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Dynamic Chemistry |*Hot Paper*|

Dynamic Covalent Chemistry of Aldehyde Enamines: Bi^{III}- and Sc^{III}-Catalysis of Amine–Enamine Exchange

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Abstract: The dynamic exchange of enamines from secondary amines and enolizable aldehydes has been demonstrated in organic solvents. The enamine exchange with amines was efficiently catalyzed by $Bi(OTf)_3$ and $Sc(OTf)_3$ (2 mol%) and the equilibria (60 mM) could be attained within hours at room temperature. The formed dynamic covalent systems displayed high stabilities in basic environment with $<2\%$ by-product formation within one week after complete equilibration. This study expands the scope of dynamic C–N bonds from imine chemistry to enamines, enabling further dynamic methodologies in exploration of this important class of structures in systems chemistry.

Introduction

The emergence of constitutional dynamic chemistry, relying on reversible reactions/interactions to change the constitution of systems, has led to the establishment of a range of applications.[1–14] For example, the design and discovery of ligands, receptors, reactions, and catalysts have been established,[15–30] a range of materials have been produced,[31–35] and a basic understanding of complex networks and systems has been established.[36–41] To meet with the operational requirements of generating and applying complex systems, new types of exchange reactions that enable novel constitutional diversity are in high demand. In this context, constitutional dynamic systems based on enamine exchange could be of interest. For example, the integration of enamine bonds as constitutional linkages enables the capability of *cis*/*trans* isomerization, in principle controllable by noninvasive light.[42] In addition, enamines are widely recognized as valuable activated species in many important organic transformations,[43] thus opening a pathway to catalyst discovery via dynamic chemistry.[22,44]

In contrast to extensively explored imine exchange,[45] enamine exchange has not been evaluated in dynamic covalent chemistry, other than for 3-iminoesters and ketones in equilibrium with the corresponding α,β-unsaturated carbonyl species.[46–48] This fact is most likely associated with the enhanced nucleophilic reactivity of enamines, which can lead to aldol-type reactions and thus quench the dynamic systems in the process. However, in recent studies with enamine-azide cycloadditions,[49] isolated or in situ-generated aldehyde enamines were found to be relatively stable. Moreover, a recent study also reported high stability of enamines in the presence of 1,8-diazabicycloundec-7-ene (DBU).[50] These results inspired us to explore enamines as constituents for constitutional dynamic chemistry. Since imines are generally labile under basic conditions, this furthermore renders enamine exchange unique from other CN-based dynamic covalent systems.

The understanding of enamine chemistry has expanded substantially in recent years due to the growing interest in organocatalysis mediated by secondary amines.[43,51] The relative tendencies of carbonyl compounds and amines to condense into enamines has, for example, been evaluated (Figure 1 a).[52] In general, the condensation products from aldehydes and amines display considerably higher degrees of enamines at equilibrium compared to the corresponding ketone species.[52] The condensation reactions between aldehydes and amines can furthermore be selectively accomplished at ambient tem-

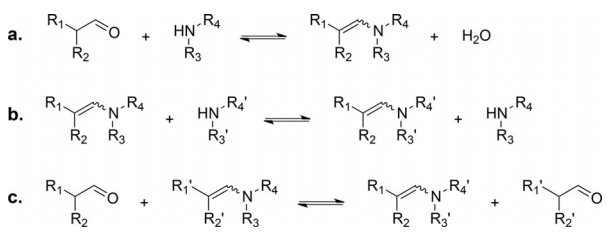

Figure 1. Exchange reactions of aldehyde enamines: (**a**) formation and hydrolysis; (**b**) amine-enamine exchange; (**c**) aldehyde-enamine exchange.

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perature in the absence of added catalysts.[53] The high chemoselectivity is in this context indicative of potential compatibility with dynamic systems composed of diverse chemical components. For aldehyde enamines, transenaminations (Figure 1 b,c) have also been reported, albeit very preliminarily.[54] These studies have been limited to pyrrolidine derivatives, mainly involving MacMillan and Jørgensen–Hayashi catalysts. For constitutional dynamic chemistry, the performance of the dynamic exchange, the reactant scope, and the robustness of the systems are of primary concern, especially regarding the modular structures required. These challenges have been targeted in the present study, where we report on efficient enamine exchange processes with respect to reaction type, solvents, catalysts and component structural effects (Figure 1).

