

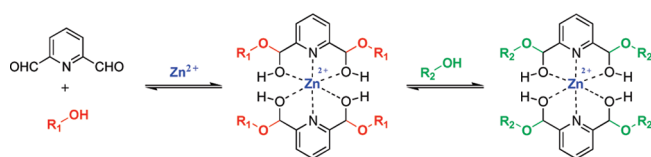
Hemiacetals in Dynamic Covalent Chemistry: Formation, Exchange, Selection, and Modulation Processes

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A reversible formation of hemiacetals represents a useful tool in covalent dynamic chemistry. Heterocyclic hemiacetals can be stabilized effectively via either protonation or metal cation coordination. The resulting hemiacetal systems are highly dynamic, show fast response, and display component selection.

Chemical entities of molecular or supramolecular nature may adapt their constitution in response to physical or chemical effectors by exchange, incorporation, exclusion, or reorganization of their components via formation or breaking of reversible covalent bonds or of noncovalent interactions, respectively. Such behavior defines constitutional dynamic chemistry (CDC) on both the supramolecular and molecular levels.¹ The latter represents a dynamic covalent chemistry (DCC)^{2,3} and rests on the introduction into molecules of bonds formed through reversible chemical reactions. It has exploited mainly the use of imine and disulfide functional groups, although some other functions have also been investigated.^{2,3} To broaden the scope of DCC, it is necessary to explore other reversible reactions presenting controllable formation efficiency and exchange kinetics.

We present here some of our results on the implementation of hemiacetals as the functional group of interest for DCC. Hemiacetals are formed from the reversible condensation of alcohols with a carbonyl group. Generally, they are rather unstable species, forming in only very small amounts, except when they are stabilized by structural effects as in the cyclic carbohydrates.^{4,5} On the other hand, they may be expected to present fast exchange kinetics, thus allowing a rapid establishment of the equilibrium dynamic library. A major task is thus to search for means of increasing and controlling their formation.

Building on the fact that nucleophilic addition to the carbonyl group increases in the presence of electron-withdrawing units, we have explored the reactions of alcohols with aldehydes of nitrogen heterocycles, in particular pyridine and pyrimidine. Such electron-deficient groups activate the carbonyl function and furthermore may provide a means to increase hemiacetal formation by protonation or metal cation coordination at the nitrogen site. In addition, the hemiacetals formed may also be stabilized by H-bonding between the OH group and the neighboring nitrogen in the heterocyclic ring. We now report some of our results on hemiacetal formation between the heterocyclic aldehydes **1–3** and various alcohols, in the absence as well as in the presence of added protons or metal ions. The processes involved are represented in Schemes 1–3. Some significant results are listed in Tables 1–4. They lead to the following comments.

1. Hemiacetal Formation from Heterocyclic Aldehydes and Alcohols. We first investigated, by proton NMR, hemiacetal formation from pyridine-2-carboxaldehyde (**1**) and various alcohols in chloroform. Pyridine-2,6-dicarboxaldehyde (**2**) and 2-phenylpyrimidine-4,6-dicarboxaldehyde (**3**) may be expected to be more reactive than **1**. Scheme 1 represents the different compounds and equilibria involved. Primary alcohols yield a small amount of hemiacetal, which increases with equivalents of alcohol added in chloroform solutions (Table 1).

For instance, 1-butanol (6 equiv) produces up to 11% hemiacetal with **1** ($0.15 \text{ mol} \cdot \text{dm}^{-3}$) in chloroform at room temperature. With more reactive difunctional aldehydes such as **2** and the even more reactive **3**, the amount of hemiacetals in the equilibrated solutions can reach 43% and 56% (monohemiacetals) and 1% and 27% (bis-hemiacetals), respectively. The less nucleophilic 2-methoxyethanol affords just a trace amount of the hemiacetal with **1**, and 3% of the monohemiacetal of **2**, whereas **3** yields almost the same results as with 1-butanol. A mixture of 1-butanol and 2-methoxyethanol (6 equiv of each) with **1** gives 11% of **4a** and 5% of **4b**. The sterically more demanding secondary alcohol 2-propanol forms just a trace amount of hemiacetal with the tested pyridine aldehydes. No hemiacetals were observed with the tertiary alcohol *t*-BuOH or with phenol.

