Synthetic Methods

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Catalyzed Dehydrogenative Coupling of Primary Alcohols with Water, Methanol, or Amines**

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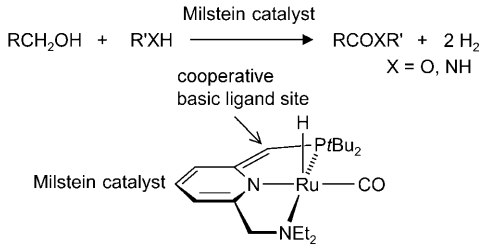
Fossil resources (petroleum, natural gas, coal) are widely used for the production of basic organic chemicals.[1] This increasingly limited feedstock is at the end of the process in which CO_2 is reduced to hydrocarbons by photosynthesis and subsequent biological and slow geochemical processes [Eq. 1].

$$n\,CO_2 + n\,H_2O + h\nu \rightarrow (CHOH)_n + n\,O_2 \rightarrow (CH_2)_n + 1/n\,O_2 \quad (1)$$

Carbonyl compounds (aldehydes, ketones, carboxylic acids and their derivatives) which are an economically highly important class of organic chemicals, are mostly produced from this oxygen-poor feedstock by oxygenation (oxidation) or carbonylation reactions. For both reaction types a wide range of rather efficient catalysts have been developed.[2] Fossil resources need to be replaced by renewable ones which are ideally neutral in CO_2 consumption/production.[3] Plant biomass, containing compounds with a relatively high oxygen content (sugars and other polyalcohols), is a rapidly renewable feedstock and uses sun light as an energy source for its formation. New catalysts and catalytic systems are needed to convert this biomass into fine-chemicals. Milstein et al. recently reported a Ru^{II} complex having a "dearomatized" aminomethyl phosphinomethyl pyridine as a pincer ligand (Scheme 1), which allowed the dehydrogenative coupling (DHC) of primary alcohols to give symmetrical esters[4] and of alcohols and amines to give amides (Scheme 1).[5] In this highly chemoselective reaction, a hydrogen acceptor is not needed and the ligand plays an active role in the hydrogen abstraction and liberation process



Scheme 1. Dehydrogenative coupling promoted by the Milstein catalyst. No hydrogen acceptor is required.

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(cooperative ligand).[6] However, the reaction requires elevated temperatures (> 100 °C) to achieve high yields of the products (> 90 %). We report herein an alternative approach which allows the chemoselective, homogeneously catalyzed DHC of primary alcohols with water, methanol, or amines to give carboxylic acids, methyl esters, or amides, respectively. The products are organic chemicals of key importance and are produced under very mild reaction conditions. The reaction can be performed such that the requisite hydrogen acceptor **A** is quantitatively regenerated with hydrogen peroxide, H_2O_2, in a second catalytic reaction. Hence the net reaction is [Eq. 2]:

$$RCH_2OH + R^1XH + 2\,H_2O_2 \rightarrow RCO(XR^1) + 4\,H_2O \quad (2)$$

Recently we described the synthesis of the rhodium(I)/diolefin amido complex $[Rh(trop_2N)(PPh_3)]$ (**2**) ($trop_2N$ = bis(5-H-dibenzo[a,d]cyclohepten-5-yl)-amide). The structure of this compound strongly deviates from the expected planar form of a tetra-coordinated ML_4 complex ($M = d^8$ metal center, $L = 2$ electron donor ligand) with a 16 valence electron configuration. Instead a saw-horse-type structure is created by the combination of two π-acceptor olefinic binding sites, and an amido and phosphane σ-donor groups each placed in a *trans*-position. As a result, the amido function is Lewis basic (the highest occupied orbital (HOMO) is localized on the N center) and the adjacent rhodium center is Lewis acidic (the lowest unoccupied orbital (LUMO) is localized on the metal center) (Figure 1). Because of this special electronic situation, **2** easily cleaves H_2 heterolytically across the Rh–N bond and is a catalyst for the hydrogenation of unsaturated compounds $R_2C{=}X$ (X = O, NR′).[7] Furthermore, complex **2** catalyzes the transfer hydrogenation of ketones and activated olefins, using ethanol as a (renewable) hydrogen source, with high efficiency.[8] Calculations indicated that in this reaction amido complex **2** not only serves as catalyst for dehydrogenation of ethanol to acetaldehyde, but also catalyzes the irreversible coupling of this aldehyde with another equivalent of ethanol to give ethylacetate.

