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Hydrogen-Bond Catalysis of Imine Exchange in Dynamic Covalent Systems

Fredrik Schaufelberger,[a] Karolina Seigel,[a] and Olof Ramström*[a],[b],[c]

The reversibility of imine bonds has been exploited to great effect in the field of dynamic covalent chemistry, with applications such as preparation of functional systems, dynamic materials, molecular machines, and covalent organic frameworks. However, acid catalysis is commonly needed for efficient equilibration of imine mixtures. Herein, it is demonstrated that hydrogen bond donors such as thioureas and squaramides can catalyze the equilibration of dynamic imine systems under unprecedentedly mild conditions. Catalysis occurs in a range of solvents and in the presence of many sensitive additives, showing moderate to good rate accelerations for both imine metathesis and transimination with amines, hydrazines, and hydroxylamines. Furthermore, the catalyst proved simple to immobilize, introducing both reusability and extended control of the equilibration process.

Introduction

Imines are ubiquitous compounds in both nature and organic synthesis.[1] During the last two decades, the imine linkage has been established as the quintessential dynamic covalent bond, with properties highly suited for dynamic covalent chemistry, systems chemistry, and stimuli-responsive and adaptive materials.[2] At high pH, imines are robust and essentially inert. However, the presence of acid catalysts renders the bonds labile and prone to exchange with amines or water.[3] Dynamic imine chemistry has, for example, been utilized for self-sorting,[4] catalysis,[5] nanotechnology,[6] molecular machines,[7] for determination of effective molarities,[8] and for synthesis of covalent organic frameworks (COFs),[9] complex architectures such as cages and catenanes,[10] and other dynamic materials.[2g, 11] The ability to toggle the system dynamics by addition or removal of acid is one of the most attractive features of C=N bonds since this adds the possibility to control systems by a simple and easily tunable input (i.e., pH). Indeed, control of imine exchange via catalysis has been significantly employed in responsive materials,[12] for COF synthesis,[9a] to facilitate challenging synthetic transformations,[13] for bioconjugation reactions,[14] and for de-crosslinking of RNA and DNA polymers.[15]

However, many applications in dynamic chemistry involve sensitive compounds and systems, where common imine exchange catalysts such as strong Lewis- or Brønsted acids are suboptimal. In organic solvents, problems may arise because of strong complexation of the catalysts with Lewis-basic moieties such as amines, leading to kinetic traps in the form of precipitation or alteration of the equilibrium position of the system.[16] To expand the applications of dynamic covalent chemistry, it is important that mild, general exchange conditions are developed. For example, the development of efficient aminocatalysis protocols have led to many new applications for dynamic imine systems.[17]

Hydrogen bond donation has been established as a highly viable activation mode for catalysis, especially with regards to asymmetric synthesis.[18] The strong interaction of hydrogen bond donors with imines is well-investigated and has some precedence in nature.[19] In many enzymatic reactions that are dependent on pyridoxal 5'-phosphate (PLP), a transimination step is catalyzed by hydrogen bond stabilization and preorganization of the substrates (Figure 1).[20]

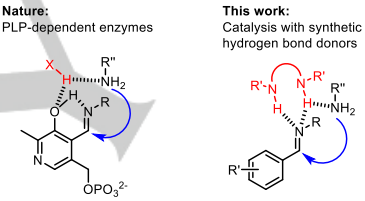

Figure 1: Hydrogen bond catalysis of transimination reactions by amino acid residues in PLP-dependent enzymes, and proposed biomimetic synthetic system.

Hydrogen-bond catalysts such as (thio)ureas and squaramides are effective under mild conditions and with low loadings, show no product inhibition, and are non-toxic, cheap, and stable to moist and air.[21] All these properties are advantageous for dynamic imine systems, which are often generated in the presence of sensitive compounds such as biomolecules,[17d, 22] and in settings where even small disturbances in the equilibration may have broad implications for the system composition.[23]

The different types of imine exchange utilized in dynamic chemistry are summarized in Figure 2. Generally, imine formation and transimination have been preferred for dynamic chemistry applications, whereas imine metathesis processes are more challenging due to the often restricted substrate scope and the need for sensitive metal catalysts.[24]

During our previous investigation of dynamic imine-based catalysts, we noticed that hydrogen-bond donors seemed to catalyze the intramolecular formation of imine bonds when the two functionalities were tethered together to the same molecular scaffold.[5b] In this study, we now demonstrate that hydrogen-bond catalysts can also effectively accelerate intermolecular imine exchange as well as transimination reactions. Furthermore, we show that the catalysts are compatible with a wide range of additives and substrates, and

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that the hydrogen-bond donors can be immobilized on solid support and used for temporal control of the equilibration in dynamic imine systems.

