** was not detected although an ion at *m/e* 284 corresponding to $M - H_2O$ was observed: exact mass calcd for $C_{20}H_{12}O_2$ ($M - H_2O$) 284.08373, observed 284.08448.

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Supplementary Material Available: ^{1}H-NMR spectra for compounds **4**, **8–12**, **14–17**, and **19** and ^{13}C-NMR spectra for compounds **8–10**, **12**, **14**, **17**, and **19** (12 pages). Ordering information is given on any current masthead page.

Reductions with NADH Models. 3. The High Reactivity of Hantzsch Amides

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Aromatic ketones and aldehydes are rapidly reduced to alcohols by various 1,4-dihydropyridines, several of which can be considered to be a model of the coenzyme NADH. The reducing agents bear amide groups and are closely related to Hantzsch esters. They exhibit the highest reactivity among NADH models so far described. In some cases, the rate and completeness of reduction by Hantzsch amides compare favorably with those of reduction by the usually employed metal hydrides.

Introduction

Performing organic reactions in a manner similar to that in which they occur in living cells is a fascinating challenge to organic chemists. The results may assist in the development of new synthetic methods of increased efficiency in terms of enhanced rate of reaction and chemo-, regio-, and stereoselectivity.

Because redox reactions are important biological processes, models of the relevant coenzymes have sometime been studied with the aim of developing new useful oxidation or reduction reagents (or catalysts) for synthetic purposes.

Simple models of NAD^+/NADH coenzymes have been synthesized and applied as reagents in biomimetic reductions.[1] All the models that have so far been described possess, as a common feature, a 1,4-dihydropyridine ring which mimics the nicotinamide fragment of the coenzyme. Most of the relevant studies have involved *N*-benzyl-1,4-dihydronicotinamide (BNAH) **1**, and its derivatives. Some bi- and tricyclic models that are structurally related to quinoline,[2] thenopyridine,[3] acridine,[4] and deazaflavin[5] have also been described.

Reduction proceeds by way of the transfer to the substrate of the equivalent of a hydride ion. The source of hydride ion is one of the two chemically equivalent hydrogens at C-4 of the dihydropyridine ring. Mechanistic assessments posit the complexation of the metal cation by the carbonyl(s) group(s) of the NADH models[1a] (Figure 1).

The reduction is catalyzed by Lewis[6] or Broensted[4] acids. In most cases, catalysis by magnesium perchlorate and

(1) (a) Ohno, A.; Ushida, S. Mechanistic Models of Asymmetric Reductions. *Lecture Notes in Bio-Organic Chemistry*; Springer-Verlag: Berlin, 1986; p 1; *Bull. Inst. Chem. Res. Kyoto Univ.* **1985**, *63*, 104. (b) Pierre, J. L. *Actual. Chim. (Paris)* **1984**, 33. (c) Kellog, R. M. *Top. Curr. Chem.* **1982**, *110*, 111.

(2) (a) Shinkai, S.; Hamada, H.; Manabe, O. *Tetrahedron Lett.* **1979**, 1387. (b) Shinkai, S.; Hamada, H.; Kusano, Y.; Manabe, O. *Tetrahedron Lett.* **1979**, 3511; *J. Chem. Soc., Perkin Trans. 2* **1979**, 699. (c) Shinkai, S.; Nakano, T.; Hamada, H.; Kusano, Y.; Manabe, O. *Chem. Lett.* **1979**, 229.

(3) Cazin, J.; Duflos, J.; Dupas, G.; Bourguignon, J.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 867.

(4) (a) Ishikawa, M.; Fukuzumi, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1353. (b) Fukuzumi, S.; Chiba, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1989**, 941.

(5) (a) Yoneda, F.; Tanaka, K.; Yamato, H.; Moriyama, K.; Nagamatsu, T. *J. Am. Chem. Soc.* **1989**, *111*, 9199. (b) Yoneda, F.; Tanaka, K. *Med. Res. Rev.* **1987**, *7*, 477.

(6) (a) Van Niel, J. C. G.; Pandit, U. *Tetrahedron* **1985**, *41*, 2745. (b) Ohno, A.; Yasui, S.; Oka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 290. (c) Gase, R. A.; Boxhoorn, G.; Pandit, U. K. *Tetrahedron Lett.* **1976**, 2889. (d) Shirai, M.; Chishina, T.; Tanaka, M. *Bull. Chem. Soc. Jpn.* **1974**, *48*, 1079.

0022-3263/92/1957-1789$03.00/0

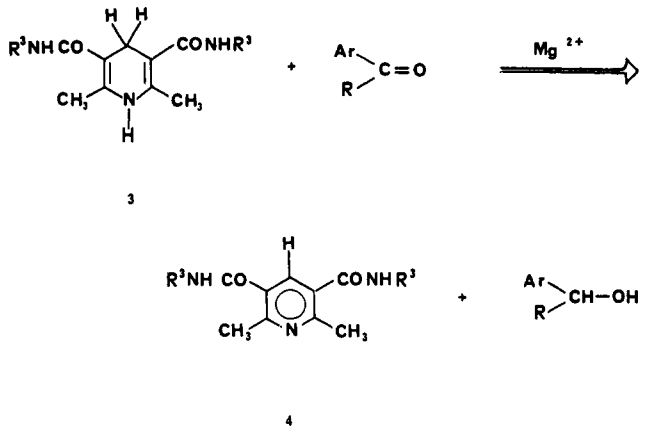

Figure 1. Reduction of carbonyl compounds by NADH models. R^3 substituents as in Table I.

