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Water-Compatible Hydrogen-Bond Activation: A Scalable and Organocatalytic Model for the Stereoselective Multicomponent Aza-Henry Reaction

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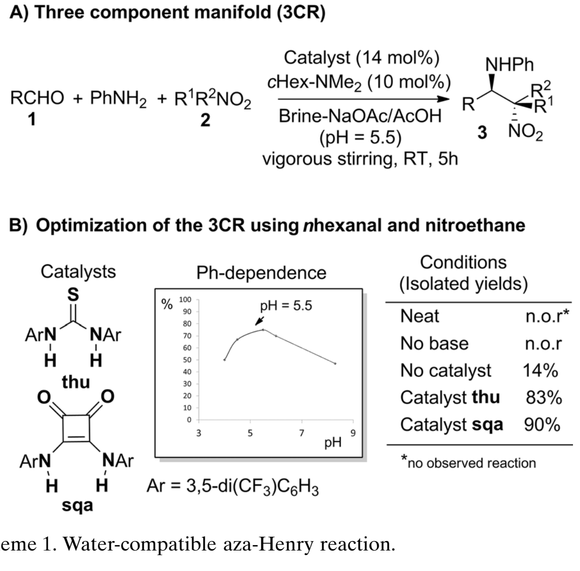
Dedicated to the Professor Julio Delgado Martín

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 et. al.[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 favor 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 1 A) 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 ≥99.5:0.5 e.r. and ≥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 impor-



Scheme 1. Water-compatible aza-Henry reaction.

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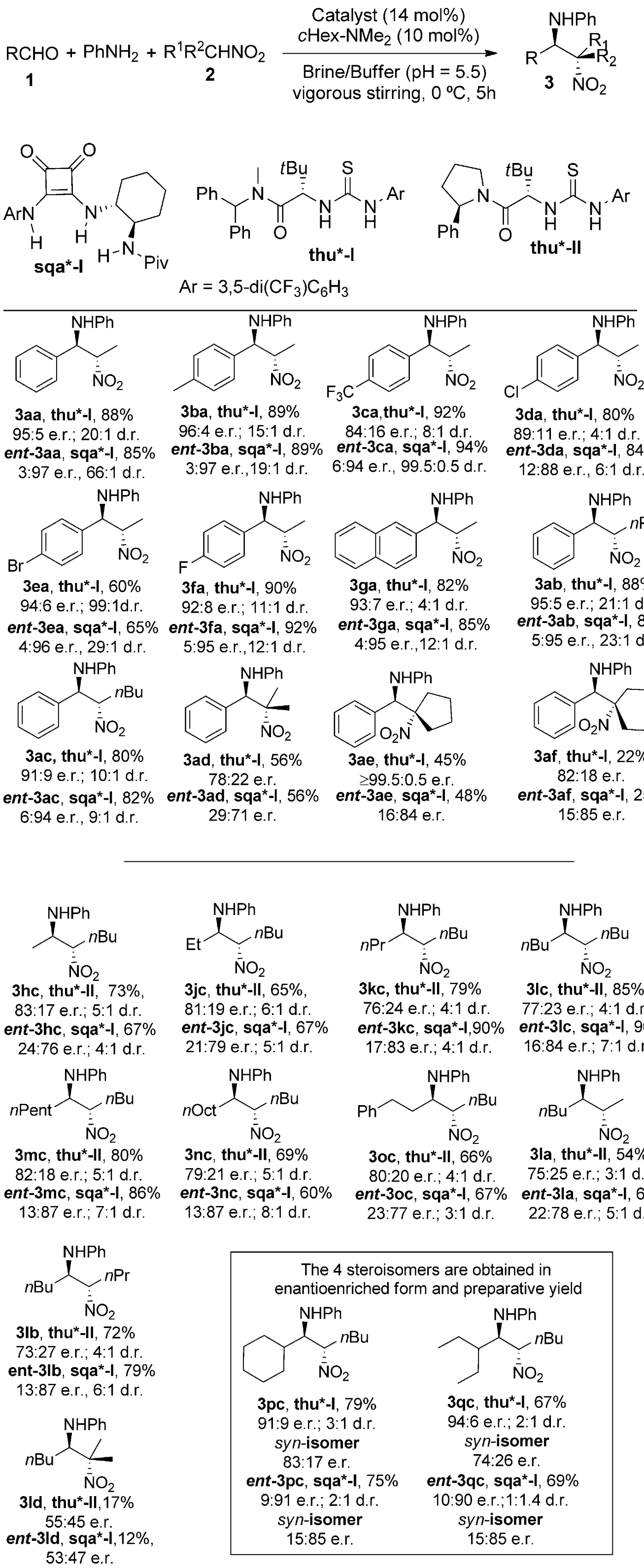
tant building blocks in an efficient, instrumentally simple, and scalable manner.