Results and Discussion

The equilibrium constants (K_{eq}) for typical secondary amines and aldehydes in different solvents were first evaluated (Table 1). This was accomplished by following the reactions by

Table 1. Equilibrium constants (K_{eq}) for enamine formation.[a]

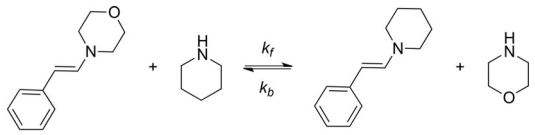
	Solvent			
Ph CHO	$CDCl_3$	>3000	1300	990
	C_6D_6	802	>300	0
	$[D_6]DMSO$	>3200	>3200	
Ph CHO	$CDCl_3$	1.4	1.1	0.14
	C_6D_6	13	11	0.68
	$[D_6]DMSO$	1200	960	68

[a] Reactions were conducted at 25 °C in $CDCl_3$, C_6D_6, and $[D_6]DMSO$, monitored by ^1H NMR. See Figure S1 for details.

^1H NMR, in accordance to a reported protocol (see supporting information for details).[52] The amines were thus added to aldehyde solutions in dry $CDCl_3$, C_6D_6 or $[D_6]DMSO$, and the equilibrations followed. A slight excess of the respective amine was used in order to avoid formation of hemiaminal-type intermediates,[55] and iminium hydroxides were only detected in trace amount in all tests.[52] All condensations proceeded smoothly without catalysts, where the equilibria in chloroform and DMSO were attained within 1 h. In benzene, on the other hand, equilibration was sluggish and the equilibrium time exceeded 10 h. Highly favored enamine equilibria ($K_{eq}>100$) were observed for phenylacetaldehyde with all secondary amines, likely due to enhanced enamine stabilization through conjugation. 3-phenylpropanal, resulting in unconjugated enamines, showed fast equilibration and yielded significant amounts of enamines (K_{eq} up to 1.4 in $CDCl_3$). Considering the amine structure, acyclic diethylamine generally showed lower enamine formation than cyclic amines, likely owing to the weaker nucleophilicity and enhanced steric hindrance. In addition, the observed equilibrium constants showed a high dependence on the solvent, where chloroform favored the enamine to a lower extent, while DMSO resulted in the highest degree of enamine formation.

The effects of Brønsted and Lewis acids on the amine-enamine exchange were subsequently evaluated. The exchange between isolated (*E*)-4-styrylmorpholine (**1**) and piperidine (**a**) was thus studied in $CDCl_3$, leading to equilibrium formation with (*E*)-1-styrylpiperidine (**2**) and morpholine (**b**, Table 2). A catalyst loading of 2 mol% was used throughout, and the process was monitored by ^1H NMR (*cf.* Supporting Information).

Table 2. Catalyzed transenamination.[a]



1 **a** **2** **b**

Entry	Catalyst[b]	Selectivity[c]	K_{obs}	k_f [M^{-1} h^{-1}][d]	Acceleration[e]
1	–	1.7	2.9	0.024±0.0005	1
2	CF_3COOH	1.7	2.9	0.17±0.01	7
3	$Bi(OTf)_3$	1.7	2.9	7.4±0.3	310
4	$Sc(OTf)_3$	1.7	2.8	7.5±0.3	310
5	$Zn(OTf)_2$	1.8	3.2	4.7±0.2	200
6	$Cu(OTf)_2$	1.4	2.1	4.3±0.3	180
7	AgOTf	1.7	2.8	0.97±0.08	40

[a] Enamine **1** (62.8 mM), piperidine (62.8 mM), in $CDCl_3$, 22 °C, monitored by ^1H NMR. [b] 2 mol% (added as 0.1 M CD_3CN solution). [c] Ratio of enamine **2**/enamine **1** at equilibrium. [d] Calculated by nonlinear regression analysis towards standard reaction model (*cf.* Supporting Information). [e] Relative ratio: k_f/k_{uncat}.

