Reactivity-Based Dynamic Covalent Chemistry: Reversible Binding and Chirality Discrimination of Monoalcohols

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Ⓢ *Supporting Information*

ABSTRACT: In an effort to develop reactivity-based dynamic covalent bonding and to expand the scope and application of the dynamic covalent chemistry, in situ-generated simple generic iminium ions were utilized for the dynamic covalent binding of monoalcohols with high affinity. Hammett analysis was conducted to manipulate the equilibrium and correlate with the reactivity of reactants. The structural features of aldehydes and secondary amines were identified, and both polar and steric effects have significant impact on the binding. In particular, the substrates which can participate in $\pi-\pi$ and polar$-\pi$ interactions are able to afford apparent equilibrium constants in the magnitude of 10^4 M^{-2}, demonstrating the power of weak supramolecular forces to stabilize the dynamic covalent assembly. The generality of the assembly was validated with a series of mono secondary alcohols. To showcase the practicality of our system, chirality discrimination and ee measurement of chiral secondary alcohols were achieved.
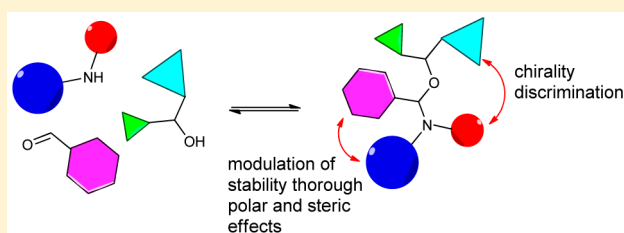
INTRODUCTION

Dynamic covalent chemistry (DCC)[1] is increasingly popular for the construction of complex assembling structures,[2] creation of novel chemosensors,[3] and modulation of stimuli responsive materials.[4] In order to achieve the aforementioned goals, it is of great significance to discover reversible covalent interactions with high affinity. Compared to the widespread use of dynamic imine formation with primary amines and carbonyls as well as metal complexes of these imines,[5] the use of iminium ions for thermodynamically driven systems has been rarely reported despite the fact that iminium ion is widely employed in asymmetric organocatalysis that is generally under kinetic control.[6] Because of their high reactivity, iminium ions can undergo a variety of transformations, such as nucleophilic additions, and hence, the utilization of iminium ions in DCC would expand the diversity and complexity of the assembling architectures and have potential applications in a variety of contexts, such as sensing[3c,7] and labeling.[8]

Monoalcohols are one of the most common functional groups in chemistry. Moreover, they are the targets of many asymmetric reactions.[9] As a result, it is of importance to develop alcohol receptors. However, due to monoalcohols' poor nucleophilicity and weak coordinating ability, their molecular recognition is challenging. For example, the use of electron-withdrawing groups was employed to enhance the binding affinity of carbonyl receptors to monoalcohols to create hemiacetals, but only to a small extent.[10] Anslyn[11] and Lehn[12] reported separately the formation of hemiacetals from pyridine-2-carboxaldehyde (2-PA) analogs and the stabilization of products with Brønsted or Lewis acids. In another study,

Lehn and Hermann explored the reversible formation of cyclic aminals and the release of volatile carbonyl compounds from them.[13] Anslyn and You used specially designed tris(pyridine)-based iminium for the binding and chirality recognition of alcohols with the formation of stable metal complexes as the driving force.[14]

We are initiating a project of reactivity-based DCC. Toward this end, simple generic iminium ions were exploited for alcohol binding, and the modulation of binding properties as well as chirality differentiation of chiral alcohols was investigated. Understanding the details should open the opportunity for the use of other reactive intermediates in dynamic assembly systems, thereby further expanding the scope and application of DCC.

RESULTS AND DISCUSSION

Model and Experiment Design. Due to the lability of iminium ions, in situ assembly reactions of an aldehyde, a secondary amine, and an alcohol were run (Figure 1). In addition to the desired hemiaminal ether (**1**), the competing reaction to create aminal **2** is likely. We postulated that once formed after the elimination of water from hemiaminal **4**, the iminium ion (**3**) would rapidly react with alcohol and amine to afford **1** and **2**, respectively. However, the hemiaminal ether functionality is thermodynamically unfavorable and can easily reverse back to the reactants. N-acylation[15] as well as cyclization[16] is normally used to stabilize the hemiaminal
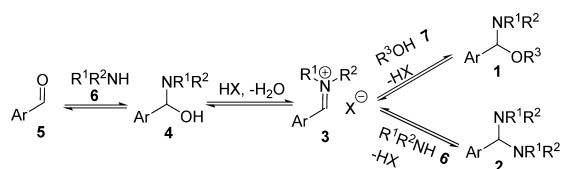
Figure 1. Proposed reaction mechanism of hemiaminal ether (**1**) formation.

ether. Instead of relying on elegant design, we conceived that the equilibrium could be manipulated through the structural features of the assembling component. In short, we sought a dynamic covalent system in which the reactivity of the iminium ion, the reversibility of the reaction, and the stability of the assembly can be balanced.