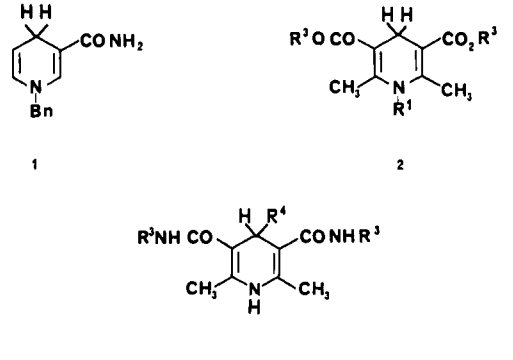

Figure 2. NADH models. R^3 and R^4 substituents as in Table I.

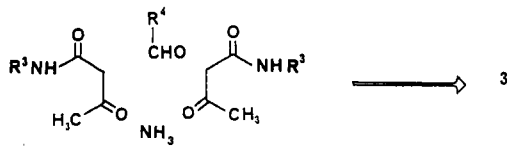

Figure 3. Preparation of Hantzsch amides through cyclization reactions.

rigorously anhydrous conditions are required for reduction to proceed.

Unfortunately, the dihydropyridine ring of BNAH 1 is subject to side reactions. It can be hydrated and also can add to the carbonyl group of the substrate.[7] However, it was reported that such problems were not encountered with certain bicyclic models.[3]

Thus, we became interested in symmetrical models that are structurally related to Hantzsch esters (HEH), 2, and amides (HAH), 3, which do not undergo unwanted side reactions (Figure 2).

HEHs 2 and HAHs 3 which bear various substituents on the dihydropyridine ring are readily accessible.[8] The synthesis of a particular compound involves the one-pot reaction of an amine, an aldehyde, and an ester or an amide of acetoacetic acid (Figure 3).

We earlier prepared chiral HEHs related to 2 which bear monosaccharide units at different positions on the dihydropyridine ring. We showed that such models reduced methyl benzoylformate to chiral methyl mandelate in up to 77% ee[9] depending on the nature of the monosaccharide. However, the rates of reduction by such models were significantly lower than those observed with the achiral model 1. Here, too, successful reduction required rigorously anhydrous conditions.

Table I. N-Substituted Hantzsch Amides 3

R^3	R^4	3	R^3	R^4	3
H	H	a	C_6H_5	H	e
CH_3	H	b	o-$(CH_3O)C_6H_5$	H	f
$CH(CH_3)_3$	H	c	$COCH_3$	H	g
$CH(CH_3)C_2H_5$	H	d	C_6H_5	p-$(CH_3O)C_6H_5$	h

A study[10] showed that the presence of trace amounts of water suppressed reduction and also led to irreversible addition of water to the ring, and therefore destruction of model compound. It thus appeared to be of great interest to develop NADH models that were highly reactive even in the presence of water.

The high reactivity displayed by model 1 is due to its carboxamide group, which can better complex with the metal cation than can the both ester groups of model 2.[11] With this in mind, we decided to prepare the amide analogues of HEH 2. These Hantzsch amides 3 are *new* models. The two carboxamide groups were expected to better complex with the magnesium cation and consequently increase the reactivity of the models.

Results and Discussion

Preparation of the Hantzsch Amides. The Hantzsch amides **3a–3g** were prepared as depicted in Figure 3 by the one-pot cyclization reaction of the corresponding acetoacetic acid amides **5** with hexamethylenetetramine in the presence of ammonium acetate.[15] Compound **3h** was prepared by the reaction of acetoacetanilide, aqueous ammonia, and *p*-methoxybenzaldehyde in aqueous ethanol. Most of the acetoacetic amides **5** were commercially available. Amide **5c** was prepared by the acetoacetylation of isopropylamine with diketene in dry ether at room temperature,[12] whereas amide **5g** was obtained from the reaction of acetamide and 2,2,2-trimethyl-1,3-dioxin-4-one in refluxing xylene.[13]

The nitrogen substituents in the β-ketoamides **5** and the HAH 3 series are reported in Table I.

The HAH precipitate from the reaction mixture as microcrystals on cooling or addition of cold water or both. Most are monohydrates, which retain water of crystallization even after oven drying. Like their HEH analogues, HAH are bright yellow solids. The UV spectra show bands at 245–280 and at 360–390 nm, in the same regions as the bands which appear in the spectra of HEH.[14a] The IR spectra of HAHs and HEHs are also similar,[14b] except that typical amide I and amide II carbonyl bands are present in the spectra of HAHs.

