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Harnessing Additional Capability from in Water Reaction Conditions: Aldol *versus* Knoevenagel Chemoselectivity

Thomas C. Nugent,*[,a] Falguni Goswami,[a] Samarpita Debnath,[a] Ishtiaq Hussain,[b] Hussein Ali El Damrany Hussein,[a] Alka Karn,[a] Srinuvasu Nakka[a]

[a] Department of Life Sciences and Chemistry, Jacobs University Bremen, 28759 Bremen, Germany, Phone: (+49) 421 200-3232, E-mail: t.nugent@jacobs-university.de
[b] Department of Pharmacy, Abbottabad University of Science and Technology, Havelian Abbottabad, 22010 Pakistan.

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Abstract. Aldol reaction chemoselectivity, racemic or enantioselective, has not been previously demonstrated in the presence of Knoevenagel active functional groups. Here, we show that unhindered β-diketones remain unreacted while a ketone moiety undergoes a highly enantioselective aldol desymmetrization resulting in three new stereogenic centers using in water reaction conditions. A mechanistic hypothesis for the chemoselective formation of either aldol or Knoevenagel products is presented. It elucidates how these amino acid catalyzed reactions completely suppress formation of the expected Knoevenagel product under heterogenous in water reaction conditions, but not when homogeneous in water reaction conditions are used. The concept permitting this new type of chemoselectivity is detailed here and expands the role of water at an organic-water interface.

Keywords: chemoselectivity; Knoevenagel condensation; aldol; organic-water interface; in water; desymmetrization

Introduction

Organic chemists rely on inventive reaction sequences to efficiently tackle and tame complex molecular architectures, but strategic creativity can be no greater than the scope of available reactions. To that end, the expansion of methods based on enantio-, diastereo-, regio-, or chemoselectivity drive the tactical advantages that permit more efficient syntheses.[1]

Aldol and Knoevenagel condensation reactions share a common electrophile: aldehydes, and due to the lower acidity of Knoevenagel nucleophiles, *e.g.*, β-diketones, malonate esters, *etc.*, precedent exists for Knoevenagel product formation in the presence of a ketone, but not *vice versa*.[2] Both of these reactions can be catalyzed by amino acids, however the catalytic role of the amine in each reaction is different.[3,4] We consequently hypothesized that exploitation of this fact could permit a new type of chemoselectivity to be identified.

Results and Discussion

Initial Reaction Development. The literature teaches us that Knoevenagel reactions are faster and higher yielding than aldol reactions under very similar reaction conditions. For example, under (S)-proline or (S)-tryptophan catalysis in DMSO or neat, acetylacetone[5,6] reacts faster than cyclohexanone[7-10] with benzaldehyde. It was therefore unremarkable that treatment of triketone **1a** and benzaldehyde (**2a**) under amino acid catalysis, resulted in ~10:1 chemoselectivity for the Knoevenagel condensation product (KCP) **4** over aldol **5a** (Scheme 1). This was possible in good yield using (S)-proline (conditions A, 69% yield) or (S)-tryptophan (conditions B, 80% yield), respectively in the reaction *media* EtOH or DMSO.

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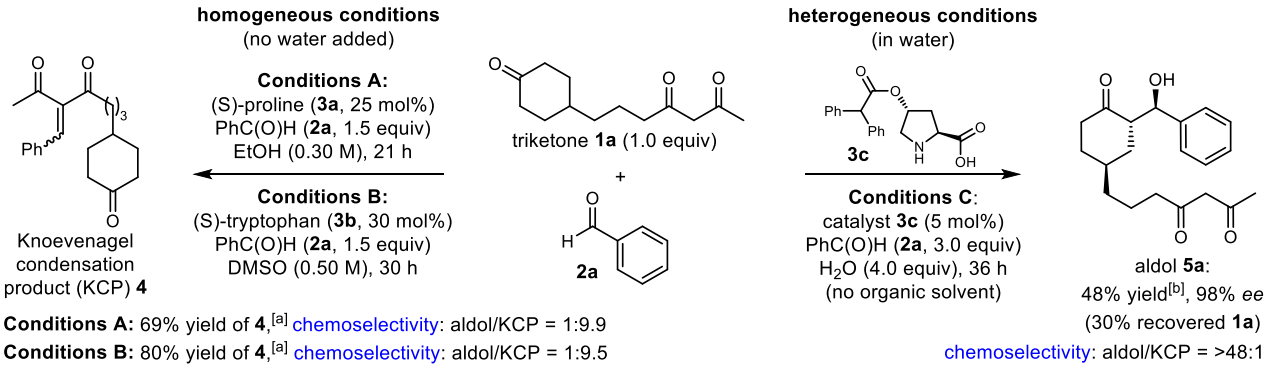


Scheme 1. A chemoselective switch: Knoevenagel condensation (**4**) or aldol (**5a**) product formation using triketone **1a**. [a] Isolated yield of product **4**, as a mixture of E and Z geometric isomers (~2:1). [b] Isolated yield of single diastereomer.

