Water-compatible Hydrogen Bond-activation: A Scalable and Organocatalytic Model for the Stereoselective Multicomponent aza-Henry Reaction.**

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Dedication ((optional))

The water paradigm has changed in organic chemistry.^[1] Multiple organic reactions have been implemented in the form of water-compatible processes with a net gain in efficiency and instrumental simplicity.^[2] Most of these reactions are currently performed either as homogeneous solutions or easily-stirred aqueous suspensions. Homogeneity requires either the use of water soluble reactants or the aid of an organic co-solvent and are governed by hydrophobic and/or hydrogen-bond (H-bond) interactions.^[3] Aqueous suspensions involve reactants that are insoluble in water and at least one of them is a liquid^[4] (the so-called “on water”^[4a] or in the presence of water^[4b] conditions). Although there is no general agreement on the chemical bases governing these reactions nor the exact place where they occur, experimental evidences suggest that these reactions must be occurring at the organic-water interface,^[5] and as a consequence, they should be influenced by the properties of water molecules and reactants at these interfaces.^[6] Although several protocols based on covalent organocatalysis have been successfully developed in water or in the presence of water,^[7] the implementation of non-covalent based protocols has proved to be more problematic due to the polar properties of the water molecule and its hydrogen bond disruptor capacity. However, recent reports^[8] have shown that the development of these reactions can be feasible in a productive manner. In a seminal communication, Schreiner and col.^[8a] established that hydrogen bonding thiourea-based catalysis can be accomplished in the presence of water and even amplified by hydrophobic hydration.^[9] More recently, Rueping and col.^[8b] reported the first example of an asymmetric Brønsted acid-catalyzed organic reaction in the presence of water, using the hydrophobic hydration

as the driving force of the reaction. Although it is well established that water should favour multicomponent reactions (MCR),^[10] the number of successfully developed water-compatible MCR^[11] remains scarce.^[12] However, the implementation of robust and efficient water-compatible MCR manifolds still remains challenging. We describe herein our efforts in the development and implementation of the first example of an H-bond based organocatalytic multicomponent manifold operating “in the presence of water” conditions.^[4b] The manifold performs a multicomponent and stereoselective version of the organocatalyzed aza-Henry reaction^[13] (Scheme 1A) and it utilizes aniline, aromatic or aliphatic aldehydes, primary or secondary nitroalkanes, *N,N*-dimethylcyclohexylamine as the catalytic base and a chiral thiourea^[14] or squaramide^[15] catalyst as the chiral source to afford the corresponding α,β -disubstituted β -nitroamine derivatives **3** in good yield and high stereoselectivity (up to $\geq 99.5:0.5$ e.r. and $\geq 99.5:0.5$ d.r., anti-adduct^[16]). The catalysis is performed through H-bond interactions between the nitroalkane and the chiral catalyst. Importantly, each family of catalysts delivers the β -nitroamine **3** with complementary enantioselectivity, allowing for the selective access to the two enantiomeric series of these important building blocks in an efficient, instrumentally simple and scalable manner.

The aza-Henry reaction is an important C-C bond-forming reaction in organic chemistry. Since the pioneer works of Shibashaki and col.^[17] (1999, metal-catalyzed) and Takamoto and col.^[18] (2004, organocatalyzed), many others catalytic asymmetric versions have been implemented.^[13] In spite of these advances, a number of problems remain to be solved. Among others, the restrictive nature of the aldimine (mainly aromatic) and the nitroalkane (mainly primary) and the large amounts of nitroalkane needed to reach good reaction rates (5-10 fold excess). Currently, the aldimines are preformed (usually as its moisture-sensitive *N*-BOC-derivative) or formed in situ from the corresponding α -amide sulfona precursor and a base.^[19] To our knowledge, the implementation of the stereoselective three component version of this reaction (3CR) has remained elusive.^[20] We tackled this challenge by designing a 3CR involving aldehydes, aniline, nitroalkanes and a catalytic amount of a small organic H-bonding donor molecule in the presence of an organic base and water. The