To test our hypothesis, ethanol was chosen as a model alcohol. A series of aromatic aldehydes were screened, with both electron-poor and electron-rich cases included. Aliphatic aldehydes were not chosen because of interfering enamine formation. For secondary amines, both aryl- and alkyl-substituted ones as well as acyclic and cyclic ones with varied bulkiness were explored. The multicomponent reactions were performed at room temperature in CD_3CN for 24 h in the presence of 3 Å molecular sieves (MS) and 0.1 equiv of methanesulfonic acid, and the mixture was characterized by ^1H NMR. No further increase in the percentage of **1** was detected after 24 h. To quantify the binding strength, the apparent equilibrium constant (K_{app}) was derived through NMR integrals and mass balance of aldehydes (see details in Supporting Information). The component distribution (yield) of the aldehyde, heminaminal ether, and aminal was also calculated from their equilibrium concentrations.

Modulation of Binding Affinity. The features and trends of aldehydes that affect the binding affinity significantly were then examined using diethylamine as a model amine (Table 1; for component distribution, see Table S1). With benzaldehyde analogs, the K_{app} value increase as the electrophilicity of aldehydes is enhanced. For example, 4-methoxy-benzaldehyde gave the poorest reaction ($K \sim 8.49$ M^{-2}), while 4-nitro-benzylaldehyde afforded a binding constant of 4160 M^{-2}, greater than benzaldehyde by 177-fold. The plot of logarithm of equilibrium constants of dynamic covalent reactions with *para*- or *meta*- substituted benzaldehydes against Hammett parameter σ gave a linear relationship with a sensitivity constant (ρ) of 2.75 ($r^2 = 0.975$, Figure 2a). This result further supports the observed trend of aldehyde electrophilicity toward addition reactions.

Having explored benzaldehyde derivatives, we next turned to heterocycle-substituted aromatic aldehydes. Formylpyridines with different substitution pattern were investigated. Among these three, pyridine-4-carboxaldehyde (**4-PA**) afforded the strongest binding ($K \sim 5540$ M^{-2}), while **2-PA** ($K \sim 1050$ M^{-2}) and **3-PA** ($K \sim 946$ M^{-2}) gave similar results. For **2-PA** and **4-PA**, resonance interaction between electronegative nitrogen and α position of carbonyl leads to an increase in electrophilicity. However, there was a 5-fold increase of binding constant for **4-PA** over **2-PA**. This difference is likely due to less stability of **2-PA** derived assembly as a result of repulsion between electron lone pairs on three neighboring heteroatoms (N, N, and O, Figure 3). In order to generate a broad range for screening of secondary amines, **2-PA** was employed.

A variety of secondary amines were then tested. For *N*-methylaniline analogs, the amine bearing an electron-donating

Table 1. Apparent Equilibrium Constant of the Multicomponent Assembly of Aldehydes, Secondary Amines, and Ethanol

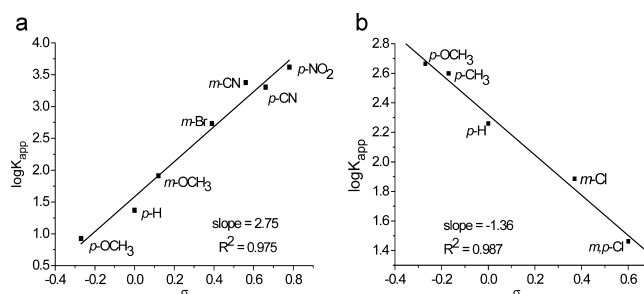| Aldehyde 5	Amine 6	K_{app}/M^{-2}	Aldehyde 5	Amine 6	K_{app}/M^{-2}
		4160			461
		2020			397
		2380			182
		541			77.0
		81.9			29.0
		23.5			7950
		8.49			821
		1050			6890
		946			11200
		5540			7530
		77500			12100
		15600			3740
		17300			1280
		2000			437
		4020			508