(7) (a) Zehani, S.; Gelbard, G. *Nouv. J. Chim.* **1986**, *10*, 511. (b) Bourguignon, J.; Queguiner, G. J. *Heterocycl. Chem.* **1989**, *26*, 1029. (c) Cazin, J.; Trefouel, T.; Dupas, J.; Bourguignon, J.; Queguiner, G. *Tetrahedron* **1988**, *44*, 1079.

(8) (a) Zehani, S.; Gelbard, G. *Bull. Soc. Chim. Fr.* **1989**, 104. (b) Kuthan, J.; Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191. (c) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (d) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

(9) (a) Zehani, S.; Lin, J.; Gelbard, G. *Tetrahedron* **1989**, *45*, 733. (b) Zehani, S.; Gelbard, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1162.

(10) (a) Tintiller, P. Ph.D. Thesis, University of Rouen, 1985. (b) Tintiller, P.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Tetrahedron Lett.* **1985**, *27*, 2357.

(11) (a) Tamagaki, S.; Simoto, Y.; Minura, T.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1593. (b) Hughes, M.; Prince, R. H.; Wyeth, P. *J. Inorg. Nucl. Chem.* **1978**, *40*, 713.

(12) Wilson, B. D. *J. Chem. Soc.* **1963**, *28*, 314.

(13) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315.

(14) (a) Brignell, P. J.; Eisner, U.; Farell, P. G. *J. Chem. Soc. B* **1963**, 1083. (b) Kinoshita, N.; Hamana, M.; Kawasaki, T. *Chem. Pharm. Bull. Jpn.* **1962**, *10*, 753.

Table II. Reduction[a] of Methyl Benzoylformate to Methyl Mandelate by HAHs 3

entry	model	catalyst	time	yield[b] (%)
1	**1**	*c*	7 h[e]	95
2	**2a**	*c*	7 h	84
3	**2b**	*c*	2 h	89
4	**2b**	*d*	46 h	41
5	**3a**	*c*	7 h	94
6	**3b**	*c*	5 min[e]	>99
7	**3b**	*d*	3 h	95
8	**3c**	*c*	5 min[e]	>99
9	**3d**	*c*	5 min[e]	94
10	**3e**	*c*	15 min	92
11	**3e**·H_2O	*c*	20 min	92
12	**3e**	*d*	4 h	>99
13	**3f**	*c*	5 min[e]	98
14	**3g**	*c*	5 days	<5
15	**3g**	*d, g*	4 days	<5
16	**3g**	*f, g*	4 days	27
17	**3h**	*c*	25 h	85

[a] Model/catalyst/substrate = 1.5:1.5:1.0, CH_3CN solution, N_2 atmosphere, 50 °C. [b] By GLC. [c] Anhydrous $Mg(ClO_4)_2$. [d] $Mg(ClO_4)_2 \cdot 6H_2O$. [e] At rt. [f] $Zn(ClO_4)_2 \cdot 6H_2O$. [g] Model **3g**/catalyst/substrate = 1.5:/3/1.0.

Most of the HAHs are prone to oxidation to the corresponding pyridines. Thus, they were handled and stored under nitrogen. The formation of products of oxidation could be detected by TLC (a nonfluorescent spot is observed) and by ^1H NMR (a singlet due to 3- and 5-CH_3 protons appears at 2.8–3 ppm in addition to the singlet at 2.3 corresponding to the reduced form). The pyridine **4e** was prepared, as a reference compound, by the oxidation of **3e** by chloranil.[15]

Reductions of Aromatic Aldehydes and Ketones. The reduction[1] of various carbonyl compounds to the corresponding alcohols was performed in acetonitrile solution under nitrogen atmosphere in the presence of a catalytic amount of magnesium perchlorate. The most commonly studied substrate, methyl benzoylformate, was examined first. The yields of methyl mandelate are reported in Table II.

$$Ph\text{-}CO\text{-}CO_2CH_3 + \mathbf{3} \rightarrow Ph\text{-}CH(OH)\text{-}CO_2CH_3 + \mathbf{4}$$

The Hantzsch ester **2a** ($R^3 = CH_3$, $R^1 = H$ in Figure 2) required heating for the yield (entry 2) to be comparable to that of reduction by BNAH **1** at room temperature (entry 1). Ester **2b** ($R^1 = R^3 = CH_3$, in Figure 2, the *N*-methyl analogue of **2a**) was much more reactive (entry 3). However, its reactivity was reduced by the presence of water as the results of the use of a hydrated magnesium salt catalyst show (entry 4).

The Hantzsch amides gave very good results: essentially quantitative yields were obtained within a few minutes (entries 6, 8, 9, 10, and 13) regardless of the the nature of the substituent on the amide nitrogen. The rates of reaction were somewhat lower at room temperature.