The aza-Henry reaction is an important C–C bond-forming reaction in organic chemistry. Since the pioneer works of Shibashaki et. al.[17] (1999, metal-catalyzed) and Takamoto et. al.[18] (2004, organocatalyzed), many other 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 design of the manifold was drafted based on our own experience on the favored 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 pK_a of the nitroalkane favoring 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 thiourea catalyst **thu** or the squaramide catalyst **sqa** (Scheme 1 B). 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 considerable experimental work, a set of optimal experimental conditions could be established for this reaction (Scheme 1 B). The reaction was pH-sensitive with an optimal value of 5.5 (see the Supporting Information, Table 1S), which is close to the value reported for the air-water interface (c.a. 4,8)[23] and that accepted as suitable for imine formation (c.a. 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

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



3aa, **thu*-I**, 88%
95:5 e.r.; 20:1 d.r.
***ent*-3aa**, **sqa*-I**, 85%
3:97 e.r., 66:1 d.r.

3ba, **thu*-I**, 89%
96:4 e.r.; 15:1 d.r.
***ent*-3ba**, **sqa*-I**, 89%
3:97 e.r.,19:1 d.r.

3ca,**thu*-I**, 92%
84:16 e.r.; 8:1 d.r.
***ent*-3ca**, **sqa*-I**, 94%
6:94 e.r., 99.5:0.5 d.r.

3da, **thu*-I**, 80%
89:11 e.r.; 4:1 d.r.
***ent*-3da**, **sqa*-I**, 84%
12:88 e.r., 6:1 d.r.

3ea, **thu*-I**, 60%
94:6 e.r.; 99:1d.r.
***ent*-3ea**, **sqa*-I**, 65%
4:96 e.r., 29:1 d.r.

3fa, **thu*-I**, 90%
92:8 e.r.; 11:1 d.r.
***ent*-3fa**, **sqa*-I**, 92%
5:95 e.r.,12:1 d.r.

3ga, **thu*-I**, 82%
93:7 e.r.; 4:1 d.r.
***ent*-3ga**, **sqa*-I**, 85%
4:95 e.r.,12:1 d.r.

3ab, **thu*-I**, 88%
95:5 e.r.; 21:1 d.r.
***ent*-3ab**, **sqa*-I**, 89%
5:95 e.r., 23:1 d.r.

3ac, thu*-I, 80%
91:9 e.r.; 10:1 d.r.
***ent*-3ac**, **sqa*-I**, 82%
6:94 e.r., 9:1 d.r.

3ad, **thu*-I**, 56%
78:22 e.r.
***ent*-3ad**, **sqa*-I**, 56%
29:71 e.r.

3ae, **thu*-I**, 45%
≥99.5:0.5 e.r.
***ent*-3ae**, **sqa*-I**, 48%
16:84 e.r.

3af, **thu*-I**, 22%
82:18 e.r.
***ent*-3af**, **sqa*-I**, 25%
15:85 e.r.

3hc, **thu*-II**, 73%,
83:17 e.r.; 5:1 d.r.
***ent*-3hc**, **sqa*-I**, 67%
24:76 e.r.; 4:1 d.r.

3jc, **thu*-II**, 65%,
81:19 e.r.; 6:1 d.r.
***ent*-3jc**, **sqa*-I**, 67%
21:79 e.r.; 5:1 d.r.

3kc, thu*-II, 79%
76:24 e.r.; 4:1 d.r.
***ent*-3kc**, **sqa*-I**,90%
17:83 e.r.; 4:1 d.r.

3lc, **thu*-II**, 85%
77:23 e.r.; 4:1 d.r.
***ent*-3lc**, **sqa*-I**, 90%
16:84 e.r.; 7:1 d.r.

3mc, **thu*-II**, 80%
82:18 e.r.; 5:1 d.r.
***ent*-3mc**, **sqa*-I**, 86%
13:87 e.r.; 7:1 d.r.

3nc, **thu*-II**, 69%
79:21 e.r.; 5:1 d.r.
***ent*-3nc**, **sqa*-I**, 60%
13:87 e.r.; 8:1 d.r.

3oc, **thu*-II**, 66%
80:20 e.r.; 4:1 d.r.
***ent*-3oc**, **sqa*-I**, 67%
23:77 e.r.; 3:1 d.r.