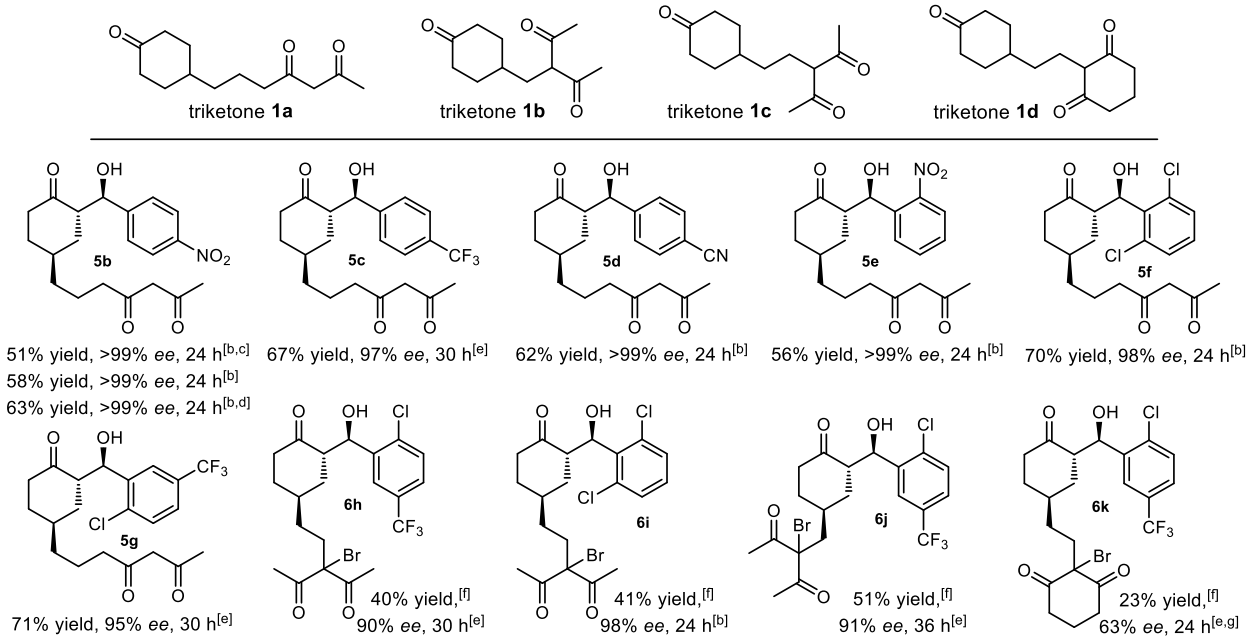


Figure 1. Aldol products from in water reaction conditions.[a]
[a] All reactions performed neat with added H_2O (4.0 equiv) and catalyst **3c** (2 mol%) unless otherwise noted. Isolated yields represent the major diastereomer. [b] Triketone (1.5 equiv) and aldehyde (1.0 equiv). [c] Catalyst **3d** (2 mol%, Figure 2) was used. [d] Catalyst **3d** (5 mol%, Figure 2) was used. [e] Triketone (1.0 equiv) and aldehyde (3.0 equiv). [f] Two step overall yield: bromination performed after the aldol reaction for characterization purposes. [g] Acetic acid (5 mol%) was added.

With the dominance of the Knoevenagel reaction established for triketone **1a**, the focus shifted to the possibility of a chemoselective switch to the aldol product. Thus, in water (heterogeneous) reaction conditions[11] were explored to undermine the Knoevenagel catalytic cycle, while continuing to promote the aldol reaction catalytic cycle. The well-established in water aldol criteria,[12,13,14a] Kobayashi category type IIIc,[11c] were satisfied by combining triketone **1a** (1.0 equiv), benzaldehyde **2a** (3.0 equiv), and (S)-proline (5 mol%) in the presence of water (4.0 equiv). A biphasic mixture, with solid catalyst fully dissolved, was established within minutes, however, work-up at 36 h only resulted in recovery of triketone **1a** (92% yield). Addition of more L-proline resulted in incomplete dissolution and this catalyst was abandoned. In a revelatory experiment, the in water aldol reaction parameters were maintained, but now 5 mol% of the Gruttadauria[14] aldol catalyst (**3c**) was employed (Scheme 1). This resulted in an enantioselective desymmetrization of **1a** with >48:1 chemoselectivity for aldol product **5a** over Knoevenagel condensation product **4** (Scheme 1). Despite the mediocre yield of **5a** (single diastereomer in 48% yield, 98% *ee*) and significant triketone (**1a**)