2. Effect of Protonation on Hemiacetal Formation. Addition of acid enhances markedly the formation of the hemiacetals. Protonation at nitrogen should increase the

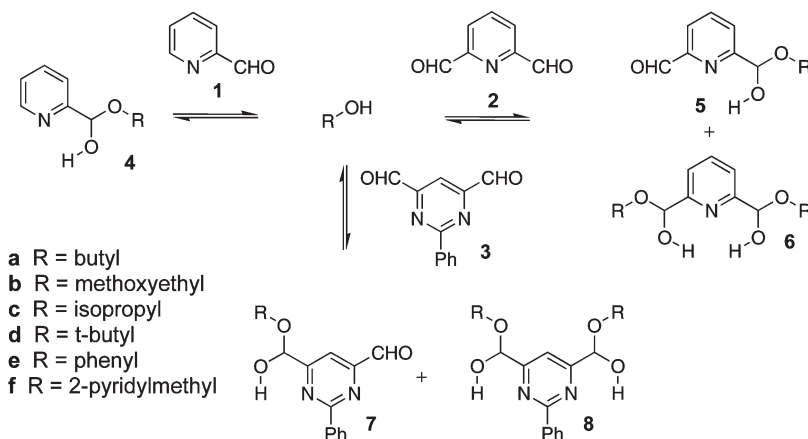
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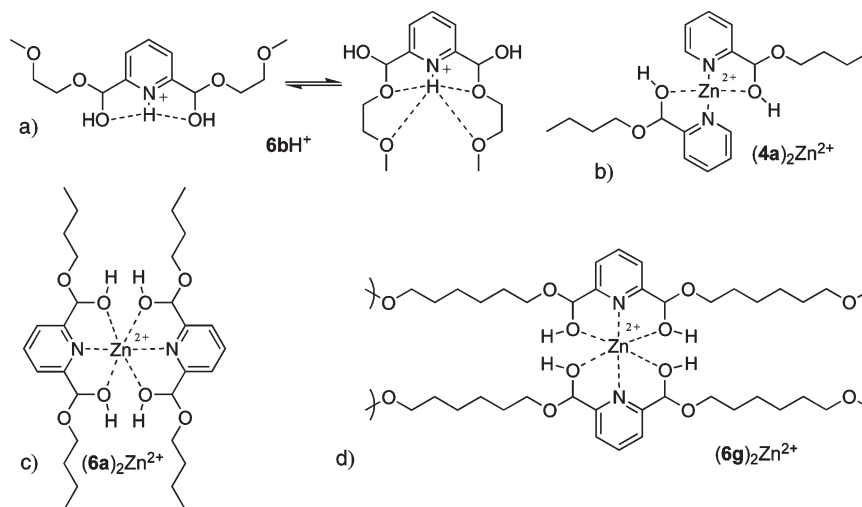
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(5) Hemiaminals are labile intermediates in imine formation and their use in DCC has been explored recently. They may be stabilized by a synthetic receptor; see: Iwasawa, T.; Hooley, R. J.; Rebek, J. *Science* **2007**, *317*, 493.

SCHEME 1. Formation of Hemiacetals from Alcohols and Heterocyclic Aldehydes^a

^a6 and 8 can in principle be a mixture of D, L, and meso forms.

SCHEME 2. Structures of Hemiacetals^a

^aPart a: Two plausible structures of the protonated bis-hemiacetal **6b**. Part b: Zinc(II) complex of hemiacetal **4a**. Part c: Zinc(II) complex of hemiacetal **6a**. Part d: Oligo/polymeric zinc(II) complex of hemiacetal **6g**.

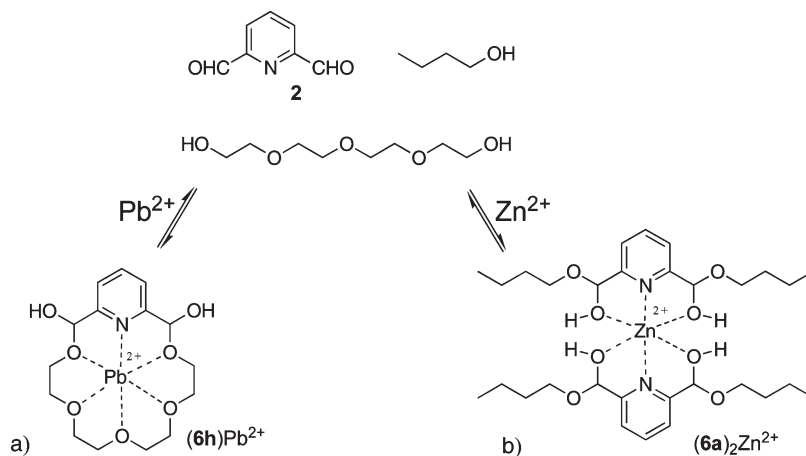
reactivity of the pyridine aldehydes. Indeed, addition of trifluoroacetic acid (TFA) to 1:1 mixtures of the aldehyde **1** and alcohols in chloroform results in greatly increased formation of hemiacetal products (for instance from 3% to 35% for **1** and 1 equiv of 1-butanol in the presence of 1 equiv of TFA), with similar yields for the different alcohols studied (Table 2). An excess of the alcohols (3 equiv) shifts the equilibrium significantly toward hemiacetals (Table S2, SI), but the trend remains the same.