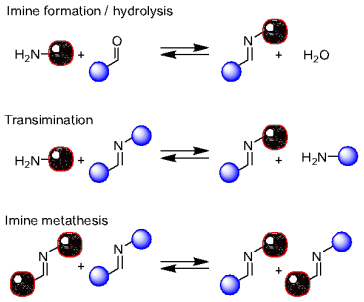


Figure 2: Overview of the three primary exchange modes in dynamic imine chemistry.

Results and discussion

Catalyst screening and optimization. Initially, a range of thiourea catalysts with different substitution patterns was synthesized (Figure 3). We primarliy focused on commercially available or easily synthesized catalysts, to facilitate their implementation in future applications. As a model system, the exchange between imines **1a** and **1b** in DMSO-d_6 was studied.[25] Since the entire exchange procedure involves hydrolysis and subsequent recombination from two different imines, the time to reach the 95% equilibration degree (χ_{95}, reaction advancement degree),[17b, 26] *i.e.*, the progress past 95% conversion towards the equilibrium distribution, was adopted for comparisons (Table 1).

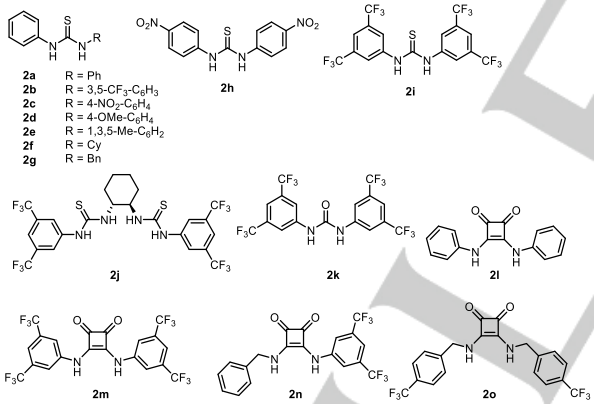
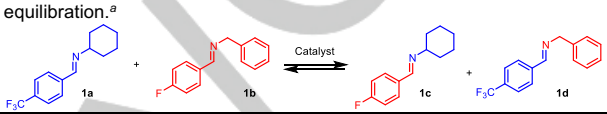


Figure 3: Hydrogen bond donor catalysts utilized in the screening.

When varying the substitution pattern on *N,N'*-disubstituted thioureas **2a**-**2g**, a clear trend in catalyst performance emerged. Catalysts with electron-withdrawing substituents on the aryl groups, such as **2b** and **2c** (Table 1, entries 3 and 4), were able to catalyze the equilibration of the small imine system, approximately reducing the time to reach equilibrium by a factor two. Conversely, electron-rich aryl substitution patterns on the thiourea slightly inhibited the background reaction, leading to lower equilibration rates (Table 1, entries 5 and 6). Switching to aliphatic or benzylic substituents also inhibited the reaction (Table 1, entries 7 and 8). Of the electron-deficient catalysts, the nitro-disubstituted electron-poor thiourea **2h** facilitated rapid equilibration in 15 h (Table 1, entry 9). Furthermore, utilization of thiourea **2i**, based on a 3,5-bis(trifluoromethyl) substitution pattern, increased the catalytic activity with equilibrium reached in 12 h, an almost eightfold faster equilibration compared to the background (Table 1, entry 10).[27] The degree of hydrolysis was consistently low (<2%) with these catalysts, and full stability of the equilibrated system was retained over several weeks.

Utilization of the multidentate catalyst **2j** (Table 1, entry 11) with dual thiourea hydrogen-bond donor motifs did, however, not improve the catalytic performance, indicating that the hydrogen-bond acidity was a more critical effect for the systems than the spatial arrangement of the hydrogen bond donor moieties. In line with this hypothesis, the less hydrogen-bond acidic urea analog **2k** of thiourea **2i** was essentially nonfunctional (Table 1, entry 12).