The steric effect of a bulky substituent at C(4) is noticeble (**3h**, entry 17) because the carbonyl group of the substrate must closely approach the hydrogen atom at C(4) for reduction to proceed at a reasonable rate. Even though the *p*-methoxyphenyl group is an electron donor, its presence at C(4) dramatically reduced the rate of reduction. The steric effect of a cyclohexyl group at C(4) of HEHs has already been described.[9a]

The effect of a hydrated catalyst was less dramatic with HAHs than with HEHs, as a comparison of the results with **3e** (entries 10 and 11) and those with HEH model **2b** (entries 3 and 4) show. It should be kept in mind that the HAHs are usually obtained as crystalline monohydrates and are most conveniently handled in that form. The water of crystallization can be removed by azeotropic distillation of a toluene suspension of the monohydrates; when this was done, a small increase in reactivity was observed. Thus, HAH **3** are very reactive, even in the presence of water. Such is *not* the case with HEHs.

Several reasons can be put forward to explain the excellent results: (i) the presence of two carboxamide groups, which are better able to complex a metal cation than ester groups, keep the magnesium cation within a socalled ternary complex[1a] that includes the model, the metal cation, and the substrate; (ii) the redox potentials of 1,4-dihydropyridines are more negative for 3-carboxamide than for 3-carboxylates,[16] and (iii) as was suggested by the results of studies of the rates of reduction of trifluoroacetophenone by model **1** and its 2-, 5-, and 6-methyl derivatives[17] in HAHs, the presence of electron-donating methyl groups at C(2) and C(6) and the absence of an electron-donating methyl group at C(5) led to increased reactivity. The HAHs **3** possess all these desirable features.

As mentioned above, the asymmetric reduction of methyl benzoylformate to optically active methyl mandelate has been achieved.[9] Because the possibility exists that asymmetric reductions by HAHs could be catalyzed by chiral Lewis acids, several *achiral* lanthanide polyfluoro-β-diketonates were evaluated as catalysts in the hope that their chiral analogues could subsequently be

Table III. Reduction[a] of Methyl Benzoylformate to Methyl Mandelate by Anhydrous Model 3e in the Presence of Lewis Acid Catalysts

entry	catalyst	time	yield[b] (%)
1	none	4 days	15
2	$Mg(ClO_4)_2$	15 min	92
3	$Mg(ClO_4)_2 \cdot 6H_2O$	4 h	>99
4	$Zn(ClO_4)_2 \cdot 6H_2O$	24 h	77
5	$Nd(F_6acac)_3$[c]	16 h	70[d]
6	$La(F_6acac)_3$[e]	15 h	77[d]
7	$Eu(fod)_3$[f]	15 h	82[d]
8	$ZnCl_2$	2 h	34

[a] Model/catalyst/substrate = 1.5:1.5:1.0, CH_3CN solution, N_2 atmosphere, 50 °C. [b] By GLC. [c] Tris(1,1,1,5,5,5-hexafluoro-2,5-pentanedionato)neodymium. [d] Model/catalyst/substrate = 1.5:0.15:1.0. [e] Tris(1,1,1,5,5,5-hexafluoro-2,5-pentanedionato)lanthanum. [f] Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

Table IV. Reduction[a] of Aromatic Ketones and Aldehydes by HAH 3

entry	model	catalyst	substrate	product	yield (%) (reaction time)
1	**3b**	*b*	C_6H_5CHO		0 (24 h)
2	**3b**	*d*	C_6H_5CHO	$C_6H_5CH_2OH$	18 (24 h)
3	**3b**	*e*	C_6H_5CHO	$C_6H_5CH_2OH$	85 (2 h)
4	**3b**	*b, c*	$C_6H_5COCF_3$	$C_6H_5CH(OH)CF_3$	79 (30 h)
5	**3e**	*b, c*	$C_6H_5COCF_3$	$C_6H_5CH(OH)CF_3$	30 (24 h)
6	**3b**	*b, c*	CH_3CO-pyr[f]	$CH_3CH(OH)$-pyr[g]	87 (24 h)
7	**3c**	*b, c*	CH_3CO-pyr[f]	$CH_3CH(OH)$-pyr[g]	93 (24 h)
8	**3d**	*b, c*	CH_3CO-pyr[f]	$CH_3CH(OH)$-pyr[g]	91 (26 h)
9	**3f**	*b, c*	CH_3CO-pyr[f]	$CH_3CH(OH)$-pyr[g]	63 (24 h)
10	**3b**	*e*	$C_6H_5COCH_3$	$C_6H_5CH(OH)CH_3$	40 (31 h)

[a] Model/substrate = 1.0:1.0, THF solution, rt. [b] Anhydrous $Mg(ClO_4)_2$. [c] As in Table I, CH_3CN solution. [d] 0.1 equiv of $AlCl_3$. [e] 2 equiv of $AlCl_3$. [f] 2-Acetylpyridine. [g] Methyl-2-pyridylcarbinol.

(15) Dubur, G.; Ogle, Z.; Uldrikis, R. *Chem. Heterocycl. Compds.* **1974**, 1642.

(16) (a) Kellog, R. M.; Piepers, O. J. *J. Chem. Soc., Chem. Commun.* **1982**, 402. (b) De Vries, J. G., Ph.D. Thesis, University of Groningen, 1979.

(17) Bossaert, J.; Domisse, R. A.; Alderweireldt, F. *Tetrahedron Lett.* **1984**, *25*, 2235; *Heterocycles* **1986**, *24*, 115.

similarly employed. The results are reported in Table III.