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A) Three component manifold (3CR)

B) Optimization of the 3CR using *n*-hexanal and nitroethane

Scheme 1. Water-compatible aza-Henry reaction.

design of the manifold was drafted based on our own experience on the favoured formation and activation of *N*-phenylaldimines in the presence of water^[21] and the reported properties of the water molecules at the organic-water interface^[22] which present a very weak bonding character and a low reactivity. Under these conditions, nitroalkanes could be recognized and activated by small H-bonding donor organic catalysts (e.g., thioureas^[14] or squaramides^[15]). The H-bond interaction between nitroalkane and catalyst should reduce the pKa of the nitroalkane favouring the formation of the corresponding nitronate species by the organic base. If this proposal were feasible, then the catalysts should be designed to be easily implemented with chiral information, which should be transferred completely to the resulting β-nitroamine. As a proof of concept, we designed a reaction prototype involving water and *n*-hexanal, nitroethane, aniline, *N,N*-dimethylcyclohexylamine (catalytic amount) and the thiourea catalyst **thu** or the squaramide catalyst **sqa** (Scheme 1B). We chose *n*-hexanal as the model aldehyde because of its lipophilic nature and because its *N*-phenylimine derivative should share the same stability and reactivity profiles than the other members of the aliphatic series, which have proved to be difficult to control in these reactions in organic media.^[13] We were delighted to observe that this catalytic reaction could be accomplished in the presence of water, confirming that our initial hypothesis was correct. After a considerable experimental work, a set of optimal experimental conditions could be established for this reaction (Scheme 1B). The reaction was pH-sensitive with an optimal value of 5,5 (see SI, Table 1S) which is close to the value reported for the air-water interface (≈ 4,8)^[23] and that accepted as suitable for imine formation (≈ 4,5),^[24] therefore, it must be also an appropriate value for the formation of the iminium ion.^[24] The pH was kept constant using an aqueous solution of NaOAc/AcOH saturated with NaCl (buffer). No reaction could be observed under neat conditions and both the base and the catalyst were needed to accomplish the reaction with efficiency. The addition order of the different reactants was critical, being optimal the sequence: nitroalkane, catalyst, base, aldehyde and aniline. The nitroalkane amount and the catalyst and base loadings were also examined, establishing a minimal threshold of 14 mol% for the catalysts, a 10 mol% for the base and a 2-fold excess for the nitroalkane (see SI, Table 2S). Although the reaction was optimized using *n*-

hexanal and nitroethane, other aldehydes (aliphatic and aromatic) and nitroalkanes (primary or secondary) were smoothly accepted.

With a non-chiral robust and reliable organocatalytic multicomponent manifold at hand, we studied the chiral implementation of this protocol using the reaction of benzaldehyde, aniline and nitroethane as model (Table 1, **3aa/ent-3aa**). We explored a survey of chiral catalyst structures incorporating a thiourea unit or a squaramide motive (see SI, Figures 1S and 2S). After a considerable experimental effort, we arrived to the Jacobsen's catalyst **thu*-I**^[25] and de novo catalyst **sqa*-I** as the best catalysts in terms of chemical efficiency, chiral induction and preparation, and 0°C as the optimal temperature for this reaction (Tables 3S). Under these conditions, both catalysts funnelled the reaction towards the corresponding β-nitroamine derivatives **3** with anti-configuration, but with complementary enantioselectivity.^[26] Benzaldehyde reacted with aniline and nitroethane in the presence of *N,N*-dimethylcyclohexylamine (10 mol%) and catalyst **thu*-I** (14 mol%) to afford the β-nitroamine **3aa** in 88% yield and excellent stereoselectivity (95:5 e.r.; 20:1 d.r.). Under the same reaction conditions, the catalyst **sqa*-I** delivered the enantiomeric product **ent-3aa** with similar efficiency (85% yield) but better stereoselectivity (97:3 e.r.; ≥ 66:1 d.r.). This discovery allowed us to gain access to the two enantiomeric series of the resulting β-nitroamine products. A set of electronically diverse aromatic aldehydes reacted with nitroethane to afford the corresponding β-nitroamines with excellent enantioselectivity in most cases and diastereomeric ratios ranging from modest (4:1) to excellent (≥99.5:0.5). Remarkably, an increase in the aromatic surface of the aldehyde did not translate into a higher stereoselectivity or efficiency (compare β-nitroamines **3aa/ent-3aa** with **3ga/ent-3ga**). The reaction accepted both primary and secondary nitroalkanes although with different effectiveness (compare β-nitroamines **3aa-3ac** with **3ad-3af** and their corresponding enantiomers).