Figure 2. Hammett plots of the reaction of (a) substituted benzaldehydes, diethylamine, and ethanol and (b) **2-PA**, *N*-methylaniline analogs, and ethanol.
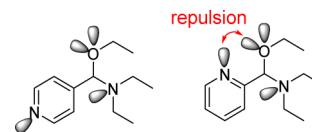

Figure 3. Interaction of electron lone pairs within **4-PA** and **2-PA** derived assembly.

p-OCH$_3$ was the best ($K \sim 461$ M^{-2}), while no desired product was detected with *N*-methyl-4-nitroaniline. The equilibrium constants correlate well with the nucleophilicity of amines with the reaction better promoted by stronger nucleophiles. A linear relationship was obtained when log K was plotted against the Hammett value σ ($\rho = -1.36$, $r^2 = 0.987$, Figure 2b). For *N*-methyl-3,4-dichloroaniline, the sum of the corresponding Hammett parameter of *m*-Cl and *p*-Cl was utilized for analysis. Aminal **2** was not detected for the reactions with these aromatic amines or diethyl amine (Table S1).

In general, aliphatic amines afforded stronger binding affinity than their aromatic counterparts, and a similar trend regarding nucleophilicity was observed (Table 1). Moreover, steric interactions have significant effects on the reversible reactions described herein. For example, the reaction of piperidine ($K \sim$ 7950 M^{-2}) gave a much larger equilibrium constant than diethylamine ($K \sim$ 1050 M^{-2}). Meanwhile, the interference with aminal formation was much more pronounced for cyclic amines, such as piperidine and morpholine, whose reaction mixtures contained 36% and 53% aminal **2**, respectively (Table S1). To minimize the side product, bulkier amines were used as sterically congested aminal would be disfavored. For example, the assembly with 2-methylpiperidine afforded the hemiaminal ether in good yields (71%), and aminal **2** was not observed. However, 2-methylpiperidine also gives a smaller binding constant (821 M^{-2}). Hence, a delicate balance between reactivity and sterics must be established.

The Effect of π Interactions. One surprising result was obtained with benzylamine derivatives. An equilibrium constant of 12100 M^{-2}, that is a 24-fold enhancement compared to N-methylpropylamine (508 M^{-2}), was found for multicomponent assembly with N-methylbenzylamine. Such a sharp increase in binding affinity cannot be explained with simple inductive effects since phenyl is slightly electron-withdrawing, while 1-propyl is electron-donating. We postulated that the assembly is stabilized through $\pi-\pi$ stacking interaction between pyridine and phenyl planes (Figure 4a).[17] The use of intramolecular π
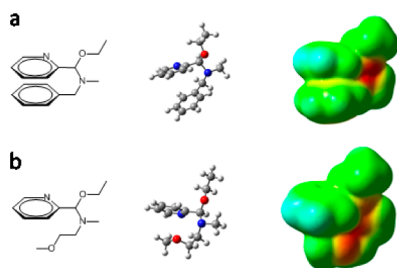

Figure 4. (a) Proposed and computational structures of (a) $\pi-\pi$ interaction between pyridine and phenyl planes and (b) polar–π interactions between pyridine plane and methoxy group. The electrostatic potential maps were also shown.

interactions to stabilize acyclic dynamic covalent assemblies has been rarely reported. The placement of the pyridine and phenyl unit here is similar to that of two phenyl groups of 1,8-diarylnaphthalenes in which the sandwich conformation is favored over the edge to face orientation.[18] To gauge the possibility of and gain further insights into proposed π interactions within dynamic covalent assemblies, computational studies were conducted (Figure 4a). Although not perfectly parallel, the two interacting arenes can adopt an orientation between parallel-stacking and parallel-offset arrangements.[19]

Inspired by this finding, we tested other secondary amines with nearby functionalities that can participate in π interactions. First, more benzylamine analogs were explored. N-methyl-3-fluoroaniline and 3-[(methylamino)methyl]pyridine gave an equilibrium constant of 11200 and 7530 M^{-2}, respectively. Second, we conceived that polar–π interaction[20] would have a similar impact as $\pi-\pi$ stacking, and hence, several amines with nearby polar groups were examined. N,N,N'-trimethyl-1,3-propanediamine and (2-methoxyethyl)methylamine afforded a yield of more than 80% with only residue amounts of aminals.