The lanthanide β-diketonates (entries 5–7) were more catalytically active at lower concentrations than was $Mg(ClO_4)_2$ (entries 2 and 3), although their efficiencies were estimated to be only one-sixth that of $Mg(ClO_4)_2$, which is, at the moment, the best catalyst. Thus, it does appear possible that chiral lanthanide polyfluoro-β-diketonates can be used as catalysts for asymmetric reductions by HAHs.

Less reactive carbonyl compounds were also reduced at room temperature by the amides **3** in the presence of magnesium perchlorate. In Table IV are reported the results of the reduction of benzaldehyde (entries 1–3), trifluoroacetophenone (entries 4, 5), 2-acetyl pyridine (entries 6–9), and acetophenone (entry 10).

Benzaldehyde was reduced within 2 h at room temperature (entry 3). This is the best result reported so far for this compound.[18] However, catalysis by $AlCl_3$ was required.

Trifluoroacetophenone and 2-acetylpyridine required a day-long reaction, but the yields of the corresponding alcohols compared favorably with those obtained by reductions with BNAH **1**.[19]

Acetophenone was reduced to methylphenylcarbinol in moderate yields (entry 11). This is the first report of the reduction of that ketone by a NADH model.

It is clear that Hantzsch amides, a new family of NADH models, are stable under the reaction conditions in which they were employed and they exhibit high reactivity even in the presence of water. In some cases, the rate and the completeness of reduction were comparable to those of reductions with the usually employed metal hydrides.[20]

Studies of the asymmetric reduction of carbonyl compounds by HAHs catalyzed by polyflouro-β-diketonates are now under way. The results will be reported in due course.

Experimental Section

Solvents, substrates, reference alcohols, and catalysts were pure grade and were used as received. CH_3CN and THF were dried by passage through a column of basic Al_2O_3 (grade I) and deaerated by sonication under a stream of N_2. Diketene was distilled before use and was kept in a freezer. 1-phenylethanol, 2,2,2-trifluoro-2-phenylethanol, and 2-(1-hydroxyethyl)pyridine were prepared by reduction of the corresponding ketones.[21] The lanthanide catalysts were described earlier.[9b]

UV spectra were obtained in 95% EtOH. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6. GLC analyses were conducted on a 2-m 20% 20M PEG column using diphenyl ether as an internal standard, except for reduction of benzaldehyde, where methyl benzoate was employed.

Acetoacetamides 5. The amides **5a**, **5e**, and **5f** were commercially available. Technical-grade aqueous solutions of the amides **5b** and **5d** were gifts from Lonza A.G. (Basle). The other amides were prepared by the general methods of Wilson[12] and Kato.[13]

***N*-Methylacetoacetamide (5b).** Distillation of its aqueous solution afforded the neat amide: $bp_{0.1mm}$ 96–98 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.21 (s, 3 H, CH_3CO), 2.84 (d, J = 4.8 Hz, 3 H, CH_3NH), 3.46 (s, 2 H, $COCH_2CO$), 7.3 (m, 1 H, NH); IR (neat) 3343 (ν_{N-H}), 1707 ($\nu_{C=O}$ ketone), 1652 ($\nu_{C=O}$ amide), 1562 cm^{-1}. Anal. Calcd for $C_5H_9NO_2$ (MW = 115.1): C, 52.16; H, 7.88; N, 12.17. Found: C, 52.23; H, 8.04; N, 11.55.

***N*-Isopropylacetoacetamide (5c).** A solution of diketene in dry Et_2O was added dropwise to an equivalent amount of *i*-$PrNH_2$ in dry Et_2O. External cooling was maintained during addition. The mixture was then allowed to stand for several hours at rt, whereupon the solvent was evaporated and the oil was distilled. **5c**: $bp_{0.01mm}$ = 77–79 °C (yield 95%); ^1H NMR (60 MHz, $CDCl_3$) δ 1.14 (d, 6 H, CH_3CHCH_3), 2.22 (s, 3 H, CH_3CO), 3.30 (s, 2 H, CH_2), 4.0 (m, 2 H, CH), 7.0 (1 H, NH); IR (KBr) 3297 (ν_{N-H}), 1720 ($\nu_{C=O}$ ketone), 1649 ($\nu_{C=O}$ amide), 1387, 1360, 1161, 1130 (δ_{C-H} *gem* CH_3) cm^{-1}. Anal. Calcd for $C_7H_{13}NO_2$ (MW = 143.2): C, 58.80; H, 9.16; N, 9.80. Found: C, 57.95; H, 9.47; N, 9.93.

***N*-*sec*-Butylacetoacetamide (5d).** Distillation of its aqueous solution afforded the neat amide: $bp_{0.5mm}$ 95–96 °C; ^1H NMR (80 MHz, $CDCl_3$) δ 0.88 (t, 3 H, CH_3CH_2), 1.15 (d, 3 H, CH_3CH), 1.45 (dxq, 2 H, CH_2CH_3), 2.27 (s, 3 H, CH_3CO), 3.50 (s, 2 H, $COCH_2CO$), 3.93 (m, 1 H, –CH–); IR (KBr) 3300 (ν_{N-H}), 2978, 2940, 1725 ($\nu_{C=O}$ ketone), 1650 ($\nu_{C=O}$ amide), 1550 ($\nu_{C=O}$ amide) cm^{-1}. Anal. Calcd for $C_8H_{15}NO_2$ (MW = 157.2): C, 61.12; H, 9.62; N, 8.91. Found: C, 60.68; H, 9.70; N, 8.67.