The unprecedented activity of a catalyst for this type of reaction led us to investigate the possibility of using **1** as a catalyst for the DHC of primary hydroxy groups in compounds **4**–**14** with water, methanol, or amines to furnish carboxylic acids, methyl esters, or amides, respectively. Because the amido complex **2** is air-sensitive, it was generated in situ using an alkoxide or hydroxide base and the stable $[Rh(trop_2NH)(PPh_3)]^+$ ($CF_3SO_3^-$) (**1**). A simplified catalytic cycle is shown in Scheme 2. We chose cyclohexanone (cHexO) as the hydrogen acceptor **A** because a) it has a high heat of hydrogenation (18.4 kcal mol^{-1} versus 16.6 kcal

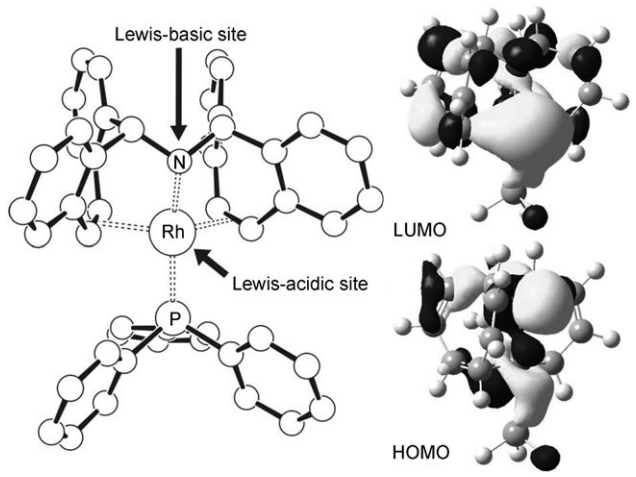
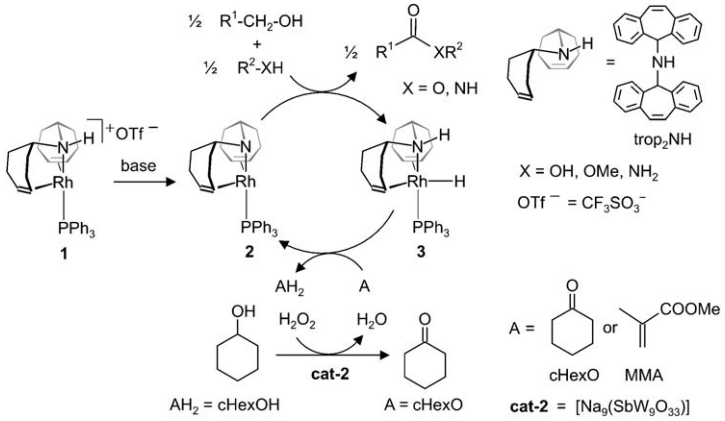


Figure 1. Structure of **2** indicating the Lewis acidic and basic sites. Plots of the DFT calculations of the HOMO and LUMO.[7]



Scheme 2. Simplified catalytic cycle with **2** as the catalyst or **1** as the catalyst precursor for the dehydrogenative coupling (DHC) of variously functionalized primary alcohols with water, methanol, or amines.