The resulting reactions with bismuth triflate $Bi(OTf)_3$ (Table 2, entry 3) and scandium triflate $Sc(OTf)_3$ (Table 2, entry 4) displayed the highest rates (7.4–7.5 $M^{-1}h^{-1}$) in attaining enamine equilibria, and >300 times rate enhancement compared to the uncatalyzed transenamination reaction (Table 2, entry 1). It can be noticed that this rate is generally >2 orders of magnitude higher than $Sc(OTf)_3$-catalyzed imine exchange under identical conditions, thus supporting the use of catalyzed transenamination for generation of constitutional dynamic systems.[40] Other Lewis-acidic metal salts, including $Zn(OTf)_2$, $Cu(OTf)_2$ and AgOTf, also displayed catalytic effects, but to lower extents (Table 2, entries 5–7). In contrast to the Lewis acids, the use of trifluoroacetic acid only resulted in 4 times rate enhancement (Table 2, entry 2). In general, the equilibrium ratios remained unchanged upon addition of catalysts, with selectivities very close to the uncatalyzed reaction (selectivity ≈1.7). Addition of $Cu(OTf)_2$, however, was found to shift the equilibrium to some extent (selectivity = 1.4). The reason for this effect was in part associated with a higher degree of by-product formation (≈4% after 10 h).

The effect of the catalyst loading was then studied on the model transenamination reaction (Figure 2, and Table S1). The rates increased linearly with increased catalyst loading (<8%) (Figure S3), indicating a process first order in catalyst. The fraction of enamine **2** at equilibrium was gradually influenced at higher catalyst loadings. For $Bi(OTf)_3$, loadings at 4–20 mol%

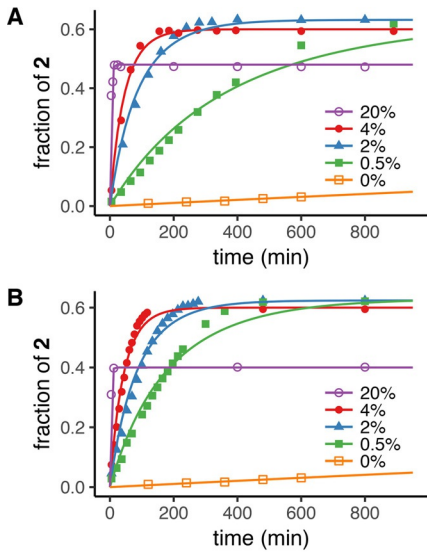


Figure 2. Equilibration process between enamines **1** and **2** (initial concentration of **1**: 62.8 mM), at different loadings of $Sc(OTf)_3$ (**a**), and $Bi(OTf)_3$ (**b**). Determined by ^1H NMR following the enamine signals at 23 °C in $CDCl_3$.

resulted in fractions of enamine **2** of 60–48% (respectively), as compared to the case with <2 mol% catalyst, which resulted in 63%. The shift was even more significant when $Sc(OTf)_3$ was used, where 4–20 mol% catalyst yielded fractions of 58–40% (respectively). Similar observations have also been recorded for Sc^{III}-catalyzed imine exchange.[56] Coordination of the amines to the metal cations may explain these equilibrium fraction shifts, and the weaker coordination between the softer bismuth(III) and the amine nitrogen correlates with a lower degree of equilibrium shift compared with the Sc^{III} species. With a catalyst loading of <2 mol%, the final equilibrium remained the same as in the uncatalyzed system.

The performance of the catalysis was also evaluated in four typical solvents (Table 3). The rates of the forward reaction in the uncatalyzed process ($k_{f,uncat}$) were relatively strongly influenced by the solvent, with a solvent order for the transenamination rate of MeCN > DMSO ≈ $CDCl_3$ > benzene, which correlated well with the solvent effect of the condensation process. The catalytic effects of Sc^{III} and Bi^{III} varied with the different solvents, and the rate acceleration was most pronounced in benzene. Furthermore, the use of coordinating solvents, such as DMSO, decreased the catalytic effects substantially. Similar effects were also observed in $Sc(OTf)_3$-catalyzed imine exchange.[40] The fastest equilibrium formation of the model reaction was observed in CD_3CN using $Bi(OTf)_3$, where a forward rate of 16.0 $M^{-1}h^{-1}$ was achieved.