Table 1: Screening of hydrogen bond donor catalysts for imine exchange equilibration.[a]



Entry	Catalyst	$t(\chi_{95})$ h[b]	Eq. composition (%, 1a:1b:1c:1d)[c]
1	-	90	27 : 26 : 23 : 24
2	**2a**	40	26 : 26 : 24 : 24
3	**2b**	30	27 : 26 : 24 : 23
4	**2c**	40	27 : 26 : 24 : 23
5	**2d**	>90[d]	n.d.
6	**2e**	>90[d]	n.d.
7	**2f**	>90[d]	n.d.
8	**2g**	>90[d]	n.d.
9	**2h**	15	28 : 25 : 23 : 24
10	**2i**	12	26 : 26 : 24 : 24
11	**2j**	50	27 : 24 : 26 : 23
12	**2k**	90	n.d.
13	**2l**	50	28 : 24 : 24 : 24
14	**2m**	10	26 : 26 : 23 : 25
15	**2n**	50	28 : 25 : 24 : 23
16	**2o**	40	27 : 28 : 22 : 22

[a]Conditions: **1a** (0.05 mmol), **1b** (0.05 mmol), catalyst (10 %), DMSO-d_6/H_2O 99:1 (0.50 mL), air, r.t. [b]Time to χ_{95} (95% equilibration degree).[17b, 26] [c]Estimated from ^{1}H-NMR spectroscopy. n.d. = not determined. [d]Equilibration occurred in 100-120 h; minor decomposition was observed after this time.

A range of squaramide catalysts was also evaluated since this compound class is known to be stronger hydrogen bond donors than thioureas.[28] Among these, *N,N'*-3,5-bis(trifluoromethyl)phenyl-substituted catalyst **2m** performed even better than its corresponding thiourea analog (Table 1, entries 10 to 14). However, even though compound **2m** was the most potent hydrogen bond donor catalyst discovered in this study, solubility issues in other solvents than DMSO-d_6 prompted the evaluation (cf. Table S1) of the more soluble

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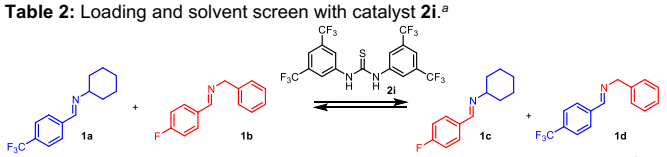
analogs **2n** and **2o** (cf. Table S1). However, these compounds also proved less efficient at catalyzing the imine exchange (Table 1, entries 15-16), and, for this reason, thiourea **2i** was selected as the most promising candidate based on a combination of efficiency, stability, and solubility.

Next, the catalyst activity for the model equilibration was evaluated with different loading and solvents (Table 2). Lowering the loading to 2% still yielded fast equilibration (entry 3). Increasing the loading to one full equivalent provided faster equilibration, though a higher degree of hydrolysis (~ 8%) was observed in this system compared to the other reactions (entry 4). Hydrogen-bond catalysis with compound **2i** was also efficient in a range of solvents, with the highest relative accelerations provided in the non-coordinative solvents toluene-d_8 and $CDCl_3$ (entries 6 vs. 7, and 10 vs. 11).

No precipitation or complexation was observed in any reaction, in contrast to many Brønsted or Lewis acid-based protocols. The systems were also stable for several weeks at equilibrium under ambient conditions. Although the catalyst activities observed are lower than for some optimized Lewis acid-based protocols, approximately the same efficiency as with most Brønsted acid catalysts was recorded.[16a, 16c]

Table 2: Loading and solvent screen with catalyst **2i**.[a]

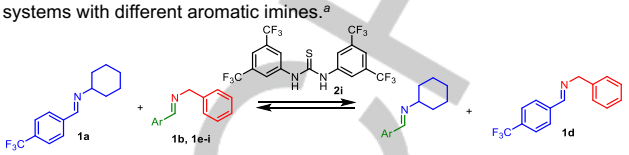


Entry	Loading 2i (%)	Solvent	$t(\chi_{95})$ (h)[b]
1	10	DMSO-d_6/H_2O 99:1	12
2	5	DMSO-d_6/H_2O 99:1	16
3	2	DMSO-d_6/H_2O 99:1	18
4	100	DMSO-d_6/H_2O 99:1	5
5	-	DMSO-d_6/H_2O 99:1	90
6	10	$CDCl_3$/H_2O[c]	1
7	-	$CDCl_3$/H_2O[c]	10
8	10	MeCN-d_3/H_2O 99:1	1
9	-	MeCN-d_3/H_2O 99:1	5
10	10	Toluene-d_8/H_2O[c]	2
11	-	Toluene-d_8/H_2O[c]	40

[a]Conditions: **1a** (0.05 mmol), **1b** (0.05 mmol), **2i** (see table for loading), solvent (0.50 mL), air, r.t. For system compositions at equilibrium, see SI. [b]Time to χ_{95} (95% equilibration degree).[17b, 26] [c]Water-saturated solvent.