The less basic **2** is less effectively activated compared to **1**. For dialdehyde/alcohol 1:2 ratios, the maximum yields of the hemiacetals do not exceed 37% for both 1-butanol and 2-methoxyethanol (Table 2, middle). 2-Propanol gives only about 8% of bis-hemiacetals. A larger excess of the alcohols (6 equiv) pushes the equilibrium toward the hemiacetals, but the activation is not as strong as for **1** (Table S2b, SI). An interesting effect has been observed in the case of 2-methoxyethanol. The proton NMR spectra of the hemiacetal region show only one sharp singlet of the bis-hemiacetal, whereas the same experiment with 1-butanol gives split signals, in

agreement with the presence of two diastereomeric chiral centers at the hemiacetal carbon atoms. Unless there is an accidental overlap, this means that the monohemiacetal of 2-methoxyethanol **5b** probably induces chirality at the second carbon atom to form the corresponding bis-hemiacetal species **6b** diastereoselectively. A plausible explanation may lie in the interactions of the proton at nitrogen with the oxygen atoms of the two 2-methoxyethanol units (Scheme 2a, **6bH**⁺). Difunctional alcohols (3 equiv), namely diethylenglycol, triethylenglycol, and tetraethylenglycol, form complex mixtures of bis-hemiacetal species with **2**. The yields of the hemiacetals (containing possibly macrocyclic as well as oligo and/or polymeric species as well) are very similar for all the glycols, about 70% in the presence of 8 equiv of TFA. This result points to the possibility of generating highly dynamic covalent polymers.

Protonic amplification of hemiacetal formation is not effective in the case of the relatively reactive and nonbasic aldehyde of **3**. Thus, the sequential addition of TFA to **3** decomposes the hemiacetals formed in favor of the starting

SCHEME 3. Component Selection by Metal Cations



Part a: Lead(II) ions lead to the formation of the macrocycle of tetraethyleneglycol. Part b: Zinc(II) ions yield the bis-dibutoxy hemiacetal complex.

TABLE 1. Equilibrated Solutions of Alcohols with Aldehydes^a

equiv of aOH	ald. (%)			mono-hemiac. (%)			bis-hemiac. (%)	
	1	2	3	4a	5a	7a	6a	8a
1.0	97	87	68	3	13	32		
4.0	92	64	27	8	36	56		17
6.0	89	56	17	11	43	56	1	27
equiv of bOH	ald. (5)			mono-hemiac. (%)			bis-hemiac. (%)	
	1	2	3	4b	5b	7b	6b	8b
1.0	>99	>99	70	<1	<1	29		1
4.0	99	98	29	1	2	52		19
6.0	98	97	18	2	3	50		32

^aCDCl₃ solutions of alcohols aOH and bOH (a = 1-butyl, b = 2-methoxyethyl) with 1, 2, and 3 giving corresponding hemiacetals.

TABLE 2. Proton Modulated Formation of Hemiacetals^a

equiv of TFA-D	ald. (%) + 1 equiv ROH			hemiac. (%)					
	1 + aOH	1 + bOH	1 + cOH	4a	4b	4c			
1.0	65	70	80	35	30	20			
2.0	46	54	66	54	46	34			
5.0	24	28	44	76	72	56			
equiv of TFA-D	diald. (%) + 2 equiv ROH			mono-hemiac. (%)			bis-hemiac. (%)		
	2 + aOH	2 + bOH	2 + cOH	5a	5b	5c	6a	6b	6c
1.0	80	88	93	13	9	7	7	3	
2.0	77	86	92	8	6	5	15	8	3
5.0	64	74	89		6	3	36	20	8
equiv of TFA-D	dial. (%) + 2 equiv ROH			mono-hemiac. (%)		bis-hemiac. (%)			
	3 + aOH	3 + bOH		7a	7b	8a	8b		
0.1	34	40		57	53	9	7		
0.5	42	43		51	51	7	6		
3.0	70	60		30	40				