The binding constants are 1280 and 3740 M^{-2}, respectively, significantly higher than that of N-methylpropylamine. For (2-methoxyethyl)methylamine, molecular modeling reveals that in one isomer the methoxy group is in close contact with the pyridine plane (Figure 4b).

Expansion of Substrate Scope. Having identified the structural features of both aldehyde and secondary amines, we next set out to expand the scope of the assembly. First, **4-PA** was employed to conduct the multicomponent assembly. Representative amines were chosen to cover a broad range of chemical space: alkyl, aromatic, cyclic, and heteroatom substitution (Table 1). It was found that **4-PA** showed stronger affinity than **2-PA** in all cases, and N,N,N'-trimethyl-1,3-propanediamine, (2-methoxyethyl)methylamine as well as N-methylbenzylamine are the best with an equilibrium constant in the magnitude of 10^4 M^{-2}.

The dynamic covalent multicomponent assembly was then run with **4-PA**, (2-methoxyethyl)methylamine, and a suit of structurally diverse secondary alcohols, and the results are listed in Table 2. 2-propanol afforded ∼80% of the desired

Table 2. Yield, Binding Constant, and dr Value of the Reaction of 4-PA, (2-Methoxyethyl)methylamine, and Secondary Alcohols

Alcohol	Yield of **1**/%	K_{app}/M^{-2}	dr
OH	81	9700	-
OH	78	4770	1.47
OH	79	4220	1.54
OH	83	8610	1.09
OH	78	3480	1.48
OH	85	7270	-

hemiaminal ether with a binding constant of 9700 M^{-2}. For other secondary alcohols tested (2-butanol, 3-methyl-2-butanol, 1-phenylethanol, 1-phenyl-1-propanol, and cyclohexanol), similar extent (∼80%) of the assembly was created, confirming the binding capability of this simple system.

The aldehyde as well as its associated iminium ion intermediate is enantiotopic, and the addition of chiral alcohols (100% R or S) would lead to a pair of diastereomers. As a result, four stereoisomers would be generated with racemic chiral secondary alcohols. However, due to the principles of stereochemistry, there are two pairs of enantiomers in the mixture, and hence, only two sets of resonances were observed in ^{1}H NMR. To quantify the stereoselectivity for chiral alcohol derived assembly, the diastereomeric ratio (dr) was calculated with the integral ratio of the corresponding CH of the newly formed stereocenter (i.e., aldehyde H). For 2-butanol, 3-methyl-2-butanol, and 1-phenyl-1-propanol, the dr value was around 1.5 (Table 2).

Only a modest dr value (∼1.1) was found for 1-phenyl-ethanol. This is in sharp contrast with previously reported tris(pyridine)-substituted iminium-based assembly, in which 1-phenylethanol afforded the largest dr value (∼2.2) among the chiral alcohols tested here.[14d] We reasoned that the steric effect of phenyl group in 1-phenylethanol derived assembly is much

less pronounced due to π–π interaction between pyridine and phenyl of the alcohol (Figure S24). Such a rationalization is also supported by the fact that there are two values of Charton steric parameter for phenyl (0.57 and 1.66),[21] and the in-plane Ph (0.57) is more appropriate to describe the steric interactions here than the out-of-plane Ph (1.66). The steric parameter of methyl (0.52) is very close to that of the in-plane Ph, leading to a small dr value. This result is also in consistence with the similar equilibrium constant for 2-propanol and 1-phenylethanol (Table 2).

Investigation of Intermediates. Reaction intermediates were then explored as a means of probing the mechanism of the dynamic covalent assembly. To capture hemiaminal **4**, molecular sieves were not used. The reaction was conducted in the absence or in the presence of 1 equiv of ethanol without molecular sieves. Without alcohol, both the hemiaminal and aminal were detected, and the latter had a higher percentage than the former (Figure 5a). With 1 equiv of ethanol, the
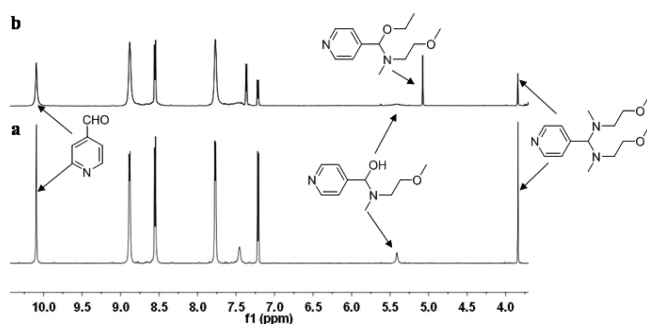
Figure 5. ^{1}H NMR spectra of the reaction of **4-PA** and (2-methoxyethyl)methylamine (a) without or (b) with 1 equiv of ethanol. Molecular sieves were not used.

hemiaminal ether appeared, though aldehyde, hemiaminal, and aminal all existed (Figure 5b). The corresponding iminium ion was also observed in ESI mass spectrum, further supporting the pathway shown in Figure 1.