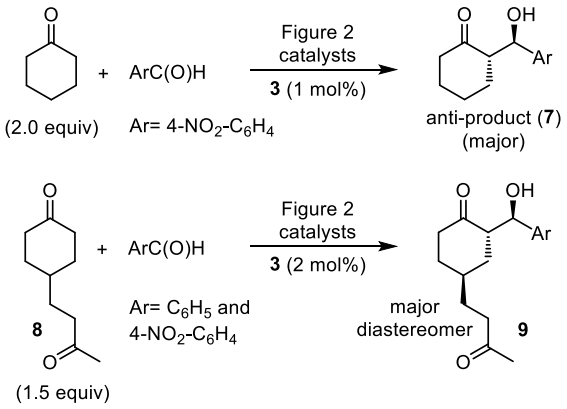
recovery (30%),[15] these findings validated the premise that aldol over Knoevenagel chemoselectivity can be achieved.

Aldol product scope and profile. The high chemoselectivity for aldol product formation encouraged us to examine alternative aldehyde substrates with triketone **1a** and to examine triketones **1b-d** (Figure 1). The product results are summarized in Figure 1 and characterized by: *no Knoevenagel by-product formation*, a lowered catalyst loading (2 mol% of **3c**), high *ee*, and improved yield over the first example with benzaldehyde (Scheme 1). Furthermore, the yields for **5a-g** and **6h-k** (Scheme 1 and Figure 1) represent those of single diastereomeric products.[15] For β-hydroxyketones **6h-k** (Figure 1), a two-step overall yield is shown: aldol, followed by bromination (NBS). The latter reaction was required for characterization purposes, *i.e.*, at the aldol stage the minor and major diastereomers of **5h-k**, not shown, could not be separated. The **5a-k** *drs* ranged from 1.3:1 to 8.8:1 and represent the *anti*-major (4-substituent up) and *anti*-minor (4-substituent down) products.[16] The protocol also flexibly permitted either starting material to be the limiting reagent (Figure 1, see footnotes [b] and [e]). We speculate that the Figure 1 yields might be raised if Bolm's ball-mill technique, devised for chiral-amine-catalyzed aldol reactions, were applied.[9] The technique is both relevant to our work and appealing because we often recovered starting material.[15]

Gong was the first to report enamine based desymmetrizations of 4-substituted cyclohexanones exemplified by **1a–d**.[17–19] But, our demonstrations are the first to move beyond simple 4-alkyl- or 4-phenyl substituted cyclohexanones, and so should increase the application utility. Remarkably, aldol product formation supersedes Knoevenagel and enaminone formation. The latter reaction occurs when amines (here our catalysts) are combined with β-diketones, and have been reported when using water as a solvent.[20]

Finally, presumably due to its lower pK_a (~5), triketone **1d** defined a substrate limit. Preliminary ^1H NMR analysis of crude and semi-purified products allow us to speculate that four equally represented diastereomers formed. Furthermore, an intramolecular reaction product of **1d**, representing ring closure from cyclohexanone onto a carbonyl unit of the 1,3-diketone, may have formed. Addition of 5 mol% AcOH significantly improved the aldol product diastereoselectivity for **1d**, permitting isolation of the major diastereomer, albeit in poor yield and 63% *ee* (Figure 1, compound **6k**). The reduced *ee* was apparently due to the presence of acetic acid, whose increased loading (100 mol%) resulted in 44% *ee*.

Catalyst Optimization. Before large quantities of triketone **1a** were in hand, we pre-emptively began catalyst screening. To that end, cyclohexanone and then a 4-substituted diketone (**8**), containing a linear tether approximating that found in **1a**, were examined (Scheme 2). The examined catalysts (**3c–p**) are shown in Figure 2. Summarizing for the cyclohexanone reaction, **3c** and **3d** provided the best product profile with an optimized catalyst loading of 1 mol%. For these two catalysts, there was no discernible difference in reaction time (12 h), *dr* (> 20:1), *ee* (99%), and isolated yield of **7** (> 90%). Further details are found in the Supporting Information (Section 8, Table S1).



Scheme 2. Catalyst screening prior to triketones **1a-d**.