^aBy deuterated TFA from alcohols ROH (aOH = 1-butanol, bOH = 2-methoxyethanol, cOH = 2-propanol). Hemiacetal formation equilibria of (top) 1 with 1 equiv of ROH, (middle) 2 with 2 equiv of ROH, and (bottom) 3 with 2 equiv of ROH.

dialdehyde (Table 2, bottom). The ratios are very similar for both 1-butanol and 2-methoxyethanol; however, the hemiacetals of the latter show slightly higher stability, possibly due to the higher basicity of 1-butanol compared to 2-methoxyethanol.

3. Effect of Metal Ion Coordination on Hemiacetal Formation. Of particular interest is the fact that the formation and the stabilization of the hemiacetal species also may be

promoted via coordination of metal ions. The activation of the selected aldehydes by Zn²⁺ and Pb²⁺ salts (triflates, trifluoroacetates) has been tested in acetonitrile solution at room temperature. Thus, the hemiacetals are present in the solutions as ionic metal complexes of defined stoichiometry.

Effect of Zinc(II) Coordination. For 1, the most effective activation has been achieved for a 2:1 1/Zn²⁺ ratio. It is comparable to that produced by addition of 1 equiv of TFA

TABLE 3. Effect of Zinc(II) Ions in the Formation of Hemiacetals^a

eq. Zn ²⁺	ald. (%) + 1 eq. ROH				hemiac. (%)							
	1 + aOH	1 + bOH	1 + cOH	1 + dOH	4a	4b	4c	4d				
0.2	67	74	80	94	33	26	20	6				
0.5	59	67	69	92	41	33	31	8				
1.0	68	78	77	99	32	22	23	1				
equiv of Zn ²⁺	diald. (%) + 2 equiv ROH				mono-hemiac.				bis-hemiac.			
	2 + aOH	2 + bOH	2 + cOH	2 + dOH	5a	5b	5c	5d	6a	6b	6c	6d
0.2	40	47	51	76	4				56	53	49	24
0.5	19	30	30	57					81	70	70	43
1.0	18	30	27	50					82	70	73	50

^aROH (aOH = 1-butanol, bOH = 2-methoxyethanol, cOH = 2-propanol, dOH = *tert*-butyl alcohol): (top) **1** with 1 equiv of ROH, (bottom) **2** with 2 equiv of ROH.

TABLE 4. Formation of Hemiacetals with Mixture of Alcohols

equiv of Zn ²⁺	ald. 1 (%)	hemiac. 4a (%)	hemiac. 4b (%)	hemiac. 4c (%)
0.2	62	19	8	11
0.5	5	46	21	28
1.0	5	45	21	29
equiv of TFA-D	ald. 1 (%)	hemiac. 4a (%)	hemiac. 4b (%)	hemiac. 4c (%)
0.5	79	16	3	2
1.0	60	26	9	5
2.0	33	40	17	10

1 with a mixture of alcohols ROH (3 equiv of each, aOH = 1-butanol, bOH = 2-methoxyethanol, cOH = 2-propanol): (top) presence of Zn(II) ions, (bottom) presence of TFA.

(Table 2, top). Further addition of zinc(II) salt decreases the amount of the hemiacetal species. The trend is general for all zinc(II) complexes of the hemiacetals of **1**. An excess of the alcohols shifts the equilibrium toward hemiacetals, but the 2:1 ligand/Zn²⁺ ratio remains the optimal one. The reactivity of the alcohols has been found in the expected order: 1-butanol > 2-methoxyethanol > 2-propanol > *tert*-butyl alcohol (Table 3, top). 2-Pyridylmethanol yields up to 29% of the hemiacetal. Phenol is unreactive for all tested substrates. According to the optimal ratio, the zinc(II) coordination center should be surrounded by at least two hemiacetal ligands (Scheme 2b, (4a)₂Zn²⁺). The 2:1 hemiacetal complex may be transformed to other coordination species by higher amounts of zinc(II) ions.

The formation of such 2:1 complexes suggests that oligo- and/or polymeric species might be formed in the presence of diols. Thus, **1** and 1,6-hexanediol (2:1) yield 42% hemiacetal, but the formation of polymers (the proton NMR spectra shows sharp well-resolved signals and about 58% of **1** remains untouched in the solution) has not been observed under these conditions (concentration of **1** *c* = 0.15 mol·dm⁻³)!