Chirality Discrimination. To demonstrate the application potential of this dynamic covalent assembly, chiral iminium ions were employed to differentiate enantiomers of chiral secondary alcohols. Chirality plays a vital role in the development of asymmetric transformations, and as a result, the detection of chirality is generating significant interest within organic and supramolecular chemistry community.[22] NMR spectroscopic methods have been commonly employed,[23] but prederivatization of the analytes is often required, especially for weakly coordinating guest, such as monoalcohols. To take advantage of the high-affinity dynamic covalent assembly described herein and avoid additional synthesis as well as isolation, an in situ derivatization with a commercially available chiral auxiliary S-2-(methoxymethyl)pyrrolidine was conducted. One reason for the selection of this amine is its structural similarity with (2-methoxyethyl)methylamine. Moreover, facile recovery of the analytes could be achieved due to the dynamic nature of our assembly.

The assembly of **4-PA**, R-1-phenylethanol, and S-2-(methoxymethyl)pyrrolidine afforded two diastereomers (yield ∼86%), and the proton on the hemiaminal ether carbon was at 5.43 and 5.13 ppm, respectively (see Supporting Information). The dr value was 2.8. For S-1-phenylethanol, the methine protons shifted to 5.22 and 5.19 ppm, with a dr value

of 3.2 (yield ∼86%). The change in dr is due to differential chirality induction as a result of varied stability of created diastereomeric assemblies. When a racemic sample was tested, four separated methine peaks were observed, further supporting the discrimination (Figure 6). The corresponding methine
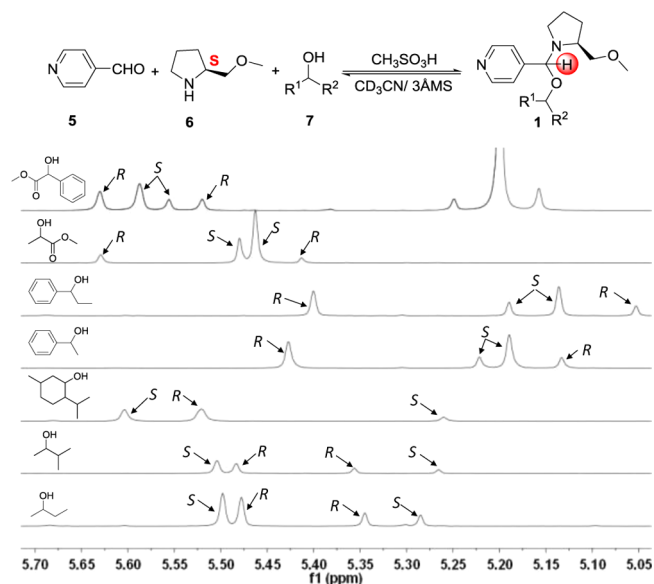
Figure 6. Partial ^{1}H NMR spectra of the reaction of **4-PA**, S-2-(methoxymethyl)pyrrolidine, and racemic 2-butanol, 3-methyl-2-butanol, menthol, 1-phenylethanol, 1-phenyl-1-propanol, methyl lactate, or methyl melate. The peaks of the proton (marked in red) on the hemiaminal ether carbon from R or S alcohol derived assemblies were labeled.

proton peaks from R or S alcohol derived hemiaminal ether **1** were assigned by comparison with the NMR of the assembly from two enantiomerically pure alcohols, respectively (see Supporting Information).