Substrate scope and functional group tolerance. Next, the generality of the equilibration procedure was addressed. Using $CDCl_3$ as solvent and thiourea **2i** as catalyst, a small screen of aromatic imines was first conducted, with focus on substrates which we,[29] and others,[4a, 16c] had found incompatible or problematic with other catalysis protocols (Table 3). For example, imines with coordinating *ortho*-substituents tend to bind strongly to Lewis acids, partly inhibiting turnover and leading to perturbed equilibria. The substrate screen results proved satisfactory, and all tested substrates underwent equilibration with the hydrogen-bond catalyst. Identical equilibrium positions were furthermore reached with and without catalyst. Clear rate accelerations were observed in all cases except for pyridine-substituted imine **1f**, where the background reaction *per se* was rapid. It was also noticed that imidazole-based imine **1i** showed lower relative rate accelerations compared to structurally analogous imines **1e** and **1f**, indicating that the basic imidazole moiety impacted the catalysis negatively.

Table 3: Substrate screen of thiourea-catalyzed equilibration of dynamic systems with different aromatic imines.[a]



Ar	Imine	$t(\chi_{95})$ w/ 2i (h)[b]	$t(\chi_{95})$ w/o 2i (h)[b]
4-Fluorophenyl	**1b**	0.8	10
2-Furanyl	**1e**	4	14
2-Pyridyl	**1f**	3	4
2-Salicyl	**1g**	15	168[c]
2-Pyrrolyl	**1h**	16	240[c]
1-Me-2-imidazoyl	**1i**	5	10

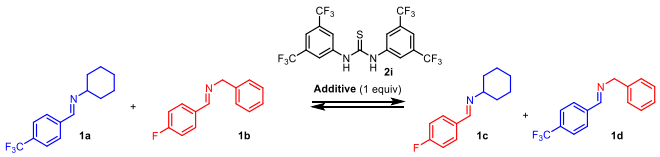
[a]Conditions: **1a** (0.05 mmol), **1b,e-i** (0.05 mmol), **2i** (10%), water-saturated $CDCl_3$ (0.50 mL), air, r.t. Cf. SI for system compositions at equilibrium. [b]Time to χ_{95} (95% equilibration degree).[17b, 26] [c]Partial system degradation occurs before equilibrium was reached.

Dynamic covalent chemistry is commonly used in complex functional systems, where it is important that equilibration protocols have a broad substrate tolerance and can operate in the presence of different functional groups and processes.[2] Traditional imine equilibration protocols are lacking in this regard, as many common functional groups are incompatible with acids and metal catalysts. However, hydrogen-bond catalysis is exceptionally mild, and due to the weak coordination there is a low propensity for catalyst inhibition.[18a]

In order to test the robustness and compatibility of our hydrogen bond catalyzed imine exchange protocol towards different functional groups, a robustness screen was performed.[30] One equivalent of a range of different additives was thus mixed into an equilibrating imine exchange reaction and the effects recorded (Table 4). In the absence of additive, the reaction went to completion in slightly less than 1 h (Table 2, entry 6). Most additives had no impact on the reaction time, the degree of hydrolysis, or the equilibrium position. Furthermore, even Lewis-basic substrates such as bipyridines, phosphines, and nitrogen-containing heterocycles were well-tolerated, with no noticeable impact on the equilibration (Table 4 entries 1-4). Sensitive substrates such as thiolesters worked well (Table 4 entry 5), as did nitriles and nitroaromatics, which coordinate strongly to thioureas (Table 4 entries 6-7). Moreover, the presence of free thiols and alcohols was also tolerated, despite the risk of intervention in the equilibrium network by the formation of thioaminals and hemiaminals (Table 4 entries 10-11).[4e, 31] However, strong Brønsted bases retarded the reaction significantly. One equivalent triethylamine increased the equilibrium time to around 24 h, while DABCO led to equilibration in ca 5-6 h (Table 4 entries 12-13). The stronger base 1,8-diazobicycloundec-7-ene (DBU) shut down the reaction

completely (Table 4 entry 14), and led to substrate and catalyst decomposition. However, the background equilibration was completely inhibited in basic environments, and the equilibration times with compound **2i** together with NEt_3 or other bases were almost identical to those obtained with $Sc(OTf)_3$.[16c]