***N*-Acetylacetoacetamide (5g).** A modified literature method[13] was employed. A solution of acetamide (8 g, 135.4 mmol) and 2,2,6-trimethyl-1,3-dioxin-4-one (20.50 g, 144.2 mmol) in dry xylene (135 mL) was refluxed for 30 min. The solvent was then evaporated. The residual solid was recrystallized (Et_2O/CH_2Cl_2) to yield **5g** (11.5 g, 59%): mp = 88 °C (lit.[13] mp = 84–86 °C); ^1H NMR (60 MHz, $CDCl_3$) δ 2.0 (s, $CH_3C(OH)$ enol), 2.20 (s, 3 H, CH_3CONH), 2.25 (s, 3 H, CH_3CO), 3.78 (s, 2 H, $COCH_2CO$), 5.77 (s, H vinyl), 9.50 (m, 1 H, NH), 16.4 (m, OH); IR (KBr) 3274 (ν_{N-H}), 3180, 1741, 1723, 1700 ($\nu_{C=O}$ amide I), 1510, 1530 ($\nu_{C=O}$ amide II) cm^{-1}. Anal. Calcd for $C_6H_9NO_3$ (MW = 143,14) C, 50.34; H, 6.34; N, 9.78; O, 33.53. Found: C, 50.78; H, 6.40; N, 9.98; O, 33.19.

Hantzsch Amides 3. A modification of the method of Duburs[15] was employed.

1,4-Dihydro-2,6-dimethyl-3,5-bis(aminocarbonyl)pyridine (3a). A suspension of acetoacetamide **5a** (6 g, 60 mmol), hexamethylenetetramine (4 g, 28.5 mmol), NH_4OAc (3 g, 38.9 mmol), and deaerated water (15 mL) was heated for 15 min at 80 °C under a stream of N_2. A voluminous yellow solid precipitated. The mixture was cooled in an ice bath, and the solid was collected by filtration through a fritted Schlenk tube. It was then washed with cold deaerated water and was dried in vacuo at 70 °C to yield **3a** (1.7 g, 30%): mp > 260 °C; ^1H NMR (80 MHz, DMSO-d_6/HMDS) δ 2.60 (s, 6 H, 2- and 6-Me), 3.25 (s, 2 H, H-4), 7.50 (m, 4 H, NH_2); IR (KBr) 3523, 3453, 3343 (ν_{N-H} amide and pyridine); 1668 ($\nu_{C=O}$), 1626, 1592 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3O_2$ (MW = 196.02): C, 55.14; H, 6.68; N, 21.44; O, 16.32. Found: C, 55.58; H, 6.73; N, 21.50; O, 16.97.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (3b). In the manner described above, amide **5b** (1.5 g, 10.7 mmol), after reaction for 30 min, yielded 2 g (54%) of **3b**: mp = 219–221 °C; ^1H NMR (80 MHz, DMSO-d_6/HMDS) δ 2.05 (s, 6 H, 2- and 6-Me), 2.65 (d, J = 4 Hz, 6 H, MeN), 3.10 (s, 2 H, H-4), 6.96 (d, J = 4 Hz, 2 H, MeNH), 7.40 (s, 1 H, NH pyridine); IR (KBr) 3363, 3273 (ν_{N-H} amide and pyridine), 1670 ($\nu_{C=O}$), 1592, 1530 cm^{-1}. Anal. Calcd for $C_{11}H_{17}N_3O_2$ (MW = 224.07): C, 58.96; H, 7.65; N, 18.75; O, 14.28. Found: C, 59.17; H, 7.67; N, 18.50; O, 14.90.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(isopropylamino)carbonyl]pyridine (3c). In the same manner described above, the amide **5c** (2.9 g, 20 mmol), after reaction for 1 h at 80 °C, yielded **3c** (2.3 g, 77%): mp = 155 °C dec; ^{H} NMR (80 MHz, DMSO-d_6 δ 1.1 (d, 12 H, J = 6 Hz, CH_3CHCH_3), 1.98 (s, 6 H, 2- and 6-Me), 3.08 (s, 2 H, CH_2-4), 4.00 (m, 2 H, CH_3CHCH_3), 6.82 (d, 2 H, NHCO), 7.3 (s, 1 H, NH); IR (KBr) 3462, 3309, 3271 (ν_{N-H}), 1679, 1390, 1384, 1170, 1140 (δ *gem*-dimethyl) cm^{-1}; UV 357.0 (ε = 8.54 × 10^3), 243.5 (ε = 9.6 × 10^3) nm. Anal. Calcd for $C_{15}H_{25}N_3O_2 \cdot H_2O$ (MW = 297.42): C, 60.57; H, 9.15; N, 14.13; O, 16.14. Found: C, 59.96; H, 9.00; N, 13.97; O, 17.27.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(*sec*-butylamino)carbonyl]pyridine (3d). In the manner described above, amide **5d** (2.9 g, 20 mmol), after reaction for 45 min at 90 °C, yielded **3d** (1.2 g, 62%): mp = 180 °C dec; IR (KBr) 3280, 1680, 1637 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 0.62–1.62 (m, 16 H, CH_3CHCH_2), 1.95 (s, 6 H, 2- and 6-Me), 3.1 (s, 2 H, H-4), 3.5–4.0 (m, 2 H, CH), 6.75 (d, 2 H, NHCO), 7.25 (s, 1 H, NH). Anal. Calcd