mol^{-1} for acetone which is commonly used as hydrogen acceptor[9]) and b) more importantly, it can be easily and almost quantitatively recycled from cyclohexanol (cHexOH) with diluted aqueous hydrogen peroxide (3%) in the presence of 0.1 mol% $[Na_9(SbW_9O_{33})]$ (**cat-2**).[10] Alternatively, methylmethacrylate (MMA) is a suitable hydrogen acceptor **A**, especially for the syntheses of methyl esters[11] and amides **27**–**31** (Table 1). A high reaction rate and catalytic turn over was achieved under mild reaction conditions ($T \leq 25\,°C$). In the synthesis of the acids (or their sodium salts) **15**–**23**, a biphasic reaction mixture is obtained wherein the sodium salts of the carboxylic acids dissolve in the aqueous phase, and can be conveniently isolated after the reaction is complete. The easily separable organic phase consists of cyclohexanol and cyclohexanone, and is recycled using H_2O_2/**cat-2**. Various aryl and alkyl alcohols can be converted and a variety of functional groups, such as methoxy or methylthio groups (**16** or **17**), C=C double bonds (**9**), or epoxy functional groups (**14**) are tolerated. Especially remarkable is the highly chemoselective DHC of polyalcohols **10**–**13** that proceed without the need to use protecting group strategies.[12] For example, 2,3-dihydroxy-propanoic acid (**23**) was isolated as its calcium salt as the sole product of the DHC reaction (the relatively low yield is due to the difficulty in extracting the product from the aqueous phase). Methylesters such as **24** or **25** were obtained efficiently after the DHC of geraniol (**9**) or 4-thiomethyl benzyl alcohol (**6**), respectively, with methanol in the presence of cHexO or MMA as the hydrogen acceptor **A**.[13] Especially remarkable are the dehydrogenative coupling reactions with ammonia, which lead to the isolation of amides **26**–**29** in very high yields. Sterically demanding primary amines like isopropylamine can be employed, but secondary amines do not react. Double DHCs are possible as demonstrated for 1,3-propanediol (**11**) which is quantitatively converted into the bis(amide) **33**. The DHC between the epoxy alcohol glycidol (**14**), readily available through dehydration of glycerin, and benzylamine leads almost quantitatively to the crystalline β-amino-α-hydroxy-amide **34**.

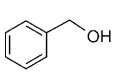
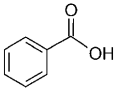
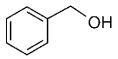
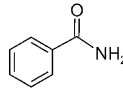
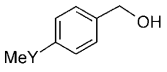
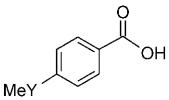
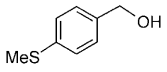
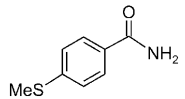
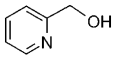
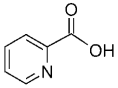
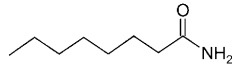
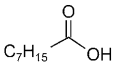
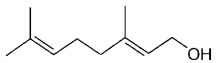
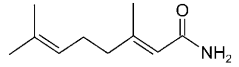
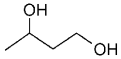
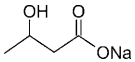
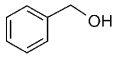
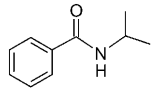
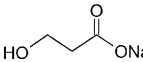
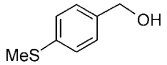
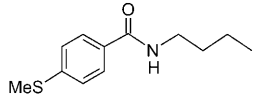
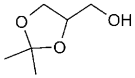
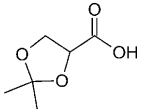
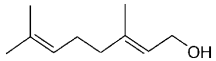
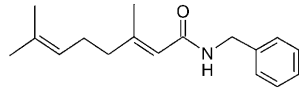
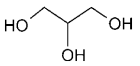
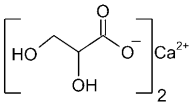
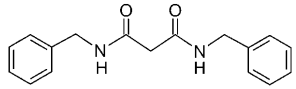
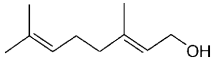
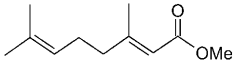
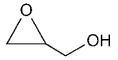
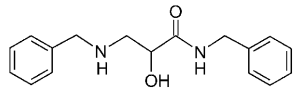
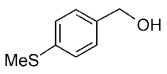
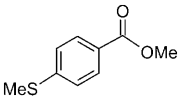
By using simplified model complexes **a**–**j** (the benzo groups of the $trop_2N$ ligand were omitted and the phenyl groups on PPh_3 in **2** were replaced by hydrogen atoms) the role of **2** as the catalyst in the mechanism of a model DHC reaction [Eq. 3] was

$$H_3CCH_2OH + H_2O + \mathbf{2a} \rightarrow H_3CCOOH + \mathbf{2e} \qquad (3)$$