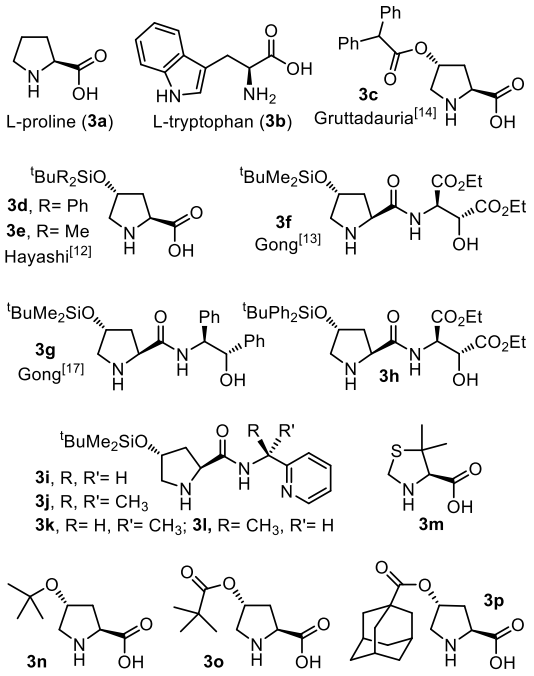
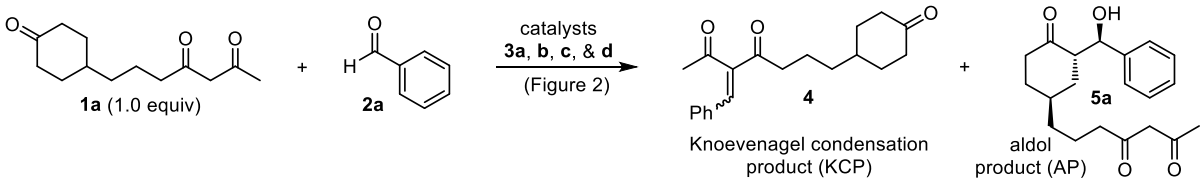


Figure 2. Sixteen catalysts examined (Section 8, Supporting Information gives details).

Uncertain if this trend would continue for a triketone like **1a**, we screened diketone **8** with many of the same catalysts (Scheme 2). During that study, **8** was reacted with 4-nitrobenzaldehyde and benzaldehyde (Supporting Information, Section 8, Tables S2 and S3). Interestingly, the same catalyst trend noted for

cyclohexanone was again noted, albeit catalyst **3c** facilitated small yield increases over the use of catalyst **3d**. Increased yield was also noted when using catalyst **3c** with triketone **1a** (Figure 1, see product **5b** yield examples).

Table 1. Knoevenagel *versus* aldol chemoselectivity: Effect of heterogeneous and homogeneous water conditions.[a]



entry	description[b]	catalyst	mol%[c]	solvent	M[d]	time (h)	**4** / **5a**[e]	**4** (% yield)	**5a** (% yield)	**1a** (%)[f]
1[g]	homogeneous[h]	**3a**	25	EtOH	0.30	21	9.9:1.0	69	7	18
2[g]	homogeneous[h]	**3b**	30	DMSO	0.50	30	10:1.0	80	8	7
3[22]	homogeneous[h]	**3c**	5	EtOH	0.30	21	2.5:1.0	10	4	79
4	homogeneous[h]	**3d**	25	EtOH	0.30	21	3.6:1.0	36	10	36
5	homogeneous[h]	**3d**	30	DMSO	0.50	30	15:1.0	59	4	35
6	homogeneous	**3d**	30	DMSO + H_2O (4 equiv)	0.50	30	2.8:1.0	37	13[i]	46
7	homogeneous	**3d**	30	DMSO + H_2O (16 equiv)	0.50	30	1.1:1.0	37	35[i]	28
8	homogeneous[h]	**3c**	5	neat	-	36	1.0:1.3	21	28[i]	36
9[g]	heterogeneous	**3c**	5	neat + (4 equiv H_2O)	-	36	1.0:>48	<1	48[i]	30

[a] Entries 1-7, **1a**/**2a** stoichiometry = 1.0:1.5; entries 8 and 9, **1a**/**2a** stoichiometry = 1.0:3.0. [b] All solid reactants and catalysts were fully dissolved, see Supporting Information Section 7. [c] Catalyst mol%. [d] Molarity of EtOH or DMSO. [e] Knoevenagel to aldol product chemoselectivity. [f] Recovered triketone. [g] Scheme 1 result. [h] No intentional addition of H_2O. [i] Entries 6 and 7 represent the isolated yield of the major and minor aldol diastereomers, entries 8 and 9 only represent the isolated yield of the major aldol diastereomer.[15]

In total, the screening studies revealed dual H-bond donor containing catalysts **3f**,[13] **g**,[17] and **h**[21] to be inferior to single H-bond containing catalysts **3c**,[14] **d**,[12] and **e**.[12] Thus, the latter set mediated product formation with higher *dr* and *ee*. Using catalyst **3c** we also synthesized a derivative of **9**, and subjected it to X-ray crystallographic analysis. By this means, the relative and absolute stereochemistry of the products were established (Supporting Information, Sections 9 and 10).