(18) Ohno, A.; Ishihara, Y.; Ushida, S.; Oka, S. *Tetrahedron Lett.* **1982**, *23*, 3185.

(19) Ohno, A. Mechanistic Considerations of Biomimetic Asymmetric Reduction. *Asymmetric Reactions and Processes in Chemistry*; ACS Symposium Series; American Chemical Society: Washington, DC, 1982; Vol. 185, p 219.

(20) Seyden-Penne, J. *Réductions par les Alumino- et Borohydrures en Synthèse Organique*; TecDoc Lavoisier: Paris, 1988.

(21) Friedlander, M. *J. Org. Chem.* **1964**, *29*, 2895.

for $C_{17}H_{29}N_3O_2 \cdot H_2O$ (MW = 325.45): C, 62.73; H, 9.60; N, 12.91; O, 14.74. Found: C, 62.89; H, 9.40; N, 12.60; O, 13.74. Because the starting amide **5d** is racemic, the product is a mixture of stereoisomers which could not differentiated by either TLC or ^1H NMR.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(phenylamino)carbonyl]pyridine (3e). In the manner described above, amide **5e** (10.6 g, 60 mmol), after reaction for 10 min at 80 °C, yielded **3e** (1.2 g, 83%): mp = 210–215 °C (lit.[22] mp = 220–225 °C). Anal. Calcd for $C_{21}H_{21}N_3O_2 \cdot H_2O$ (MW = 365.42): C, 69.04; H, 6.30; N, 11.51; O, 13.15. Found: C, 68.61; H, 6.20; N, 11.51; O, 12.99. The anhydrous product was obtained by the azeotropic distillation of a toluene suspension of the monohydrate under N_2. Anhydrous **3e**: mp = 232–234 °C; ^1H NMR (80 MHz, DMSO-d_6) δ 2.03 (s, 6 H, 2- and 6-Me), 3.45 (s, 2 H, 4-H), 7–7.9 (m, 11 H, aromatic H + NH pyridine), 9.22 (s, 2 H, NH amide); IR (KBr) 3432, 3341, 3253, 3220 (ν_{N-H}), 1673 ($\nu_{C=O}$), 1625, 1593, 1522, 1495, 1436, 752, 697 (δ_{Ar-H}) cm^{-1}; (UV) 369.5 ($\epsilon = 1.02 \times 10^4$), 266.5 ($\epsilon = 2.38 \times 10^4$) nm. Anal. Calcd for $C_{21}H_{21}N_3O_2$ (MW = 347.40): C, 72.60; H, 6.09; N, 12.10; O, 9.21. Found: C, 72.80; H, 6.06; N, 12.01; O, 9.50.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(*o*-anisylamino)carbonyl]pyridine (3f). In the manner described above, amide **5f** (0.67 g, 4.8 mmol), after reaction for 1 h at 80 °C, yielded **3f**. The product was precipitated from the cooled reaction mixture by the addition of cold aqueous EtOH and was then dried to yield **3f** (0.38 g, 57%): mp 89–91 °C; ^1H NMR (80 MHz, DMSO-d_6) δ 2.18 (s, 6 H, 2- and 6-CH_3), 3.45 (s, 2 H, CH_2-4), 3.88 (s, 6 H, OCH_3), 6.75–7.25 and 8.04 (8 H, ArH), 7.92 (s, 1 H, NH), 8.18 (2 H, s, CONH); IR (KBr) 3432, 3395, 3290, 1677, 1600, 1524, 1484, 1459 ($\nu_{C=C}$ Ar and δ_{Ar-H}), 750 (δ_{Ar-H}) cm^{-1}. Anal. Calcd for $C_{23}H_{25}N_3O_4 \cdot {}^1/_2H_2O$ (MW = 416.46): C, 66.33; H, 6.29; N, 10.09; O, 17.29. Found: C, 66.62; H, 6.38; N, 9.96; O, 17.19.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(acetylamino)carbonyl]pyridine (3g). In the manner described above, amide **5g** (8 g, 55.9 mmol), after reaction in water for 70 min at 95 °C, yielded **3g** (4.1 g, 52%): mp 198–200 °C; ^1H NMR (80 MHz, DMSO-d_6) δ 2.10 (s, 6 H, CH_3CO), 2.30 (s, 6 H, 2- and 6-Me), 3.26 (s, 1 H, pyridine NH), 3.32 (s, 2 H, 4-H), 8.29 and 9.72 (bs, 2 H, imide NH and enolic H); IR (KBr) 3327 (ν_{N-H}), 1734, 1688, 1664, 1639, 1610 ($\nu_{C=O}$) cm^{-1}; UV 393 ($\epsilon = 1.02 \times 10^4$), 281.5 ($\epsilon = 1.13 \times 10^4$, 232.5 ($\epsilon = 1.68 \times 10^4$) nm. Anal. Calcd for $C_{13}H_{17}N_3O_4$ (MW = 279.3): C, 55.9; H, 6.14; N, 15.04; O, 22.92. Found: C, 55.18; H, 6.09; N, 14.88; O, 23.45.