Table 4: Robustness screen with catalyst **2i** to test influence of additives on equilibration rate and equilibrium.[a]



Entry	Additive	Eq. (1h)	Eq. (5h)	Eq. (24h)	Additive remaining (%)[b]	Hydrolysis (%)	Eq. composition (%, 1a:1b:1c:1d)
1		✓	✓	✓	>99	2.8	24 : 28 : 24 : 24
2		✗	✓	✓	>99	2.6	26 : 26 : 24 : 24[c]
3		✓	✓	✓	>99	2.9	28 : 25 : 23 : 24
4	Ph_3P	✓	✓	✓	98	2.8	25 : 27 : 24 : 24[d]
5		✓	✓	✓	>99	3.5	26 : 27 : 24 : 24
6	PhCN	✓	✓	✓	>99	2.8	25 : 27 : 24 : 24
7	$PhNO_2$	✓	✓	✓	>99	3.2	26 : 26 : 24 : 24
8	PhOH	✓	✓	✓	>99	4.6	52 : 23 : 25[e]
9		✓	✓	✓	>99	4.7	25 : 28 : 23 : 25
10	nBuOH	✓	✓	✓	>99	1.9	25 : 27 : 24 : 24
11	EtSH	✓	✓	✓	84	3.1	26 : 27 : 24 : 24
12	NEt_3	✗	✗	✓	>99	1.8	52 : 23 : 25[e]
13	DABCO	✗	✓	✓	>99	3.2	26 : 26 : 24 : 24
14	DBU	✗	✗	✗	55	N/A	n.d.
15	$PhCO_2Me$	✓	✓	✓	>99	2.7	25 : 27 : 23 : 25
16	None	✓	✓	✓	N/A	3.0	26 : 26 : 23 : 25

[a]Conditions: **1a** (0.05 mmol), **1b** (0.05 mmol), **2i** (10%), water-saturated $CDCl_3$ (0.50 ml), additive (0.05 mmol), air, r.t. System monitored at specified time points, check mark indicates system is at or close to equilibrium, cross indicates system at less than χ_{85} (85% equilibration degree) at specified time. [b]Determined after 24 h by ^{1}H-NMR spectroscopy. [c]Partial overlap of additive peak with imine peaks. [d] ^{31}P-NMR spectroscopy used to quantify additive. [e]Imine peaks from **1a** and **1b** merged.

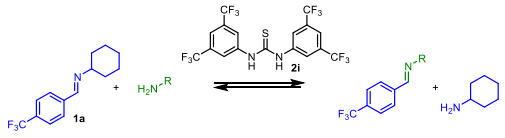
Catalysis of transimination pathways. Transimination through the addition of a free amine to an imine is a key pathway in dynamic imine chemistry (Figure 1). In order to test if hydrogen-bond catalysis was also applicable to this type of exchange, catalyst **2i** was utilized with imine **2a** and benzylamine under moisture-free conditions. Rapid equilibration was observed, with equilibrium reached in about 6-8 min as estimated by ^{1}H-NMR spectroscopy (Table 5, entry 1). Also, catalyst loading could be lowered as far as 1% while still achieving equilibrium within 1 h (Table 5, entry 3).

While the relative instability of imines precludes their use in many applications, analogous compounds such as oximes and hydrazones are considerably more stable. When evaluating transimination-type reactions with phenylhydrazine and benzylhydroxylamine, respectively, minor rate enhancements were also observed (Table 5, entries 5 and 7). Though the accelerations were relatively low, these results suggest a degree of generality to the hydrogen-bond catalysis approach to dynamic systems equilibration.