Table 3. Catalyzed transenamination between compounds **1** and **2** in different solvents.[a]

Entry	Solvent	k_f [$M^{-1}h^{-1}$][c] Bi^{III}[b]	Acc[d]	Sc^{III}[b]	Acc[d]	Control
1	$CDCl_3$	7.4 ± 0.3	310	7.5 ± 0.3	310	0.024 ± 0.0005
2	C_6D_6	4.0 ± 0.2	270	4.1 ± 0.2	280	0.015 ± 0.001
3	[D_6]DMSO	0.090 ± 0.003	2.9	0.11 ± 0.009	3.6	0.031 ± 0.001
4	CD_3CN	16.0 ± 1.1	54	15.0 ± 1.0	49	0.30 ± 0.2

[a] Enamine **1** (62.8 mM), piperidine (62.8 mM), 22 °C, monitored by ^1H NMR. [b] 2 mol% (added as 0.1 M in CD_3CN). [c] Calculated by nonlinear regression analysis towards standard reaction model (*cf.* Supporting Information). [d] Acceleration; relative ratio: k_f/k_{uncat}.

The influence of the amine structure on the kinetic (k_f) and thermodynamic (selectivity) parameters of the exchange process was studied with enamine **1** and diethylamine (**c**), *N*-methyl-1-phenylmethanamine (**d**), (*S*)-(−)-*N*,α-dimethylbenzylamine (**e**), dibenzylamine (**f**) and pyrrolidine (**g**) (Figure 3)). The

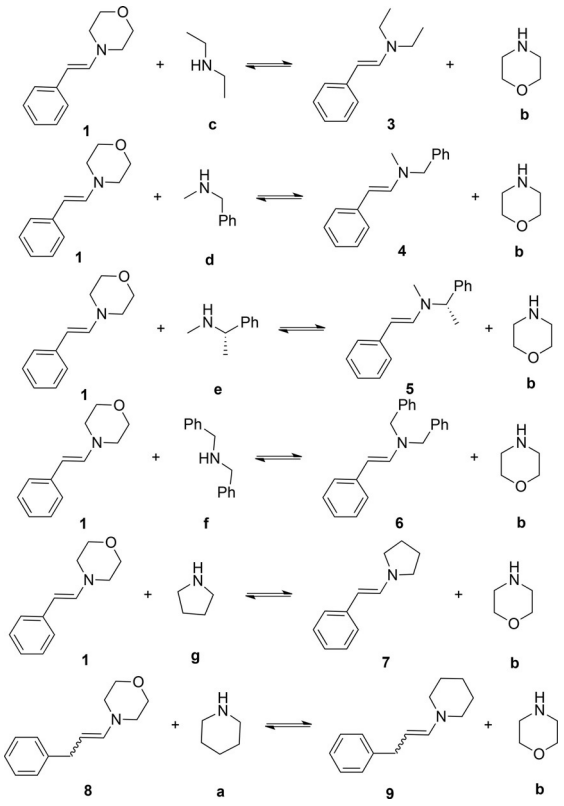


Figure 3. Exchange reactions between enamines (**1** or **8**) and secondary amines.

selectivity under both catalyzed and uncatalyzed conditions followed the order: enamine **7** > **2** > **4** > **1** > **6** > **3** ≈ **5**, which correlated well with the stability trend of the enamine formation, where amines with higher nucleophilicities led to more stabilized enamines. Interestingly, the best selectivity among acyclic amines was recorded for *N*-methyl-1-phenylmethanamine (**d**), presumably owing to lower steric hindrance, thus leading to a more stable enamine compared with other amines (**e**, **f**).

The selectivity values recorded for the Bi^{III}- and Sc^{III}-catalyzed reactions were for most systems analogous to the corresponding uncatalyzed reactions (Table 4). A slight shift towards the pyrrolidine-based enamine **7** was however observed with Sc^{III} (Table 4, entry 6). Furthermore, all acyclic and cyclic amines displayed relatively close selectivity values in the exchange reactions with enamine **1**. This isoenergetic effect is advantageous

Table 4. Selectivities and exchange rates between enamines **1** and **8** and secondary amines.[a]