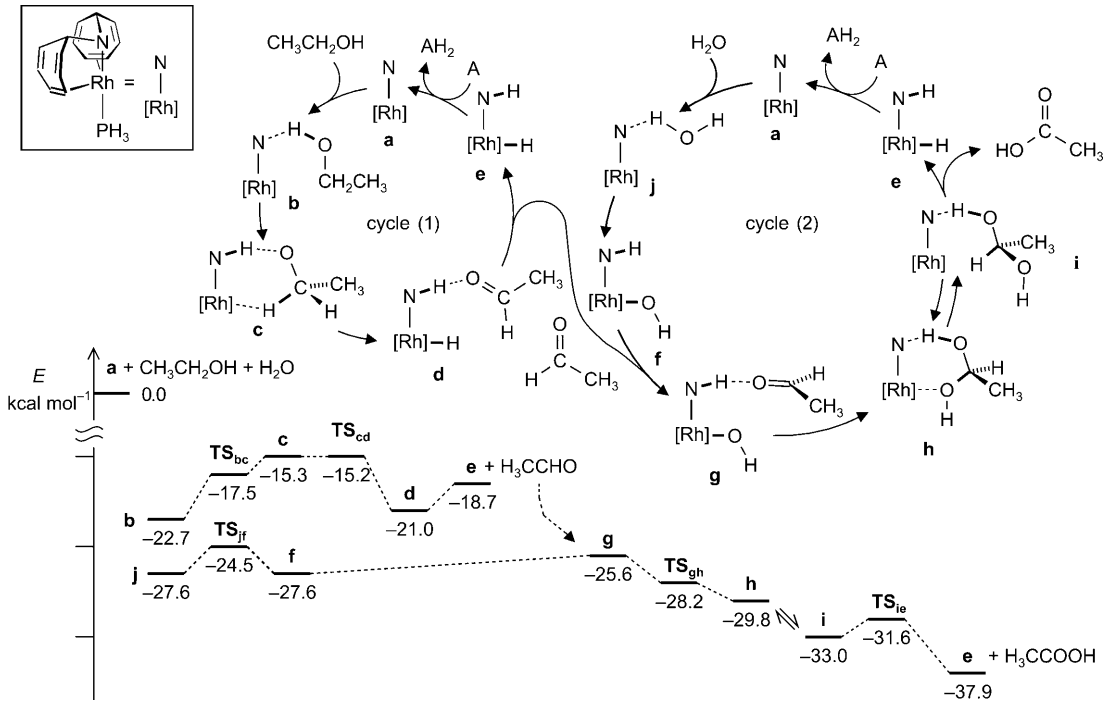
studied by using density functional theory (DFT) calculations, specifically the B3PW91 level of theory as it is implemented in the GAUSSIAN 03 program suite (Scheme 3).[14] Amido complex **a** reacts exothermically either with ethanol or water (Scheme 3) to give adducts **b** and **j**, respectively. The former is converted, by a Noyori-type mechanism[15] via the intermediates **c** and **d**, into the amino hydride **e** and acetaldehyde. In the water adduct **j**, one O–H bond is broken to give the amino hydroxide complex **f** to which acetaldehyde is bonded to give **g**. In this adduct, the acetaldehyde molecule is activated and held in proximity to the hydroxide by an NH···O=CHMe hydrogen bridge, which then attacks the carbonyl group to form the hemiacetal complex **h**. The latter may easily rearrange into the isomer **i**, which has (like intermediate **c**) the correct conformation for the concerted heteropolar H_2 transfer from the NH^+ and CH^- groups to give the amino hydride **e** and the final acetic acid product. In the reaction with the hydrogen acceptor **A**, the amino hydride **e** is converted into the amide **a** and the catalytic cycle restarts.[16] The calculated energies of the transition-state $\mathbf{TS_{jf}}$ for the cleavage of the O–H bond in **j**, and $\mathbf{TS_{ie}}$ for the hydrogen transfer in **i** are very low (≤ 3 kcal mol^{-1}). At the level of theory employed and with the inclusion of the zero-point energy (ZPE), the transition-states $\mathbf{TS_{bc}}$, $\mathbf{TS_{cd}}$, and $\mathbf{TS_{gh}}$ are even lower in energy than one of the intermediates to which they are connected. Whereas this is not meaningful, it indicates that the minimum energy reaction pathways (MERPs) are flat in this region and the activation barriers are very low. We estimate that the highest barrier in this multistep reaction is approximately 8 kcal mol^{-1}, which corresponds to the energy difference between **b** and **c**.