Mechanistically, the precise interaction mode of imines with thioureas is still not a resolved issue.[27b] However, a chelating coordination mode of the thiourea N-H bonds to the imine can be envisioned, where one hydrogen atom coordinates to the nucleophile and one to the electrophile, prearranging the two reactants by bringing them into close proximity. Conspicuously, the kinetic profile of the imine exchange reaction with catalysts **2i** and **2m** was distinctly sigmoidal in shape (Figure S1-S2), suggesting a change in the rate-limiting reaction of the imine system as the process progresses. It can thus be suggested that the rate-limiting reaction during the initial stage of

the reaction is the thiourea-catalyzed hydrolysis of the initial imine pair. Once a certain threshold of free amine is reached, the hydrogen-bond catalyst catalyzes the transimination pathway more efficiently. In support of this hypothesis, increasing the water content to 5% in DMSO-d_6 indeed significantly accelerated the equilibration time from 12 h to ca 5 h.

Table 5: Catalysis of transimination-type reactions with thiourea **2i**.[a]

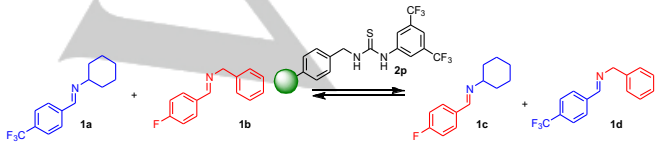


Entry	R	Product imine	Loading 2i (%)	$t(\chi_{95})$ (h)[b]	$\chi_{95,cat}/\chi_{95,uncat}$[c]	Eq. composition (%, 1a/product)[d]
1	-Bn	**1c**	10	0.1	200[e]	49 : 51
2	-Bn	**1c**	2	0.4	50[e]	49 : 51
3	-Bn	**1c**	1	1.0	20	49 : 51
4	-Bn	**1c**	-	20		49 : 51
5	-NHPh	**1j**	10	24	5	99 : 1
6	-NHPh	**1j**	-	120[d]		99 : 1
7	-OBn	**1k**	10	40	3	86 : 14
8	-OBn	**1k**	-	120		86 : 14

[a]Conditions: **1a** (0.05 mmol), amine (0.05 mmol), **2i** (10%), $CDCl_3$ (0.50 mL), air, r.t. [b]Time to χ_{95} (95% equilibration degree).[17b, 26] [c]Determined by ^{1}H-NMR spectroscopy. [d]Degradation of system components.

Solid-supported hydrogen-bond catalysts. Heterogeneous reaction systems remain rare in dynamic chemistry, to some extent associated with the inherent difficulties in analyzing complex mixtures in two-phase systems.[16c, 32] Nevertheless, control of dynamic systems is simplified with immobilized catalysts, since simple filtration can halt or stop the equilibration procedure. To this end, polystyrene-bound thiourea **2p** was prepared following an established protocol.[33] The ligand density on the beads was determined to 1.52 ± 0.08 mmol/g using an Acid Orange 7 UV/Vis assay (Figure S4-S5).

The solid-supported thiourea **2p** was found to be an active catalyst for the imine exchange, but with decreased activity compared to homogenous catalyst **2i** (Scheme 1). This effect is not surprising, given the lower hydrogen bond donor strength as well as the generally lower activity of immobilized catalysts. However, by increasing the approximate loading to 20%, equilibrium could still be attained within 1 h in $CDCl_3$, as compared to 10 h for the uncatalyzed reaction. In addition, the beads were actively catalyzing the imine exchange even at loadings as low as 3%, although a longer time (around 2.5 h) was required. Interestingly, no rate enhancement was observed with the parent amino-functionalized polystyrene beads, suggesting that primary amine catalysis pathways were not operating to a significant extent within the system. Furthermore, even after prolonged reaction times, the concentration of the equilibrated imines in the solution phase did not change, indicating low levels of adsorption or chemisorption of the imines onto beads.



Scheme 1. Catalysis of imine exchange with solid-supported thiourea.

The recyclability of the solid-supported catalyst was also tested by reusing the beads over five equilibration cycles. During this time, no decrease in catalyst performance was observed. Furthermore, the beads could be utilized to turn on and off the equilibration through simple addition and filtration (Figure 4). The reaction was conducted in the absence of catalyst for 1 h (area I), after which time the thiourea-functionalized beads **2p** were added. This induced a significant rate acceleration (area II). Filtering off the beads again retarded the equilibration rate (area III), while the addition of a fresh bead-batch again initiated a burst in reaction rate (area IV). This experiment demonstrated how the equilibration properties of the system could be modulated through simple addition and removal of the solid-supported catalyst.