Next, we studied the extension of this catalytic system to aliphatic aldehydes (Table 1). We found that the catalyst **thu*-I** was consistently much less efficient when the aldehyde was aliphatic. Fortunately, the catalyst performance could be increased changing the *N*-terminal *N*-methyl-1,1-diphenylmethanamine motive by the more compact (*R*)-2-phenylpyrrolidine unit (**thu*-II**).^[27] We also found that the nitroalkane amount could be reduced to a slight 10% excess (1.1 equiv). Under these new conditions, 1-nitropentane reacted with a representative set of linear aldehydes to deliver the expected α,β-dialkyl β-nitroamines **3hc-3oc** [**ent-(3hc-3oc)**] with good yield (74% average yield) but moderate to good stereoselectivity [(75-85): (25-15) e.r.; (4-8):1 d.r.]. It is interesting to note that 3-phenylpropanal and *n*-butanal, which markedly differ in the lipophilic nature of the group at the end of the chain (Ph versus Me), afforded the corresponding products **3kc** and **3oc** (and their enantiomers) with similar stereoselectivity but with different efficiency: the less lipophilic *n*-butanal rendered the corresponding β-nitroamine with roughly 20% higher yield than the more lipophilic 3-phenylpropanal. Nitroethane and 1-nitrobutane smoothly reacted with *n*-pentanal to give the corresponding α,β-dialkyl β-nitroamines **3la-3lb** [**ent-(3la-3lb)**] in good yields but moderate enantioselectivity. Branching in the nitroalkane proved to be harmful for the reaction both in terms of yields (≤ 20%) and stereoselectivity (almost - racemate). An interesting outcome was observed in the reactions of

Table 1. Scope of the water-compatible stereoselective 3CR aza-Henry.

Reported yields are isolated yields. Enantiomeric and diastereomeric ratios were determined by chiral HPLC analysis and they refer to the *anti*-isomer and to the *anti/syn* ratio respectively.

cyclohexanecarboxaldehyde and the 3-pentanecarboxaldehyde with 1-nitropentane in the presence of each catalyst (see square inside Table 1). The flash chromatography of each one of the

obtained diastereomeric mixtures allowed us to obtain each one of the all of possible stereoisomers associated with these structures in pure and enantioenriched form. These examples highlight the potential of this methodology for the synthesis of stereochemically diverse libraries of nitrogen-containing small molecules for mapping bioactivity in the chemical space.^[28]

The reaction was scaled up (up to 20 mmol) without significant erosion in yield or stereoselectivity [Eq. (1)]. A simple decantation-trituration protocol allowed us the isolation of β-nitroamine **ent-3aa** (87%; ≥ 95% pure; 98:2 e.r.; 30:1 d.r.) and the full recovery of the chiral catalyst. Remarkably, a large scale reaction using the recycled waters and recovered catalyst afforded **ent-3aa** with roughly the same efficiency and stereoselectivity (see SI for details).

Although we have performed this study using aniline, the reaction can be performed using 2-methoxyaniline which introduces the synthetic advantage of the direct transformation of the products into their free amine form^[29] (See SI for experimental details).