Although we cannot exclude that the intermediates $R^1CH(OH)(XR^2)$ ($XR^2 = OH$, OMe, NHR^3) are also

Table 1: Dehydrogenative coupling of primary alcohols with H_2O, MeOH, or $R'NH_2$ using complex **1** as the catalyst precursor or **2** as the catalyst.

Entry	Substrate		Product		Reagent/ time	Yield [%]	Entry	Substrate		Product		Reagent/ time	Yield [%]
1		**4**		**15**	H_2O/2 h	94[a]	11		**4**		**26**	NH_3/4 h	94[d]
2		**5** (Y = O) **6** (Y = S)		**16** **17**	H_2O/4 h	88[a] 86[a]	12		**6**		**27**	NH_3/4 h	92[d]
3		**7**		**18**	H_2O/4 h	96[a]	13	$(H_{15}C_7)CH_2OH$	**8**		**28**	NH_3/4 h	94[d]
4	$(H_{15}C_7)CH_2OH$	**8**		**19**	H_2O/4 h	89[a]	14		**9**		**29**	NH_3/4 h	82[d]
5		**10**		**20**	H_2O/ 12 h	67[a]	15		**4**		**30**	$iPrNH_2$/ 4 h	93[d]
6		**11**		**21**	H_2O/ 12 h	72[a]	16		**6**		**31**	$nBuNH_2$/ 4 h	93[d]
7		**12**		**22**	H_2O/ 12 h	89[a]	17		**9**		**32**	$BnNH_2$/ 4 h	89[d]
8		**13**		**23**	H_2O/ 12 h	63[a]	18		**11**		**33**	$BnNH_2$/ 4 h	90[d]
9		**9**		**24**	MeOH/ 20 min	79[b] (91)[c]	19		**14**		**34**	$BnNH_2$/ 4 h	86[d]
10		**6**		**25**	MeOH/ 4 h	86[b] (94)[c]							

[a] **1** (0.1 mol%), H_2O (66 equiv), NaOH (1.2 equiv), cyclohexanone (5 equiv), $T = 25\,^{\circ}C$; [b] **1** (0.1 mol%), methanol (10 equiv), K_2CO_3 (5 mol%), cyclohexanone (5 equiv), $T = 0\,^{\circ}C$; [c] Slightly better yields are obtained with MMA (3 equiv) as hydrogen acceptor **A**, **2** (0.1 mol%), methanol (10 equiv), $-30 \rightarrow 25\,^{\circ}C$; [d] **2** (0.2 mol%), R^2NH_2 (1.5 equiv), MMA (3 equiv), $-30 \rightarrow 25\,^{\circ}C$.



Scheme 3. Energy diagrams for the reaction mechanism of the conversion of ethanol and water into acetic acid promoted by the model complex **a**.

formed from aldehyde intermediates (R^1CHO and R^2XH) in the nonmetal assisted reactions, the calculations for the model reaction strongly imply that all transformations are efficiently catalyzed by the amido complex [Rh(trop$_2$N)(PPh$_3$)] (**2**). This assertion is additionally bolstered by the observation that **2** catalyzes the reaction between benzaldehyde and MeOH with unmatched efficiency to give methyl benzoate and benzyl alcohol.[17]

Importantly, the amido ligand in **2** is a cooperative ligand actively participating in a reversible manner in the catalytic cycles leading to compounds **15**–**34**. Many methods are available for the syntheses of carboxylic acids, esters, and amides, but dehydrogenative coupling reactions are less common. The reactions described herein nicely complement the DHC reactions reported by Milstein et al. which do not require a hydrogen acceptor **A**. Our method is also advantageous because of the mild reaction conditions, low catalyst loadings, functional group tolerance, simple protocols, easy workup, and especially the chemoselectivity. The proposed reaction mechanism may contribute to the development of a better understanding of the catalytic conversion of readily available, low-cost materials from biomass into valuable fine chemicals. Emphasizing the role of the cooperative amido ligand may help to replace the expensive rhodium center with cheaper metals, an important goal yet to be achieved.