Entry	Enamines	Selectivity			k_f [$M^{-1}h^{-1}$][c]			k_f(Bi):k_f(Sc):k_f(control)
		Bi^{III}[b]	Sc^{III}[b]	Control	Bi^{III}	Sc^{III}	Control	
1	**1/2**	1.7	1.7	1.7	7.4±0.3	7.5±0.3	0.024±0.0005	310:310:1
2	**1/3**	0.4	0.5	0.4	3.1±0.04	2.8±0.06	0.015±0.0008	210:190:1
3	**1/4**	1.5	1.5	1.5	270±40	260±30	0.87±0.02	310:300:1
4	**1/5**	0.4	0.4	0.4	13±0.1	12±0.2	0.052±0.01	250:230:1
5	**1/6**	0.3	0.3	0.3	20±1.2	9.8±0.3	0.26±0.01	75:37:1
6	**1/7**	4.0	5.4	4.0	12±1.3	6.8±1.0	0.038±0.002	320:180:1
7	**8/9**	1.8	1.8	1.7	166±11	178±12	0.54±0.003	310:330:1

[a] Enamine (62.8 mM), amine (62.8 mM), 22 °C, in $CDCl_3$, monitored by ^1H NMR. [b] 2 mol% (added as 0.1 M CD_3CN solution). [c] Calculated by nonlinear regression analysis towards standard reaction model (cf. Supporting Information). [d] Relative ratio: k_f/k_{uncat}.

for dynamic covalent reactions that are aimed for more complex constitutional systems.

The rates (k_f) of the Bi^{III}-catalyzed and uncatalyzed enamine exchange reactions both followed the same order (Table 4, entries 3>5>4>6>1>2). The highest rate (Table 4, entry 3) was observed for *N*-methyl-1-phenylmethanamine (**d**), being more than one order of magnitude faster than all the other amines. However, the relative rate enhancements of the catalyzed reactions compared to the uncatalyzed counterparts ($k_f/k_{f,uncat}$) followed a different order of amine substrates (for Bi^{III}: Table 4, entries 3>6>1>4>2>5). Sc^{III} behaved similar to Bi^{III}, mainly differing for amines **6** and **7** (Table 4, entries 5 and 6), where the rates were almost a factor two lower. The relative results for the non-conjugated enamine exchange (Table 4, entry 7) were very similar to those for the corresponding conjugated enamine (Table 4, entry 1).

High constitutional stabilities were observed at equilibrium for both the catalyzed- and uncatalyzed transenamination reactions. As monitored by ^1H NMR, <3% variations in the spectra were recorded for up to 7 days. In these tests, two equivalents of amine were added together with one equivalent of aldehyde, in congruence with the situation in the amine-enamine exchange reactions. As expected, the major side reaction recorded was the aldol condensation, identified in independent experiments (*cf.* Supporting information).

Conclusion

In summary, reversible exchange reactions of aldehyde enamines (C=C–N) have been studied, showing comparable capabilities of generating constitutional dynamic system as other reversible C–N bonds, such as imines. Different amines and aldehydes were evaluated, for which efficient exchange reactions in general could be shown. Secondary amines and aldehydes thus readily condensed to enamines at room temperature in various organic solvents, and the equilibration constants were shown to be influenced by the solvent properties. More importantly, both Bi^{3+} and Sc^{3+} were found to catalyze the exchange transenamination process efficiently. Under catalytic conditions, equilibrium formation was accomplished within hours. Complementary to imine systems, the current dynamic enamine systems showed improved stability with less side reactions under basic conditions. The results support the potential of using enamine-mediated exchange processes to generate constitutional dynamic systems for different applications in dynamic chemistry.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · bismuth · enamines · scandium · systems chemistry