At this stage of the work, we do not have a theoretical-supported model able to explain the role played by the water molecules in the reaction mechanism and in the chiral information transfer process (e.g., water molecules catalyze reactions by directly participating in the transition state, reducing geometrical strains and lowering its energy). These reactions are performed under non homogeneous conditions and involve a complex sequence of steps which turn the full understanding of the reaction mechanism and the water role very challenging. However, reactive water, in parallel to the complex fluids where biological reactions occur, must be well removed from the place where these reactions take place (otherwise, the activated imines could not survive). If these reactions are taking place at the organic-water interface as postulated by Huck and col,^[5] and the water molecules in this interface behave similarly to the water molecules at the vapour-water interface as postulated by Richmond and Chandler,^[23] then the low reactivity and weak binding character of these water molecules should enable the observed H-bond interaction between the chiral catalyst and the nitroalkane and the subsequent reactions affording the β-nitroamine product. Therefore, more experimental and theoretical work is needed to fully understand and instrumentalize the rich potential that this chemistry can offer, and importantly, to take advantage of its capacity to mimic the chemistry accomplished in the very complex biological media where pure water is absent.^[9]

In summary, we have demonstrated that H-bond based asymmetric organocatalysis can be performed under the so-called “in the presence of water” conditions.^[4b] As a proof of concept, we have described the first example of a stereoselective multicomponent aza-Henry reaction catalyzed by a combination of a chiral H-bond donor organic molecule (thiourea or squaramide) and a Lewis base (*N,N*-dimethylcyclohexylamine) in the presence of water. Each family of catalysts selectively funnels

the reaction towards one of the two enantioenriched forms of the corresponding β -nitroamine derivatives with moderate to good *anti*-diastereoselectivity. From the synthetic point of view, the reaction furnishes enantioenriched β -nitroamines decorated with aromatic or aliphatic substituents at the amine centre and a different set of alkyl chains or rings attached to the carbon bearing the nitro functionality. Importantly, the reaction can be scaled up without losing yield and stereoselectivity and with full recovery of the catalyst. Finally, the reaction can be conveniently performed with 2-methoxyaniline allowing for a potential synthetic access to the free 1,2-diamino derivatives.

Experimental Section

General procedure. To a 0 °C cooled and vigorously stirred aqueous solution of NaOAc/AcOH saturated with NaCl (8 mL; 20 mM, pH = 5.5) were sequentially added nitroalkane (1.40 mmol for aromatic aldehydes; 0.77 mmol for aliphatic aldehydes), catalyst (14 mol%), dimethylcyclohexylamine (10 mol%), benzaldehyde (0.70 mmol) and aniline (0.70 mmol) and the resulting suspension was vigorously stirred for 5 h at 0 °C. The organic residues were taken into dichloromethane (2 x 10 mL) and decanted off. The combined organic fractions were dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel) using a mixture of hexanes/ethyl acetate (95:5 v/v). **N-((1*R*,2*S*)-2-nitro-1-phenylpropyl)aniline (3aa and *ent*-3aa).** Following the general procedure, **3aa** (catalyst **thu***) and **ent-3aa** (catalyst **sqa***) were isolated in 88% and 85% yield respectively as amorphous pale yellow solids. ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.28 (m, 5H), 7.13–7.08 (m, 2H), 6.72 (appt, ³J_(H,H) = 7.4 Hz, 1H), 6.56 (appd, ³J_(H,H) = 7.7 Hz, 2H), 5.01 (dd, ³J_(H,H) = 6.5, 4.9 Hz, 1H), 4.90 (dq, ³J_(H,H) = 6.8, 4.9 Hz, 1H), 4.43 (brd, ³J_(H,H) = 6.5 Hz, 1H), 1.56 (d, ³J_(H,H) = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CHCl₃) δ 146.0, 137.5, 129.2 (2C), 129.0 (2C), 128.4, 126.8 (2C), 118.8, 114.1 (2C), 86.4, 77.3, 76.6, 60.8, 13.8. IR (CHCl₃) ν = 3419, 1605, 1552 cm⁻¹; HR-MS: calculated for [M]: 256.1212, measured: 256.1205. The e.r. and d.r. were determined by HPLC using a Chiralpack AD-H column [hexane/isopropanol (90:10 v/v)]; flow rate 0.5 mL/min. **3aa**: $\tau_{\text{major}} = 26.6$ min, $\tau_{\text{minor}} = 20.6$ min (e.r.: 95:5, d.r.: 20:1). **ent-3aa**: $\tau_{\text{major}} = 20.8$ min, $\tau_{\text{minor}} = 26.2$ min (e.r.: 3:97, d.r.: $\geq 66:1$).