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[1] K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*, 4th compl. rev.ed., Wiley-VCH, Weinheim, **2003**.
[2] See for example: M. Beller, C. Bolm, *Transition metals for Organic Syntheses*, Wiley-VCH, Weinheim, **2004**.
[3] N. Armaroli, V. Balzani, *Angew. Chem.* **2007**, *119*, 52; *Angew. Chem. Int. Ed.* **2007**, *46*, 52.
[4] a) J. Zhang, M. Gandelman, L. J. W. Shimon, H. Rozenberg, D. Milstein, *Organometallics* **2004**, *23*, 4026; b) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840; for catalytic systems capable of dehydrogenating alcohols to symmetrical esters in the presence of a suitable hydrogen acceptor, see: c) Y. Blum, Y. Shvo, *J. Organomet. Chem.* **1985**, *282*, C7; d) Y. Blum, Y. Shvo, *J. Organomet. Chem.* **1984**, *263*, 93; e) S. I. Murahashi, T. Naota, K. Ito, Y. Maeda, H. Taki, *J. Org. Chem.* **1987**, *52*, 4319; f) T. Suzuki, K. Morita, M. Tsuchida, K. Hiroi, *Org. Lett.* **2002**, *4*, 2361; g) R. H. Meijer, G. Ligthart, J. Meuldijk, J. Vekemans, L. A. Hulshof, A. M. Mills, H. Kooijman, A. L. Spek, *Tetrahedron* **2004**, *60*, 1065; h) T. Suzuki, T. Yamada, T. Matsuo, K. Watanabe, T. Katoh, *Synlett* **2005**, 1450; for a recent example with oxygen as the hydrogen acceptor, see i) S. Arita, T. Koike, Y. Kayaki, T. Ikariya, *Chem. Asian. J.* **2008**, *3*, 1479.
[5] C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790.
[6] H. Grützmacher, *Angew. Chem.* **2008**, *120*, 1838; *Angew. Chem. Int. Ed.* **2008**, *47*, 1814.
[7] P. Maire, T. Büttner, F. Breher, P. Le Floch, H. Grützmacher, *Angew. Chem.* **2005**, *117*, 6477; *Angew. Chem. Int. Ed.* **2005**, *44*, 6318.
[8] T. Zweifel, J. Naubron, T. Büttner, T. Ott, H. Grützmacher, *Angew. Chem.* **2008**, *120*, 3289; *Angew. Chem. Int. Ed.* **2008**, *47*, 3245.
[9] Oxidation potentials of aldehydes and ketones: a) H. Adkins, R. M. Elofson, A. G. Rossow, C. C. Robinson, *J. Am. Chem. Soc.* **1949**, *71*, 3622; for other successful applications of cyclohexanone as hydrogen acceptor, see: b) G. R. A. Adair, J. M. J.

Williams, *Chem. Commun.* **2005**, 5578; c) N. J. Wise, J. M. J. Williams, *Tetrahedron Lett.* **2007**, *48*, 3639.

[10] We refined the protocol given by H. Rohit Ingle, N. K. Kala Raj, P. Manikandan, *J. Mol. Catal. A* **2007**, *262*, 52 and obtained excellent yields (see the Supporting Information for details).

[11] The dehydrogenation of primary alcohols to methyl esters under harsh reaction conditions using crotonitrile was described: N. A. Owston, A. J. Parker, J. M. J. Williams, *Chem. Commun.* **2008**, 624.

[12] R. W. Hoffmann, *Synthesis* **2006**, 3531.

[13] This coupling reaction proceeds with high efficiency because catalyst **2** converts methanol very slowly into methylformate. The initial step, the dehydrogenation of MeOH into formaldehyde, is significantly thermodynamically less favorable than the dehydrogenation of higher alcohols (RCH_2OH), to their corresponding aldehydes (see also reference [7]).

[14] R. D. Gaussian 03, M. J. Frisch et al., see the Supporting Information.

[15] R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931.

[16] The mechanism of the reaction between the amino hydride **e** and hydrogen acceptor **A** is simply given by the counter-clockwise reading of the catalytic cycle, that is, **e**→**d**→**c**→**b**→**a** in Scheme 3.

[17] The reaction: $2\,PhCH{=}O + MeOH \rightarrow PhCO(OMe) + PhCH_2OH$ is catalyzed by 0.001 mol% **1** in the presence of a small amount K_2CO_3 (1 mol%) and is complete in 10 minutes at room temperature. Benzaldehyde (3 M) in MeOH was used. One equivalent of benzaldehyde served as the hydrogen acceptor.