1,4-Dihydro-2,6-dimethyl-3,5-bis[(phenylamino)carbonyl]-4-(*p*-methoxyphenyl)pyridine (3h). A solution of acetoacetanilide (4.4 g, 24.6 mmol), 20% aqueous NH_3 (1.2 mL, 30 mmol), *p*-methoxybenzaldehyde (1.7 g, 12.7 mmol), and 20 mL of EtOH was refluxed for 6 h under an atmosphere of N_2. The solution was partially concentrated in vacuo. Then, it was cooled and was poured into excess water. The solid that precipitated was collected by filtration under N_2. It was dissolved in DMF (5 mL) and was again precipitated from solution by the addition of water (20 mL). The precipitate was collected and dried in vacuo to yield 2.45 g (45%) of **3h**: mp 240–242 °C; ^1H NMR (80 MHz, DMSO-d_6) δ 2.15 (s, 6 H, 2- and 6-Me), 3.70 (s, 3 H, MeO), 5.07 (s, 1 H, NH pyridine), 6.7–7.8 (m, 14 H, Ar), 9.25 (s, 2 H, NH amide). IR (KBr) 3293 (ν_{N-H}), 1652 ($\nu_{C=O}$), 1594, 1504, 1490, 1432 ($\nu_{C=C}$ Ar and δ_{C-H}), 833, 746, 682 (δ_{Ar-H}) cm^{-1}. Anal. Calcd for $C_{28}H_{27}N_3O_3$ (MW = 453.52): C, 74.17; H, 5.96; N, 9.27; O, 10.59. Found: C, 73.74; H, 6.07; N, 9.02; O, 10.24.

2,6-Dimethyl-3,5-bis[(phenylamino)carbonyl]pyridine (4e). A solution of chloranil (0.28 g, 1.2 mmol) in benzene (5 mL) was added to a solution of **3e** (0.44 g, 1.13 mmol) in benzene (50 mL). The mixture was heated for 15 min at 70 °C. Then, it was filtered while still hot: mp > 260 °C dec; ^1H NMR (80 MHz, DMSO-d_6) δ 2.67 (s, 6 H, CH_3), 7.6 (m, 12 H, aromatic H), 9.32 (s, 2 H, CONH).

General Procedure for the Reductions. The reductions were performed on a millimolar scale in small glass vessels which were opaque to UV light. The vessels was charged with the NADH model, the catalyst, and the substrate. The ratio was 1.5:1.5:1.5. Then, the GLC internal standard and a small magnetic stirrer were introduced. The vessel was closed with a rubber septum and was connected to a vacuum line, whereupon it was purged several times with N_2. The solvent (5 mL) was then injected through the septum. The progress of the reduction was monitored by GLC. Samples were withdrawn at regular intervals and were quenched by adding an equal volume of 5% methanolic HCl and a drop of DMF before analysis.

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Registry No. **2a**, 17438-14-1; **2b**, 91645-64-6; **3a**, 56401-26-4; **3b**, 138571-03-6; **3c**, 138571-04-7; **3d**, 138571-05-8; **3e**, 55275-91-7; **3f**, 138571-06-9; **3g**, 138571-07-0; **3h**, 138571-08-1; **4e**, 55275-98-4; **5a**, 5977-14-0; **5b**, 20306-75-6; **5c**, 41153-91-7; **5d**, 41153-91-7; **5e**, 102-01-2; **5f**, 92-15-9; **5g**, 27091-70-9; NADH, 58-68-4; $C_6H_5CH_2OH$, 100-51-6; $C_6H_5CH(OH)CF_3$, 340-04-5; $CH_3CH(OH)$-pyr, 18728-61-5; $C_6H_5CH(OH)CH_3$, 98-85-1; C_6H_5CHO, 100-52-7; $C_6H_5COCF_3$, 434-45-7; CH_3CO-pyr, 1122-62-9; $C_6H_5COCH_3$, 98-86-2; $Mg(ClO_4)_2$, 10034-81-8; $Zn(ClO_4)_2$, 13637-61-1; $Nd(F_6acac)_3$, 47814-18-6; $La(F_6acac)_3$, 14640-64-3; $Eu(fod)_3$, 17631-68-4; $ZnCl_2$, 7646-85-7; methyl benzoylformate, 15206-55-0; methyl mandelate, 771-90-4.