To examine the generality of the assay, more chiral secondary alcohols were studied to span a range of chemical space of substitutions on the stereocenter, including linear alkyl (2-butanol), branched alkyl (3-methyl-2-butanol), cyclic aliphatic (menthol), and aromatic (1-phenyl-1-propanol). Furthermore, bifunctional substrates (methyl lactate and methyl melate) were explored. The dynamic reactions were run with both enantiomers and racemic sample of these alcohols (yield more than 60%, Table 3), and the R or S stereoisomers were successfully differentiated (Figure 6). For alcohols with two sp^3 carbons attached on the α carbon (2-butanol, 3-methyl-2-butanol, and menthol), NMR peaks of the proton on the hemiaminal ether carbon from R alcohol derived assembly fell between those from S alcohol derived assembly. For alcohols with one or two sp^2 carbons attached on the α carbon (1-phenylethanol, 1-phenyl-1-propanol, methyl lactate, and methyl melate), the opposite trend was observed.

The integrals of methine protons in four diastereomers of hemiaminal ethers (Figure 6) were obtained. First, the dr value for R or S alcohol derived assembly was calculated (dr/1_R and dr/1_S in Table 3). As the case with 1-phenylethanol, R or S enantiomer of 2-butanol, 3-methyl-2-butanol, 1-phenyl-1-propanol, and methyl lactate afforded different dr. The dr value for R-menthol was not available due to overlap of the NMR peaks. Furthermore, there is a reversal of the trend of dr for 1-phenyl-1-propanol compared to 1-phenylethanol. Con-

Table 3. Discrimination of Enantiomers of Chiral Secondary Alcohols: Chemical Shifts, dr Values, Yield, and Ratio of R and S Alcohol Derived Assembly for Different Racemic Chiral Alcohols[a]

R¹R²OH	$\delta/1_R{}^a$	$\delta/1_S{}^b$	$dr/1_R{}^c$	$dr/1_S{}^d$	$1_R\%/1_S\%{}^c$	Yield/%
OH (2-butanol)	5.48/5.35	5.50/5.29	2.4	3.0	0.95	75
OH (3-methyl-2-butanol)	5.48/5.36	5.50/5.27	2.1	4.0	0.87	80
OH (menthol)	5.52/5.52	5.60/5.26	-	4.3	0.93	61
OH (1-phenylethanol)	5.43/5.13	5.22/5.19	2.8	3.2	0.85	86
OH (1-phenyl-1-propanol)	5.40/5.05	5.19/5.14	3.0	2.4	0.84	79
OH (methyl lactate)	5.63/5.41	5.48/5.46	1.7	2.3	0.17	72
OH (methyl melate)	5.63/5.52	5.59/5.56	1.9	1.9	1.00	66

[a]Note: a and b, chemical shift (in ppm) of the proton on the hemiaminal ether carbon from R and S alcohol derived assembly, respectively; c and d, diastereomeric ratio of R and S alcohol derived assembly, respectively; e, concentration ratio of R and S alcohol derived assembly.

sidering that the only difference between 1-phenyl-1-propanol and 1-phenylethanol is one methylene group, this result demonstrates the sensitivity of our system toward subtle structural changes. Second, the percentage of total integral of R or S alcohol derived assembly ($1_R\%$ and $1_S\%$, respectively) was obtained, and their ratio ($1_R\%/1_S\%$) is listed in Table 3. For racemic 2-butanol, 3-methyl-2-butanol, menthol, 1-phenyl-ethanol, 1-phenyl-1-propanol, and methyl lactate, $1_R\%/1_S\%$ is <1. For racemic methyl melate, the value of $1_R\%/1_S\%$ is 1.0, in agreement with the result that the R or S isomer of methyl melate afforded identical dr value.

Having achieved the discrimination of two enantiomers of a series of chiral alcohols, quantitative correlation of NMR integrals with enantiomeric composition was explored using 1-phenylethanol as a model. ¹H NMR titration experiment was performed with 3 equiv of alcohol samples at 11 ee values covering the whole range (−100, −80, −60, −40, −20, 0, 20, 40, 60, 80, and 100%, Figure 7a). The existence of all four stereoisomers at all ee values except −100 and 100 further supports that the assembly is thermodynamically driven. The value of $1_R\%$ and $1_S\%$ was calculated through NMR integrals and plotted against real ee values to generate the calibration curve. A slight curvature was notable. We rationalize this observation as different $1_R\%/1_S\%$ as a function of ee because of varied stabilities of their respective diastereomers. Nevertheless, the linear fit of the calibration curve was excellent ($R^2 = 0.996$, Figure 7b). The six unknown samples were tested with the linear fitting, and the average absolute error for ee was 3.0% (Table 4).