3la, **thu*-II**, 54%,
75:25 e.r.; 3:1 d.r.
***ent*-3la**, **sqa*-I**, 65%
22:78 e.r.; 5:1 d.r.

3lb, **thu*-II**, 72%
73:27 e.r.; 4:1 d.r.
ent-3lb, **sqa*-I**, 79%
13:87 e.r., 6:1 d.r.

3ld, **thu*-II**,17%
55:45 e.r.
***ent*-3ld**, **sqa*-I**,12%,
53:47 e.r.

The 4 steroisomers are obtained in
enantioenriched form and preparative yield

3pc, **thu*-I**, 79%
91:9 e.r.; 3:1 d.r.
syn-**isomer**
83:17 e.r.
***ent*-3pc**, **sqa*-I**, 75%
9:91 e.r.; 2:1 d.r.
syn-**isomer**
15:85 e.r.

3qc, **thu*-I**, 67%
94:6 e.r.; 2:1 d.r.
syn-**isomer**
74:26 e.r.
***ent*-3qc**, **sqa*-I**, 69%
10:90 e.r.;1:1.4 d.r.
syn-**isomer**
15:85 e.r.

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.

and the catalyst were needed to accomplish the reaction with efficiency. The addition order of the different reactants was critical, the optimal sequence being: 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 two-fold excess for the nitroalkane (see the Supporting Information, 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.

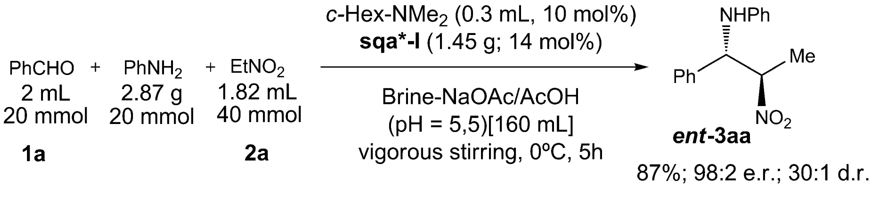
With a non-chiral robust and reliable organocatalytic multicomponent manifold at hand, we studied the chiral implementation of this protocol using the reaction of benzaldehyde, aniline, and nitroethane as a model (Table 1, **3aa**/***ent*-3aa**). We explored a survey of chiral catalyst structures incorporating a thiourea unit or a squaramide motive (see the Supporting Information, Figure 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 funneled 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-phenyl-propanal. 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 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 the Supporting Information 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 the Supporting Information 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. These reactions are performed



(1)

under non homogeneous conditions and involve a complex sequence of steps, which make gaining a full understanding of the reaction mechanism and the role of water very challenging. However, reactive water, in parallel to the complex fluids in which 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 co-workers,[5] and the water molecules in this interface behave similarly to the water molecules at the vapor–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 biological chemistry accomplished in confined spaces in which pure water is absent.[10]

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 a synthetic point of view, the reaction furnishes enantioenriched β-nitroamines decorated with aromatic or aliphatic substituents at the amine center 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 × 10 mL) and decanted off. The combined organic fractions were dried over Na_2SO4, 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*-I**) and ***ent*-3aa** (catalyst **sqa*-I**) were isolated in 88 and 85 % yield, respectively, as amorphous pale yellow solids. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.28 (m, 5 H), 7.13–7.08 (m, 2 H), 6.72 (appt, $^3J_{(H,H)} = 7.4$ *Hz*, 1 H), 6.56 (appd, $^3J_{(H,H)} = 7.7$ Hz, 2 H), 5.01 (dd, $^3J_{(H,H)} = 6.5$, 4.9 Hz, 1 H), 4.90 (dq, $^3J_{(H,H)} = 6.8$, 4.9 Hz, 1 H), 4.43 (brd, $^3J_{(H,H)} = 6.5$ Hz, 1 H), 1.56 ppm (d, $^3J_{(H,H)} = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.0$, 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 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3419$, 1605, 1552 cm^{-1}; HRMS (EI/TOF): *m*/*z* calcd for: $C_{15}H_{16}N_2O_2$: 256.1212 [*M*]; found: 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^{-1}. **3aa**: $\tau_{major} = 26.6$ min, $\tau_{minor} = 20.6$ min (e.r.: 95:5, d.r.: 20:1). ***ent*-3aa**: $\tau_{major} = 20.8$ min, $\tau_{minor} = 26.2$ min (e.r.: 3:97, d.r.: $\geq 66:1$).

Acknowledgements

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Keywords: asymmetric organocatalysis · hydrogen bond · multicomponent reactions · nitro-mannich · water

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