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- [1] M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415–1427.
- [2] a) U. M. Lindstrom, in *Organic Reactions in Water: Principles, Strategies and Applications*, Blackwell, **2007**; b) C.-J. Li, T.-H. Chan, in *Comprehensive Organic Reactions in Aqueous Media*; Wiley, **2007**; c) S. Kobayashi, *Pure Appl. Chem.* **2007**, *79*, 235–245; d) B. Cornils, W. A. Hermann, in *Aqueous phase organometallic catalysis*; Wiley, **2004**.
- [3] a) J. B. F. N. Engberts, M. J. Blandamer, *Chem. Commun.* **2001**, 1701–1708; b) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159–164.
- [4] a) “On water” conditions are defined as those conditions arising when insoluble reactant(s) are stirred in aqueous emulsions or suspensions without the addition of any organic co-solvents. S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339–3343; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279; b) “In the presence of water” conditions are defined as those conditions in which water forms a second phase that affects the organic reaction occurring at the concentrated organic phase. Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.
- [5] S. Mellouli, L. Bousekkine, A. B. Theberge, W. T. S. Huck, *Angew. Chem.* **2012**, *124*, 8105–8108; *Angew. Chem. Int. Ed.* **2012**, *51*, 7981–7984.
- [6] a) J. K. Beattie, C. S. P. McErlean, C. B. W. Phippen, *Chem. Eur. J.* **2010**, *16*, 8972–8974; b) Y. S. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502; c) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746–747. (d) L. L. Thomas, J. Tirado-Rives, W. L. Jorgensen, *J. Am. Chem. Soc.* **2010**, *132*, 3097–3104; e) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302–6337.
- [7] a) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33–57; b) M. Raja, V. K. Singh, *Chem. Commun.* **2009**, 6687–6703; c) J. Paradowska, M. Stodulski, J. Mlynarski, *Angew. Chem.* **2009**, *121*, 4352–4362; *Angew. Chem. Int. Ed.* **2009**, *48*, 4288–4297.
- [8] a) C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315–4317; b) M. Rueping, T. Theissmann, *Chem. Sci.* **2010**, *1*, 473–476.
- [9] P. Ball, *Chem. Rev.* **2008**, *106*, 74–108.
- [10] M. C. Pirrung, K. D. Sarma, *Tetrahedron* **2005**, *61*, 11456–11472.
- [11] K. Kumaravel, G. Vasuki, *Curr. Org. Chem.* **2009**, *13*, 1820–1841.
- [12] For selected examples: a) M. W. Powner, J. D. Sutherland, J. W. Szostak, *J. Am. Chem. Soc.* **2010**, *132*, 16677–16678; b) N. Shapiro, A. Vigalok, *Angew. Chem.* **2008**, *120*, 2891–289; *Angew. Chem. Int. Ed.* **2008**, *47*, 2849–2852; c) M. C. Pirrung, K. D. Sarma, *J. Am. Chem. Soc.* **2004**, *126*, 444–445.
- [13] a) A. Noble, J. C. Anderson, *Chem. Rev.* **2013**, *113*, 2887–2939; b) E. Marqués-López, P. Merino, T. Tejero, R. P. Herrera, *Eur. J. Org. Chem.* **2009**, 2401–2420.
- [14] Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.
- [15] J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899.
- [16] We use the *syn/anti* nomenclature considering the amino and nitro functionalities as the substituents of the carbon chain oriented in a zigzag disposition.
- [17] K.-I. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 3713–3715; *Angew. Chem. Int. Ed.* **1999**, *38*, 3504–3506.