[1] B. L. Miller, Dynamic Combinatorial Chemistry: In Drug Discovery, Bioorganic Chemistry, and Materials Science John Wiley & Sons, Inc., Hoboken, NJ, **2010**.
[2] J. N. H. Reek, S. Otto, *Dynamic Combinatorial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2010**.
[3] M. Barboiu, *Constitutional Dynamic Chemistry*, Springer Verlag, Berlin Heidelberg, **2012**.
[4] R.-C. Brachvogel, M. von Delius, *Eur. J. Org. Chem.* **2016**, *22*, 3662–3670.
[5] I. Azcune, I. Odriozola, *Eur. Polym. J.* **2016**, *84*, 147–160.
[6] Y. Zhang, M. Barboiu, *Chem. Rev.* **2016**, *116*, 809–834.
[7] J.-M. Lehn, *Angew. Chem. Int. Ed.* **2015**, *54*, 3276–3289; *Angew. Chem.* **2015**, *127*, 3326–3340.
[8] A. Herrmann, *Chem. Soc. Rev.* **2014**, *43*, 1899–1933.
[9] A. Wilson, G. Gasparini, S. Matile, *Chem. Soc. Rev.* **2014**, *43*, 1948–1962.
[10] M. C. Misuraca, E. Moulin, Y. Ruff, N. Giuseppone, *New J. Chem.* **2014**, *38*, 3336–3349.
[11] L. Hu, F. Schaufelberger, B. J. J. Timmer, M. Abellán-Flos, O. Ramström, *Kirk-Othmer Encycl. Chem. Technol.* **2014**, 1–25.
[12] Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634–6654.
[13] E. Moulin, G. Cormos, N. Giuseppone, *Chem. Soc. Rev.* **2012**, *41*, 1031–1049.
[14] G. Gasparini, M. Dal Molin, L. J. Prins, *Eur. J. Org. Chem.* **2010**, *13*, 2429–2440.
[15] É. Bartus, Z. Hegedüs, E. Wéber, B. Csipak, G. Szakonyi, T. A. Martinek, *ChemistryOpen* **2017**, *6*, 236–241.
[16] J. Soubhye, M. Gelbcke, P. Van Antwerpen, F. Dufrasne, M. Y. Boufadi, J. Nève, P. G. Furtmüller, C. Obinger, K. Zouaoui Boudjeltia, F. Meyer, *ACS Med. Chem. Lett.* **2017**, *8*, 206–210.
[17] N. Busschaert, S. Thompson, A. D. Hamilton, *Chem. Commun.* **2017**, *53*, 313–316.
[18] S. Albano, G. Olivo, L. Mandolini, C. Massera, F. Ugozzoli, S. Di Stefano, *J. Org. Chem.* **2017**, *82*, 3820–3825.
[19] A. G. Orrillo, A. M. Escalante, R. L. E. Furlan, *Chem. Eur. J.* **2016**, *22*, 6746–6749.
[20] F. Schaufelberger, L. Hu, O. Ramström, *Chem. Eur. J.* **2015**, *21*, 9776–9783.
[21] Y. Zhou, Y. Yuan, L. You, E. V. Anslyn, *Chem. Eur. J.* **2015**, *21*, 8207–8213.
[22] F. Schaufelberger, O. Ramström, *Chem. Eur. J.* **2015**, *21*, 12735–12740.
[23] L. Hu, O. Ramström, *Chem. Commun.* **2014**, *50*, 3792–3794.
[24] M. Mondal, N. Radeva, H. Köster, A. Park, C. Potamitis, M. Zervou, G. Klebe, A. K. H. Hirsch, *Angew. Chem. Int. Ed.* **2014**, *53*, 3259–3263; *Angew. Chem.* **2014**, *126*, 3324–3328.