Due to its tridentate nature, **2** may be expected to form much more stable zinc(II) complexes of the hemiacetals compared to **1**. A combination of the higher reactivity of **2** itself with zinc(II) activation results indeed in much higher yields of hemiacetals. The reactivity of the alcohols follows the same order as for the reaction with **1** (Table 3, bottom). The yields of the hemiacetals with 1-butanol and 2-methoxyethanol reach average values as high as about 80% and 70%, respectively, for a 1:2 **2**/alcohol ratio. An excess of alcohol may increase the yields over 90% (Table S3b, SI). A secondary alcohol such as 2-propanol gives up to 73% yield, and even the sterically demanding *tert*-butyl alcohol shows a rather good yield up to 50% (Table 3, bottom). All the indicated yields are for the bis-hemiacetals. An excess of zinc(II) ions above over 2:1 ratio does not result in a decrease

of the amount of hemiacetal species. The two hemiacetal ligands probably form a hexacoordinated complex with the zinc(II) metal centers in an octahedral coordination geometry as represented by (6a)₂Zn²⁺ (Scheme 2c). Such complexes are expected to be much more stable than those of the monohemiacetals of **1**. However, they remain highly dynamic. The NMR spectra display rather broad bands, signaling the occurrence of exchange processes among the complexes.

Reactions with diols give complex mixtures of oligo-/polymeric hemiacetals in contrast to **1**. In this case, based on the proton NMR experiments showing generally broad signals and very broad hemiacetal signals, we expect formation of the oligomeric species. The di-, tri-, and tetraethyleneglycols as well as 1,5-pentanediol, 1,6-hexanediol, 1,7-heptanediol, and 1,8-octanediol give complex mixtures of hemiacetals (that may contain macrocyclic entities) in yields up to 80% for the aliphatic diols (dial/diol, 1:1, 1 equiv of Zn²⁺) (e.g., Scheme 2d, (6g)₂Zn²⁺). Less nucleophilic glycols give up to 50% complex hemiacetals under the same conditions. The composition of the sample remains stable even after 7 days.

Effect of Lead(II) Coordination. Lead(II) salts are also capable of activating effectively **2** toward formation of hemiacetals. Activation by lead(II) ions is highest at 1:1 aldehyde/cation ratio, as compared to 2:1 for zinc(II) cations, and it gives usually lower yields in comparison to zinc(II) under the same conditions (e.g., 6 equiv of 1-butanol give 83% of bis-hemiacetal complex in the presence of Pb²⁺ and 97% in the presence of Zn²⁺, respectively). In addition, the NMR spectra show very broad signals, indicating even much more fluctuating character of the lead(II) complexes compared to that of the zinc(II) complexes. Glycols yield macrocyclic complexes. Thus, tetraethyleneglycol forms with 1 equiv of **2** a macrocycle of aza-18-crown-6 type in up to 82% yield (Scheme 3a, (6h)Pb²⁺, proton NMR, see the

SI), increasing to over 95% with 2 equiv of tetraethyleneglycol. The macrocycle is formed immediately after mixing the components with lead(II) ions. Herein, lead(II) ions play at least two important roles: activation of the aldehyde and stabilization of the final macrocyclic structure by complexation.

4. Component Exchange Dynamics. Exchange processes and equilibration in the reaction mixtures of hemiacetals alone as well as in the proton modulated systems are very fast, features of much interest in DCC. Dynamic behavior and exchange processes of zinc(II) and lead(II) complexes are fast as well. With mixtures of alcohols and hemiacetals, the equilibria were always established within the time of the ^1H NMR experiments (less than a few minutes). Repeated measurements after another few minutes or hours did not show further changes. Generally, the formation of the hemiacetals showed strong concentration dependence under these conditions. The equilibria are shifted toward starting aldehydes and alcohols in the case of diluted solutions, e.g., the population of the hemiacetal species may vary from 16% to 94% of $(\mathbf{6a})_2\text{Zn}^{2+}$ for diluted ($0.01\text{ mol}\cdot\text{dm}^{-3}$) and concentrated ($0.8\text{ mol}\cdot\text{dm}^{-3}$) solutions, respectively (see the SI). Addition of 2-propanol (3 equiv) to a mixture of 1-butanol (3 equiv) and 2-methoxyethanol (3 equiv) with **1** (1 equiv) has been tested under “proton” and “zinc(II)” conditions (Table 4). The same equilibrium compositions were observed when the alcohols have been mixed in different order or added in one portion (3 equiv of each) to **1** (Table 4). The formation of the hemiacetal with 1-butanol is preferred in the equilibria, whereas 2-methoxyethanol and 2-propanol show almost the same hemiacetal ratios.