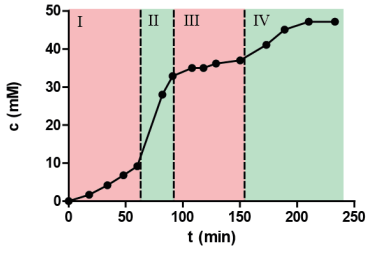


Figure 4: Controllable equilibration rates by addition and removal of solid-supported thiourea catalyst **2p**. Conditions: Stage I: Imines **1a** (0.075 mmol) and **1b** (0.075 mmol), H_2O-saturated $CDCl_3$ (0.75 ml), air. Stage II: Addition of **2p** (24 mg). Stage III: Removal of **2p** by filtration. Stage IV: Addition of **2p** (24 mg). Reaction progress monitored by ^{1}H-NMR spectroscopy.

Conclusions

In summary, we have demonstrated that hydrogen-bond catalysis is a valid approach to catalyze the equilibration of dynamic imine systems. Electron-poor thiourea- and squaramide catalysts efficiently catalyzed exchange between different imines, as well as transimination with amines, hydrazines, and hydroxylamines. Hydrogen-bond catalysis represents a very mild approach to achieve imine exchange, and the catalysts are stable to both moist and air. Furthermore, the thiourea catalysts retained their efficiency in the presence of a range of functional groups, including acid-sensitive moieties incompatible with other imine exchange conditions. Additionally, solid-supported thiourea catalysts may open new venues for dynamic- and systems chemistry, where the spatial location of the catalyst can be manipulated to create localized effects. Thus, this mode of catalysis is complementary to current catalytic systems, with potential use in the generation of complex, functional dynamic systems, molecular machines, and adaptive materials.

Experimental section

General methods and materials. All chemicals were purchased with the highest available purity from commercial suppliers. Liquid aldehydes and amines were distilled under anhydrous conditions at reduced pressure and stored under N_2 prior to use. Amino-functionalized polystyrene beads HL 100-200 mesh were purchased from Sigma-Aldrich and washed by incubation with anhydrous MeOH for 1 h, followed by filtration and subsequent rinsing with a large excess of anhydrous CH_2Cl_2 and drying under high vacuum. All other chemicals were used as received. The reactions using air- or moisture-sensitive compounds were carried out with oven-dried glassware under an N_2 atmosphere. 3 Å and 4 Å MS were pre-activated by heating to 600 °C under reduced pressure for 15 min, followed by extended storage at 150 °C. Anhydrous solvents were passed through alumina columns in a Glass Contour solvent dispensing system and stored over molecular sieves, with the exception of acetonitrile, DMSO-d_6 and *N*-methyl pyrrolidine, which were dried through fractional distillation (atmospheric pressure) over appropriate drying agent and stored over 3 Å MS. $CDCl_3$ was filtrated through a plug of anhydrous K_2CO_3 to remove acidic impurities, followed by drying over activated 4 Å MS under inert atmosphere. Solvents for workup, extractions and, flash column chromatography were of analytical grade and used as supplied. Water-saturation of solvents was achieved by the addition of 100% v/v of Milli-Q water to the solvent, followed by excessive shaking and finally withdrawal of the solvent from the two-phase mixture via syringe. Thin-layer chromatography was carried out using pre-coated Merck silica gel 60 F254 aluminum-backed plates (0.25 mm), visualized using UV light followed by staining in a solution of phosphomolybdic acid in ethanol. Flash column chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm). NMR spectroscopy was performed using Bruker Avance DMX 500 and Ascend 400 spectrometers. Chemical shifts are reported as δ values (ppm) with (residual) solvent as the internal reference.

Representative procedure for imine exchange. Imine **1a** (12.8 mg, 0.05 mmol) and imine **1b** (10.7 mg, 0.05 mmol) were mixed in anhydrous DMSO-d_6 (0.47 mL) in a dry NMR tube, and distilled H_2O (5.0 µL) was added via micropipette. Finally, catalyst **2i** in anhydrous DMSO (0.2 M, 25 µL) was added. The tube was sealed and vigorously shaken for ca 1-2 min, after which time the reaction was left at r.t. and monitored by ^{1}H-NMR analysis. Several experiments were generally performed to assess the equilibration time, and the approximate time (± 5%) when the reaction had passed χ_{95} (95% equilibration degree) was recorded. Similar protocols were used for other solvents, catalysts, and catalyst loadings.