[25] L. Hu, F. Schaufelberger, Y. Zhang, O. Ramström, *Chem. Commun.* **2013**, *49*, 10376.
[26] A. G. Santana, E. Jiménez-Moreno, A. M. Gómez, F. Corzana, C. González, G. Jiménez-Oses, J. Jiménez-Barbero, J. L. Asensio, *J. Am. Chem. Soc.* **2013**, *135*, 3347 – 3350.
[27] M. Demetriades, I. K. H. Leung, R. Chowdhury, M. C. Chan, M. A. McDonough, K. K. Yeoh, Y.-M. Tian, T. D. W. Claridge, P. J. Ratcliffe, E. C. Y. Woon, *Angew. Chem. Int. Ed.* **2012**, *51*, 6672 – 6675.
[28] A. J. Clipson, V. T. Bhat, I. McNae, A. M. Caniard, D. J. Campopiano, M. F. Greaney, *Chem. Eur. J.* **2012**, *18*, 10562 – 10570.
[29] L. You, J. S. Berman, E. V. Anslyn, *Nat. Chem.* **2011**, *3*, 943 – 948.
[30] R. Caraballo, H. Dong, J. P. Ribeiro, J. Jiménez-Barbero, O. Ramström, *Angew. Chem. Int. Ed.* **2010**, *49*, 589 – 593.
[31] J. Collins, M. Nadgorny, Z. Xiao, L. A. Connal, *Macromol. Rapid Commun.* **2017**, *38*, 1600760.
[32] L. Zhang, L. Chen, S. J. Rowan, *Macromol. Chem. Phys.* **2017**, *218*, 1600320.
[33] L. Marin, S. Moraru, M.-C. Popescu, A. Nicolescu, C. Zgardan, B. C. Simionescu, M. Barboiu, *Chem. Eur. J.* **2014**, *20*, 4814 – 4821.
[34] S. Mihai, Y. Le Duc, D. Cot, M. Barboiu, *J. Mater. Chem.* **2010**, *20*, 9443.
[35] N. Sreenivasachary, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 5938 – 5943.
[36] J. J. Armao, J.-M. Lehn, *Angew. Chem. Int. Ed.* **2016**, *55*, 13450 – 13454.
[37] F. Schaufelberger, O. Ramström, *J. Am. Chem. Soc.* **2016**, *138*, 7836 – 7839.
[38] T. Kosikova, H. Mackenzie, D. Philp, *Chem. Eur. J.* **2016**, *22*, 1831 – 1839.
[39] C.-W. Hsu, O. Š. Miljanić, *Angew. Chem. Int. Ed.* **2015**, *54*, 2219 – 2222.
[40] H. Fanlo-Virgós, A.-n. R. Alba, S. Hamieh, M. Colomb-Delsuc, S. Otto, *Angew. Chem. Int. Ed.* **2014**, *53*, 11346 – 11350.
[41] Y. Zhang, O. Ramström, *Chem. Eur. J.* **2014**, *20*, 3288 – 3291.
[42] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322 – 5363.
[43] W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580 – 591.
[44] P. Dydio, P.-A. R. Breuil, J. N. H. Reek, *Isr. J. Chem.* **2013**, *53*, 61 – 74.
[45] M. Ciaccia, S. Di Stefano, *Org. Biomol. Chem.* **2015**, *13*, 646 – 654.
[46] A. Sanchez-Sanchez, D. A. Fulton, J. A. Pomposo, *Chem. Commun.* **2014**, *50*, 1871.
[47] H. Jdrzejewska, M. Wierzbicki, P. Cmoch, K. Rissanen, A. Szumna, *Angew. Chem. Int. Ed.* **2014**, *53*, 13760 – 13764; *Angew. Chem.* **2014**, *126*, 13980 – 13984.
[48] J. Leclaire, G. Husson, N. Devaux, V. Delorme, L. Charles, F. Ziarelli, P. Desbois, A. Chaumonnot, M. Jacquin, F. Fotiadu, *J. Am. Chem. Soc.* **2010**, *132*, 3582 – 3593.
[49] S. Xie, R. Fukumoto, O. Ramström, M. Yan, *J. Org. Chem.* **2015**, *80*, 4392 – 7397.
[50] M. Schmid, K. Zeitler, R. Gschwind, *Angew. Chem. Int. Ed.* **2010**, *49*, 4997 – 5003; *Angew. Chem.* **2010**, *122*, 5117 – 5123.
[51] M. C. Holland, R. Gilmour, *Angew. Chem. Int. Ed.* **2015**, *54*, 3862 – 3871; *Angew. Chem.* **2015**, *127*, 3934 – 3943.
[52] D. Sánchez, D. Bastida, J. Burés, C. Isart, O. Pineda, J. Vilarrasa, *Org. Lett.* **2012**, *14*, 536 – 539.
[53] G. Bélanger, M. Doré, F. Ménard, V. Darsigny, *J. Org. Chem.* **2006**, *71*, 7481 – 7484.
[54] H. Carneros, D. Sánchez, J. Vilarrasa, *Org. Lett.* **2014**, *16*, 2900 – 2903.
[55] A. G. Cook, Ed., *Enamines: Synthesis Structure, and Reactions*, M. Dekker, New York, **1988**.
[56] N. Giuseppone, J.-L. Schmitt, E. Schwartz, J.-M. Lehn, *J. Am. Chem. Soc.* **2005**, *127*, 5528 – 5539.

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