- [18] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627.
- [19] a) F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 8189–8192; *Angew. Chem. Int. Ed.* **2005**, *44*, 7975. (b) C. Palomo, M. Oiarbide, A. Laso, R. López, *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623; c) E. Gomez-Bengoia, A. Linden, R. López, I. Múgica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966; d) Y. Wei, W. He, Y. Liu, P. Liu, S. Zhang, *Org. Lett.* **2012**, *14*, 704–707; e) K. Takada, K. Nagasawa, *Adv. Synth. Catal.* **2009**, *351*, 345–347; f) W. Huang, C. Peng, L. Guo, R. Hu, B. Han, *Synlett* **2011**, 2981–2984; g) K. M. Johnson, M. S. Rattley, F. Sladojevich, D. M. Barber, M. G. Nuñez, A. M. Goldys, D. J. Dixon, *Org. Lett.* **2012**, *14*, 2492–2495.
- [20] During the writing of this manuscript, a cinchona-based squaramide catalyzed one-pot three component asymmetric aza-Henry reaction was reported. Strictly speaking, this reported reaction is one pot and it cannot be considered as a truly multicomponent aza-Henry reaction. H.-X. He, W. Yang, D.-M. Du, *Adv. Synth. Catal.* **2013**, *355*, 1137–1148.
- [21] F. Cruz-Acosta, A. Santos-Expósito, P. de Armas, F. García-Tellado, *Chem. Commun.* **2009**, 6839–6841.
- [22] a) F. G. Moore, G. L. Richmond, *Acc. Chem. Res.* **2008**, *41*, 739–748; b) D. Chandler, *Nature* **2005**, *437*, 640–647.
- [23] V. Buch, A. Milet, R. Vácha, P. Jungwirth, J. P. Devlin, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 7342–7347.
- [24] A. Dirkense, T. M. Hackeng, P. E. Dawson, *Angew. Chem.* **2006**, *118*, 7743–7746; *Angew. Chem. Int. Ed.* **2006**, *45*, 7581–7584.
- [25] S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968–970.
- [26] The relative and absolute configurations were assigned following established protocols. See SI for details.
- [27] Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032.
- [28] For a selected example: N. Kumagai, G. Muncipinto, S. L. Schreiber, *Angew. Chem.* **2006**, *118*, 3717–3720; *Angew. Chem. Int. Ed.* **2006**, *45*, 3635–3638.
- [29] For a recent example, see: P. Fu, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 5530–5541.

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Layout 2:

H-bond based asymmetric organocatalysis in the presence of water

Fabio Cruz-Acosta, Pedro de Armas and Fernando García-Tellado*.....* Page – Page

Water-compatible Hydrogen Bond-activation: A Scalable and Organocatalytic Model for the Stereoselective Multicomponent aza-Henry Reaction.

H-bond catalysis in the presence of water: Non covalent organocatalysis can be efficiently performed in the presence of water. As a proof of concept, we have described the first example of a stereoselective multicomponent aza-Henry reaction catalyzed by a combination of a chiral H-bond donor organic molecule (thiourea- or squaramide-

containing catalyst) and a Lewis base (tertiary amine) in the presence of water. Each family of catalysts delivers the β -nitroamine derivative with complementary enantioselectivity, allowing for the selective access to the two enantiomeric series of these building blocks in an efficient, instrumentally simple and scalable manner.