Representative procedure for transimination. Imine **1a** (12.8 mg, 0.05 mmol) was weighed out in an Eppendorf tube and dissolved in a solution of catalyst **2i** (2.50 mg, 0.005 mmol) in anhydrous $CDCl_3$ (0.50 mL). Benzylamine (5.45 µL, 5.3 mg, 0.05 mmol) was then added, and the solution was transferred to a dry NMR tube at r.t. under N_2. The reaction was monitored by ^{1}H-NMR analysis, and the approximate time (± 5% reaction time) when the reaction had passed χ_{95} (95% equilibration degree) was recorded.

Imine exchange with solid-supported thiourea catalyst. To a screw-cap vial was added thiourea-functionalized polystyrene beads (ca 25 mg), followed by a solution of imines **1a** and **1b** (0.10 mmol each) in H_2O-saturated $CDCl_3$ (1.0 mL) under air at r.t. The suspension was stirred slowly at r.t. under air and monitored by withdrawing aliquots of the reaction mixture (50 µL), which were filtered through a cotton plug and diluted with $CDCl_3$ (0.45 mL) before NMR analysis.

Reusability of solid-supported thiourea catalyst. The reaction was carried out in a plastic syringe equipped with a cotton plug, an acrodisc, and a disc cap. After withdrawing the plunger, beads (ca 30 mg) and a solution of imines **1a** and **1b** (0.05 mmol each) in H_2O-saturated $CDCl_3$ (0.50 mL) was added at r.t. and all air bubbles were pushed out of the syringe before capping. The syringe was shaken with a mechanical shaker for 1 h, after which time the reaction solution was pushed out through the plug and the acrodisc straight into an NMR tube. The beads were washed with $CDCl_3$ (3 × 0.5 mL), which was also passed through the syringe plug. After this procedure, compressed air was passed through the syringe to dry the beads, and a new cycle was initiated by the addition of a new solution of imines.

Control of equilibration rate by addition and removal of solid-supported thiourea catalyst. Imines **1a** and **1b** (0.075 mmol each) were mixed in an NMR tube and dissolved in water-saturated $CDCl_3$ (0.75 mL) at r.t. under air. The reaction was monitored with ^{1}H-NMR spectroscopy for 1 h, after which polystyrene-bound thiourea catalyst **2p** (24 mg, ca 0.5 equiv.) was added, and the solution was shaken in a mechanical shaker in between the NMR measurements. To stop the catalysis, the beads were removed by filtering the reaction solution through a short plug of celite.

General procedure for imine synthesis. To a mixture of pre-activated 4 Å MS (1.0 g/mmol substrate) in anhydrous CH_2Cl_2 (5 mL for **1a**-**1d**, 10 mL for **1e**-**1k**), aldehyde (10 mmol for **1a**-**1d**, 1.0 mmol for **1e**-**1k**, 1 equiv.) and amine (10 mmol for **1a**-**1d**, 1.0 mmol for **1e**-**1k**, 1 equiv.) were mixed under N_2. The reaction was stirred slowly at room temperature for 14-24 h, after which time NMR analysis indicated a complete reaction. The solution was filtered through a pad of celite, washed with anhydrous CH_2Cl_2, and concentrated *in vacuo*. The obtained compounds were all evacuated at HV for 2-24 h under mild heating to remove traces of amine and aldehyde, leading to analytically pure products.

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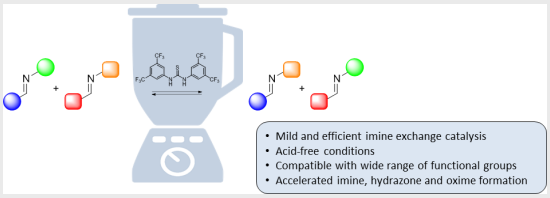

Hydrogen bond donors, such as thioureas and squaramides, has been shown to catalyze the equilibration of dynamic imine systems under unprecedentedly mild conditions. The catalytic effect takes place in different solvents and in the presence of sensitive additives, leading to rate accelerations for imine metathesis and transimination with amines, hydrazines, and hydroxylamines.

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Hydrogen-Bond Catalysis of Imine Exchange in Dynamic Covalent Systems