A mixture of **2** (1 equiv), 1-butanol (6 equiv), and 2-methoxyethanol (6 equiv) gave under zinc(II) activation a complex mixture of the hemiacetal species, as expected. On the other hand, under activation by protons instead of zinc(II) cations, the same mixture showed an interesting selectivity in the formation of the bis-hemiacetals, giving a 31%:16% mixture of bis-butyl ($\mathbf{6aH}^+$) and bis-methoxyethyl ($\mathbf{6bH}^+$) species. Mixed butyl–methoxyethyl hemiacetals were not observed in contrast to the “zinc” case, and the bis-methoxyethyl hemiacetal was formed diastereoselectively (*vide ante*) (Scheme 2a, $\mathbf{6bH}^+$). Thus, combination of the dynamic behavior of the reaction system and selectivity in the formation of the hemiacetals allows specific constituents in the DCL to be expressed.

Fast dynamic behavior and selectivity in favor of more nucleophilic reagent was shown in the following experiment. A mixture of **2** (1 equiv) and tetraethyleneglycol (1 equiv) contains ca. 46% of a complex mixture of hemiacetals of tetraethyleneglycol (oligo/polymeric) in the presence of 0.5 equiv of zinc(II) triflate in acetonitrile. Progressive addition of 1-butanol to the mixture showed an immediate change in the equilibrium in favor of $(\mathbf{6a})_2\text{Zn}^{2+}$ (Scheme 3b).

As mentioned above, the same mixture of **2** (1 equiv) and tetraethyleneglycol (1 equiv) can also be activated by lead(II) ions, giving the macrocyclic complex $(\mathbf{6h})\text{Pb}^{2+}$.

The switching between the Zn(II) and Pb(II) modes may be extended to involve component selection by the combination of the two last systems. The addition of 2 equiv of 1-butanol to the **2**:tetraethyleneglycol 1:1 mixture changes the dynamic equilibrium of the zinc(II) system in favor of butyl–hemiacetal complexes (Scheme 3), whereas the preferential formation of the macrocycle in the presence of lead(II) ions is not affected by the presence of 1-butanol (Scheme 3).

Thus, metal cation coordination to pyridine carboxaldehyde derived DCLs of hemiacetals may regulate both the formation efficiency and the selection of component alcohols.

The results presented above lead to several conclusions: (i) hemiacetal formation represents a significant and promising addition to the set of reversible reactions for covalent dynamic chemistry;^{2,3} (ii) the efficiency of formation of specific hemiacetals may be greatly increased through activations by protonation or metal ion coordination as well as by higher concentrations of components; (iii) exchange dynamics are very fast and may be modulated by such effectors; (iv) both features ii and iii, as well as component selection and type of hemiacetal product may be further modulated by the choice of the metal cation; and (v) applications may be envisaged in the controlled release of one of the partners, in particular of bioactive or home and personal care alcohol partners, as well as in the generation of highly dynamic hemiacetal-based polymers.

Experimental Section

All proton NMR experiments (400 MHz) were recorded at 25 °C in either CDCl_3 or CD_3CN . Samples were prepared by mixing of aldehydes **1**, **2**, and **3**, respectively, in volumetric flasks (1 mL) to form solutions of $0.15\text{ mol}\cdot\text{dm}^{-3}$ together with respective amount of alcohols and deuterated solvents. Protonation experiments were carried out in chloroform, and deuterated TFA ($2\text{ mol}\cdot\text{dm}^{-3}$ solution in CDCl_3) was added sequentially by microsyringe to 0.5 mL of the solutions of aldehydes and alcohols in NMR tubes. Metal-mediated experiments were performed in CD_3CN (due to solubility of metal salts) by addition of zinc(II) triflate and lead(II) trifluoroacetate solutions (both $0.5\text{ mol}\cdot\text{dm}^{-3}$ in CD_3CN), respectively, to 0.5 mL of the solutions of aldehydes and alcohols.

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Supporting Information Available: Full versions of the experimental data tables and NMR and MS spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.