The role of water. To clarify the origin of the chemoselectivity, *i.e.*, to differentiate the role of the medium from the influence of catalyst structure, additional reactions were performed (Table 1). Thus, the optimal in water catalysts, **3c** and **3d**, which provide no Knoevenagel product, were subjected to the Knoevenagel-favored reaction conditions. Those reactions were shown earlier with (S)-proline and (S)-tryptophan, respectively in EtOH and DMSO (Scheme 1 and summarized in Table 1 as entries 1 and 2). Unfortunately, catalyst **3c** was only sparingly soluble in either EtOH or DMSO, ruling out its examination at the required catalyst loading (Table 1, entry 3).[22] However, catalyst **3d** was highly soluble and provided 3.6:1 and 15:1 Knoevenagel-over-aldol selectivity (**4**/**5a**), respectively in EtOH and DMSO (Table 1, entries 4 and 5). Those results compare favorably with the natural amino acids examined in the same solvents (Table 1, entries 1 and 2).

Those findings established the importance of the reaction media. But what role, if any, was water fulfilling when the in water reaction conditions (Scheme 1 and Figure 1) provided exclusive aldol chemoselectivity (Table 1, entry 9). To probe this, the Knoevenagel chemoselective reaction with **3d** in DMSO (entry 5, **4**/**5a**, 15:1) was repeated, albeit now with 4 and 16 equiv of added H_2O. In the event, the former resulted in eroded Knoevenagel selectivity (entry 6, **4**/**5a**, 2.8:1), while the latter provided no selectivity (entry 7, **4**/**5a**, 1.1:1). Clearly, aqueous solutions of DMSO increase the aldol product content. However, even 16 equiv of water could not suppress formation of the Knoevenagel product (37% yield), and the aldol yield was low (35%) at high catalyst loading (30 mol%), see Table 1 (entry 7 and footnote i).

To further examine the role of water, the highly chemoselective aldol reaction, entry 9, was repeated, albeit now without added water. Revealingly, these

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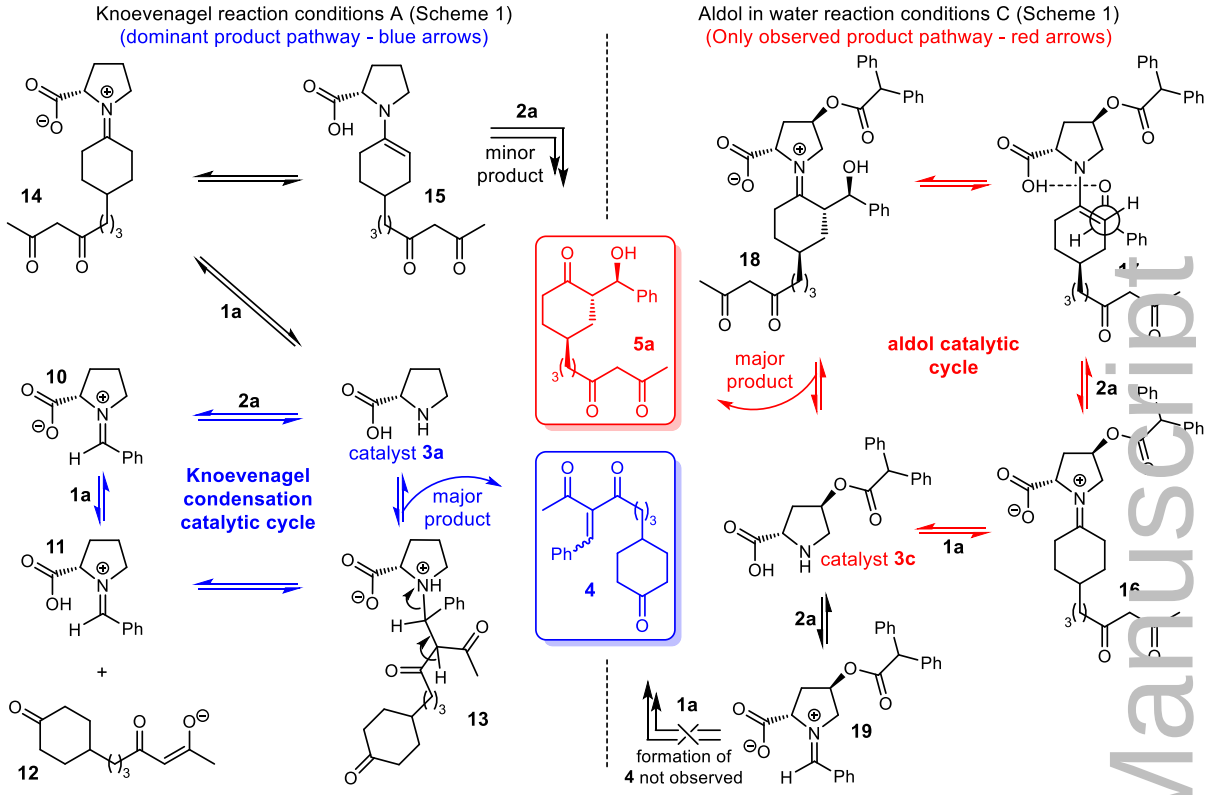
neat reaction conditions produced significant quantities of the Knoevenagel product (21% yield), but did show a chemoselective preference for the aldol product (28% yield), see Table 1 (entry 8). This finding again reinforces the need in water reaction conditions.