■ CONCLUSIONS

In summary, a dynamic multicomponent covalent assembly has been developed for the binding and chirality differentiation of
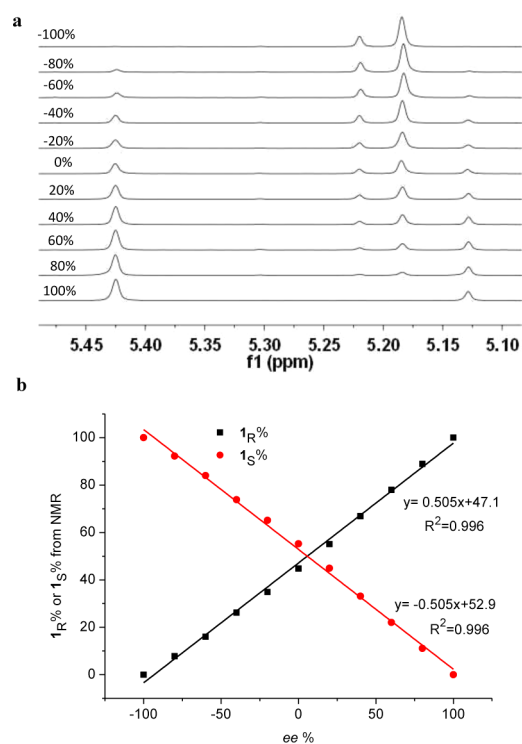

Figure 7. (a) ¹H NMR titration experiment of 1-phenylethanol with various ee. (b) The average ee calibration line for 1-phenylethanol.

Table 4. Calculated ee Values and the Associated Absolute Errors for 1-Phenylethanol[a]

$1_R\%{}^a$	$1_S\%{}^b$	calcd ee[c]	real. ee	abs. error
94.2	5.8	93.1	90	3.1
82.5	17.5	70.0	68	2.0
60.4	39.6	26.1	30	3.9
22.7	77.3	−48.4	−46	2.4
12.1	87.9	−69.4	−70	0.6
2.5	97.5	−88.2	−94	5.8

[a]Note: a and b, calculated from ¹H NMR integrals;and c, calculated from the calibration lines in Figure 7b, using $1_R\%$ or $1_S\%$.

monoalcohols. The system is based on the reactivity of simple generic iminum ions. Both aldehydes and secondary amines have significant impact on the binding affinity, and linear free energy relationship-based Hammett analysis was utilized to manipulate the equilibrium. The structural features as well as polar and steric effects were identified, with pyridine-4-carboxyaldehyde as the best aldehyde and N-methylbenzyl-amine and (2-methoxyethyl)methylamine among the best amines. Notably, weak supramolecular interactions, such as π−π and polar−π contacts, significantly stabilize the assembly. The dynamic covalent assembly afforded the desired product in high yield for a broad range of monoalcohols. Moreover, chirality discrimination was achieved with an enantiopure secondary amine, and the ee values were determined with high accuracy. Future efforts will focus on the use of the assembly to create complex architectures.

■ EXPERIMENTAL SECTION

General. ¹H NMR spectra were recorded on a 400 MHz spectrometer. ESI-mass spectra were obtained on an ion trap mass spectrometer. Commercially available reagents were used without further purification.

The Multicomponent Assembly Reaction. Assembly reactions were performed in situ in d^3-acetonitrile without isolation and purification. To a stirred solution of an aldehyde (50−55 mM, 1 equiv), a secondary amine (1.2 equiv), an alcohol (3.0 equiv), and methanesulfonic acid (0.1 equiv) in d^3-acetonitrile (0.6 mL), were added activated 3 Å molecular sieves (4−8 mesh). The mixture was stirred at room temperature overnight. The assembly solution was characterized by ^{1}H NMR and ESI-MS. For chirality analysis, chiral secondary alcohols with different ee values were used.

Molecular Modeling. All calculations were performed using the Gaussian 09 packages and Spartan 10 (Version: 1.01). For structures with proposed π interactions, conformer calculations were run by MMFF in Spartan 10 by searching the whole potential energy surface, and the one with lowest energy was selected for further geometry optimization. Geometry optimization and frequency analysis were run using density functional theory method (M06-2X). The basis set of CCPVDZ was employed. A solvent model for acetonitrile (polar continuum model) was used. The final structures were confirmed by vibration calculations without imaginary vibrational frequencies.

ASSOCIATED CONTENT

S **Supporting Information**

Component distribution at equilibrium and selected ^{1}H NMR and ESI mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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