Scheme 3. Amino acid catalytic cycles for Knoevenagel (blue) and aldol (red) product formation.



Summarizing, Table 1 shows high aldol-over-Knoevenagel chemoselectivity requires an organic-water interface. Attempts to replicate the in water (heterogeneous) result (entry 9), by employing homogeneous solutions with water cosolvents (entries 6 and 7) or neat reaction conditions (entry 8), failed. Thus, the major factor controlling chemoselectivity is the reaction medium and whether added water results in heterogeneous or homogeneous reaction conditions.

Catalytic cycles and preliminary mechanistic conclusions. Mechanistically, the Knoevenagel nucleophile is always described as the carbanion form of the active methylene partner, but the electrophile varies.[3,23] For example, secondary amine catalysis is widely employed and the intermediacy of an iminium cation, derived from the aldehydic partner, is invoked.[24,25] It is noteworthy that Knoevenagel correctly rationalized the catalytic role of primary or secondary amines in 1898.[26] The amino acid catalyzed variant was first demonstrated by Dakin in 1909, and later by Prout.[27]

The Knoevenagel catalytic cycle for the (S)-proline (**3a**) catalyzed reaction of triketone **1a** (Table 1, entry 1) is highlighted in Scheme 3 (blue arrows), and is consistent with modern interpretations of this reaction.[3,25,28] The closest reported mechanistic study involves the reaction of acetylacetone with benzaldehyde under piperidine catalysis (10 mol%) in MeOH. Three rate influencing steps (iminium cation formation, enolate addition to iminium cation, and elimination) were identified.[25] For our amino acid catalyzed reaction, the analogous reaction steps with zwitterionic and salt intermediates **10**, **11**, **12**, and **13**, would be favorably solvated in the EtOH and DMSO *media* we performed these reactions in. It is simultaneously the case that formation of iminium carboxylate **14** (Scheme 3, left panel, aldol background reaction pathway) is expected, however, **14** is not rate determining for aldol product formation.[29]

On switching to the in water reaction conditions, it is assumed that solvation of the same intermediates would only be favorable at the organic-water interface. However, the enforced proximity to water would also undermine intermediates vulnerable to hydrolysis. Thus, zwitterion **19** likely forms (Scheme 3, right panel), but rapid hydrolysis reverts it back to starting materials. Zwitterion **16** also forms and suffers from a similar hydrolysis fate. But, infrequently **16** will instead lose a proton. In doing so, it forms the enamine carboxylic acid found within pre-transition state **17**. Relative to **16**, **18**, or **19**, the enamine carboxylic acid is stable at the phase boundary. In fact, pre-transition state **17** has been

described as optimally activated *via* a water based H-bond donor capability that is unique to water at an organic-water interface.[14a] Importantly, this catalysis influences the rate determining step for enamine based aldol reactions, *i.e.*, carbon-carbon bond formation.[29]

Several important points follow for the reactions studied here: (i) good to high Knoevenagel-over-aldol chemoselectivity is expected in polar media with low or no water content, (ii) excellent aldol-over-Knoevenagel chemoselectivity is afforded in water, but not when dissolved water is present, and (iii) high enantioselectivity is imparted on the aldol product by the in water reaction conditions.

Conclusion

New examples of chemoselectivity are less often noted, arguably because they are the oldest type of selectivity studied. Here we report a new example, aldol over Knoevenagel chemoselectivity. In total, these findings re-enforce and expand the unique role of water at an organic-water interface. Unanswered, is how this previously untapped capability manifests itself. Thus, at the water interface, is meaningful H-bonding available and coupled with solvation and rapid hydrolysis for iminium cations. If so, it might explain why amino acid catalyzed aldol reactions are subordinate to Knoevenagel reactions in solutions with little or no water, while in water reaction conditions allow a complete reversal in chemoselectivity.

In short, Knoevenagel reactions rely on the persistence of iminium cations (rate determining step), with turnover only coming after elimination of the amine catalyst (Scheme 3, intermediate **13**). The aldol reaction also requires iminium cation formation, but it is not rate determining, and turnover relies on iminium cation hydrolysis (Scheme 3, intermediate **18**). It is this distinction that may be allowing the observed chemoselectivity.

The practical outcome, of this report, is access to aldol products with three stereogenic centers in high *ee*, with broadened spectator functionality (β-diketones). By extension, other Knoevenagel functional groups are expected to be compatible, *e.g.*, β-ketoesters, malonate esters, dinitriles, *etc.* Application of these findings: to enamine, imine, or iminium-based reactions, to amine catalyzed cascade reactions, or as expanded tactics for complex molecule synthesis are anticipated.

Experimental Section

Two hundred and thirty-seven pages of experimental details, spectral and chromatographic data, and XRD crystallographic data are provided.

Generic procedure for aldol product (5) formation.
Method A: To a dry screw cap V-shaped reaction vessel (2.0 mL or 5.0 mL, based on the reaction scale) containing a pyrimidal-shaped magnetic stir bar were added the catalyst (2.0 or 5.0 mol %), triketone (1.5 equiv), aldehyde (1.0 equiv), and then water (4.0 equiv) was gently added and slow stirring was administered.
Method B: Same as method A, except triketone (1.0 equiv) and aldehyde (3.0 equiv).
Reaction monitoring: TLC analysis was unreliable. Instead, the reaction time was determined by setting up two reactions and performing the work-up at 18 h and the other at 24 h. If the 24 h time did not provide sufficient consumption of the limiting reagent, two more reactions were set up and work-up was performed at 30 h and 36 h. The maximum reaction time was 36 h. A reaction was considered complete when there was <10% of the limiting reagent, based on ^{1}H NMR integration, or if any two worked-up reactions (18, 24, 30, or 36 h) provided the same starting material to product ratio (^{1}H NMR).
Work-up: The reaction was diluted with dichloromethane (2 mL for the common reaction scale of 0.33- 0.50 mmol of limiting reagent) and stirred for 2-3 min at room temperature. This solution was transferred into a separating funnel already containing water (20 mL). The reaction vial was further rinsed with dichloromethane (2.0 mL x 3) and then water (2.0 mL x 2) and transferred to the separating funnel. The biphasic solution layers were separated, and the
aqueous layer was further extracted with dichloromethane (2 x 10 mL). We advise the use of dichloromethane because the rotary evaporator bath temperature should not exceed 28 °C, or risk epimerizing the aldol product under heating. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under rotary evaporation (rotary evaporator - bath temperature never above 28 °C) to obtain a crude gummy product.
General Purification: Column chromatography was performed using either mixtures of EtOAc/petroleum ether or *i*PrOH/CH_2Cl_2. See the Supporting Information for further details.

Acknowledgements

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References

[1] T. Hudlicky and J. W. Reed in *The Way of Synthesis: Evolution of Design and Methods for Natural Products*, Wiley-VCH, Weinheim, Germany 2007.

[2] a) See the conversion of **4** to **6** within: G. S. Gadaginamath, A. G. Kamat, *Proc. Indian Acad. Sci. (Chem. Sci.)* **1994**, *106*, 857-862; b) See the conversion of **8** to **13** within: R. M. Mohareb, F. O. Al Farouk, S. M. Sherif, K. Karaghiosoff, *Med. Chem. Res.* ***2014***, *23*, 3165-3177; c) See Scheme 2 for two examples within: H. Tan, X. Chen, H.Chen, H. Liu, S. Qiu, *Eur. J. Org. Chem*. **2015**, 4956-4963; d) See the conversion of **9** to **10** within: J. Gomes, C. Daeppen, R. Liffert, J. Roesslein, E. Kaufmann, A. Heikinheimo, M. Neuburger, K. Gademann, *J. Org. Chem.* **2016**, *81*, 11017-11034.

[3] For a review on Knoevenagel condensations, see: L. F. Tietze, U. Beifuss, in *Comprehensive Organic Synthesis*, Vol. 2 (Ed.: B. M. Trost), Pergamon, Oxford, UK, **1991**, p. 341–394.

[4] For an aldol reaction review, see: B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600-1632.

[5] See Table 4 within: P. Goswami, B. Das, *Tetrahedron Lett.* **2009**, *50*, 897-900.

[6] See Table 1 and 4 within: Y. Hu, Y.-H. He, Z. Guan, *Catal. Commun.* **2010**, *11*, 656-659.

[7] See page S2 of the Supporting Information within: S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

[8] See Table 2 within: Z. Jiang, Z. Liang, X. Wu, Y. Lu, *Chem. Commun.* **2006**, 2801-2803.

[9] a) B. Rodríguez, T. Rantanen, C. Bolm, *Angew. Chem. Int. Ed.* **2006**, *45*, 6924-6926; (b) See Table 5 within: B. Rodríguez, A. Bruckmann, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 4710-4722.

[10] See Table 4 within: A. Karmakar, T. Maji, S. Wittmann, O. Reiser, *Chem. Eur. J.* **2011**, *17*, 11024-11029.

[11] a) Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.*, **2007**, *129*, 5492-5502; b) R. N. Butler, A. G. Coyne, *Org. Biomol. Chem.* **2016**, *14*, 9945-9960; c) T. Kitanosono, S. Kobayashi, *Chem. Eur. J.* **2020**, *26*, 9408-9429; d) M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou, B. H. Lipshutz, *Chem. Sci.* **2021**, *12*, 4237-4266.

[12] a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *45*, 958-961; b) S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246-10256; c) Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.

[13] J.-F. Zhao, L. He, J. Jiang, Z. Tang, L.-F. Cun, L.-Z. Gong, *Tetrahedron Lett.* **2008**, *49*, 3372-3375.

[14] a) F. Giacalone, M. Gruttadauria, P. L. Meo, S. Riela, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 2747–2760; b) F. Giacalone, M. Gruttadauria, P. Agrigento, P. L. Meo, R. Noto, *Eur. J. Org. Chem.* **2010**, 5696-5704.

[15] All yield data in this manuscript represents isolated yields. No re-calculated yields, based on recovered limiting reagent, are given. Recovered triketone is sometimes shown to demonstrate that by-product formation is minimal or not occurring.

[16] The *dr* information was determined by ^{1}H NMR for crude products **5**, and is noted for **5a-k** in the Supporting Information.

[17] J. Jiang, L. He, S. W. Luo, L. F. Cun, L.-Z. Gong, *Chem. Commun*. **2007**, 736-738.

[18] For additional selected examples of 4-substituted cyclohexanone aldol desymmetrizations, albeit without a 1,3-diketone moiety, under chiral amine catalysis, see references 9, 14a and: a) S. Li, C. Wu, X. Fu, Q. Miao, *Ind. Eng. Chem. Res.* **2011**, *50*, 13711-13716; b) S. Li, C. Wu, X. Long, X. Fu, G. Chen, Z. Liu, *Catal. Sci. Technol.* **2012**, *2*, 1068-1071; c) T. C. Nugent, F. T. Najafian, H. A. E. D. Hussein, I. Hussain, *Chem. Eur. J.* **2016**, *22*, 14342-14348; d) T. C. Nugent, P. Spiteller, I. Hussain, H. A. E. D. Hussein, F. T. Najafian, *Adv. Synth. Catal.* **2016**, *358*, 3706-3713.

[19] For an enzymatic example of diketone desymmetrization, see: T. Peschke, P. Bitterwolf, S. Gallus, Y. Hu, C. Oelschlaeger, N. Willenbacher, K. S. Rabe, C. M. Niemeyer, *Angew. Chem. Int. Ed.* **2018**, *57*, 17028-17032.

[20] a) H. A. Stefani, I. M. Costa, D. de O. Silva, *Synthesis* **2000**, 1526-1528; b) A.-I Tsai, C.-P. Chuang, *Tetrahedron* **2008**, *64*, 5098-5102.

[21] This catalyst is reported for the first time and its synthesis is found in the Supporting Information (Section 2).

[22] For completeness, entry 3 (Table 1) is included with catalyst **3c** at a 5 mol% loading, but it is not noteworthy. Note: Catalyst **3c** is only sparingly soluble in EtOH. Thus, at the required reaction concentration (0.30 M solution of **1a** in EtOH) for direct comparison with entry 1 (Table 1), **3c** was not capable of dissolving at a 25 mol% loading. **3c** was significantly more soluble in DMSO. But, at the required reaction concentration (0.5 M solution of **1a** in DMSO) for direct comparison with entry 2 (Table 1), **3c** was not capable of dissolving at a 30 mol% loading.

[23] Tertiary amine (sp^3 hybridized) catalysis is also possible, however Hann and Lapworth described it as proceeding less rapidly than under primary or secondary amine catalysis, presumably because the aldehyde is not activated. This may explain the lack of tertiary amine catalyst applications in modern times, see: A. C. O. Hann, A. Lapworth, *J. Chem. Soc.* **1904**, *85*, 46-56.

[24] See page 343 of reference 3.

[25] E. V. Dalessandro, H. P. Collin, L. G. L. Guimarães, M. S. Valle, J. R. Pliego Jr., *J. Phys. Chem. B* ***2017***, *121*, 5300-5307.

[26] E. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2596-2619.

10.1002/adsc.202100301

[27] a) H. D. Dakin, *J. Biol. Chem.* **1909**, *7*, 49-55; b) Prout hailed the use of ε-aminocaproic acid, see: F. S. Prout, *J. Org. Chem.* **1953**, *18*, 928-933.

[28] A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 1707-1710.

[29] a) N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2007**, *129*, 15100-15101; b) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, *Helv. Chim. Acta* **2007**, *90*, 425-471.

10.1002/adsc.202100301

FULL PAPER

Harnessing additional capability from in water reaction conditions: Aldol *versus* Knoevenagel chemoselectivity

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Thomas C. Nugent,* Falguni Goswami, Samarpita Debnath, Ishtiaq Hussain, Hussein Ali El Damrany Hussein, Alka Karn, Srinuvasu Nakka