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Aqueous and Solvent-Free Uncatalyzed Three-Component Vinylogous Mukaiyama–Mannich Reactions of Pyrrole-Based Silyl Dienolates

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Abstract: A catalyst-free, environmentally benign three-component vinylogous Mukaiyama–Mannich reaction of pyrrole-based silyl dienolates is presented, which works effectively in both aqueous and solvent-free environments. Both lipophilic and hydrophilic aldehyde candidates are suitable substrates, allowing access to a rich repertoire of unsaturated vicinal aminolactam structures with virtually complete γ-site selectivity and moderate to good *anti*-diastereoselectivity. The utility of this technology is highlighted by protecting group-free synthesis of densely hydroxylated, sugar-related lactam frameworks. The role of water as an indispensable H-bonding reaction propeller is demonstrated.

Keywords: catalyst-free conditions; green chemistry; Mukaiyama–Mannich reaction; synthetic methods; vinylogy; water

The development of enabling chemical methodologies that fulfil such emblematic keywords as water, solvent-free, environment awareness, atom economy, and practicality is one of the greatest challenges of contemporary organic synthesis.[1] To this goal, several aqueous and solvent-free versions of leading carbon-carbon bond-forming reactions have been successfully explored,[2] including the venerable Diels–Alder cycloaddition,[3] the aldol addition reaction,[4] the Mannich[5] and Michael couplings,[6] the Claisen rearrangement,[3b,7] to mention only a few.

As for the Mannich reaction in particular, significant progress has been made for direct and indirect, two-component and three-component executions, few of which adopting neutral water as the reaction medium or even under solvent-free conditions.[5] However, to the best of our knowledge, there are not examples available concerning the development of catalyst-free, aqueous or neat Mukaiyama-type vinylogous Mannich addition methodology,[8,9] in spite of the distinct advantage of being atom conservative and more eco-friendly as compared to the conventional organic-phase, catalyzed counterparts. To address this issue, in connection with our ongoing studies focused on the exploitation of heterocyclic silyl dienolates in the vinylogous addition to C=X bonds,[8d,10] we herein present the first uncatalyzed aqueous and solvent-free three-component vinylogous Mukaiyama–Mannich reaction (VMMnR) employing a pyrrole ketene silyl-*N*,*O*-acetal, an aromatic amine, and diverse classes of aldehydes. Two complementary protocols are established, with which both hydrophobic aldehydes (aqueous and solvent-free conditions) and hydrophilic aldehydes (aqueous conditions) operate, furnishing γ-substituted δ-aminopyrrolinone units in high isolated yields, with excellent levels of γ-site selectivity and chemoselectivity, and moderate to high diastereoselectivity in favour of *anti*-configured adducts.

We initiated our journey by evaluating the one-pot three-component VMMnR between *N*-Boc-protected trimethylsilyloxypyrrole (**1a**), 3-methylbutanal (**2a**), and aniline (**3a**) in pure neutral water under vigorous stirring at room temperature (Table 1, entry 1). Very poor amounts of the Mannich product **4a** formed after 10 h, which was accompanied by detectable

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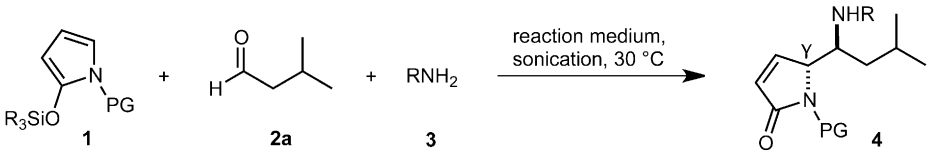
Table 1. Primary screening results of uncatalyzed, three-component VMMnR of pyrrole silyl dienolates with 3-methylbutanal and various primary amines.[a]



Entry	**1**: PG/SiR_3	**3**: R	Reaction Medium	Product	Conversion [%][b]	dr (*anti*:*syn*)[c]
1[d]	**1a**: Boc/TMS	**3a**: C_6H_5	H_2O	**4a**	30 (21)	81:19
2	**1a**: Boc/TMS	**3a**: C_6H_5	H_2O	**4a**	38 (27)	82:18
3	**1b**: Boc/TBS	**3a**: C_6H_5	H_2O	**4a**	94 (82)	92:8
4	**1c**: Boc/TES	**3a**: C_6H_5	H_2O	**4a**	55 (43)	80:20
5	**1d**: Boc/TIPS	**3a**: C_6H_5	H_2O	**4a**	60 (54)	72:28
6	**1e**: Cbz/TBS	**3a**: C_6H_5	H_2O	**4b**	61 (49)	83:17
7	**1f**: Ts/TBS	**3a**: C_6H_5	H_2O	**4c**	66 (58)	85:15
8	**1g**: Bn/TBS	**3a**: C_6H_5	H_2O	**4d**	30 (22)	85:15
9[e]	**1b**: Boc/TBS	**3a**: C_6H_5	H_2O	**4a**	96 (80)	92:8
10	**1b**: Boc/TBS	**3a**: C_6H_5	CH_2Cl_2	**4a**	46 (38)	72:28
11	**1b**: Boc/TBS	**3a**: C_6H_5	toluene	**4a**	51 (42)	78:22
12[f]	**1b**: Boc/TBS	**3a**: C_6H_5	H_2O	**4a**	95 (83)	92:8
13[g]	**1b**: Boc/TBS	**3a**: C_6H_5	H_2O	**4a**	85 (75)	92:8
14	**1b**: Boc/TBS	**3a**: C_6H_5	none	**4a**	>99 (90)	93:7
15	**1b**: Boc/TBS	**3b**: *o*-$MeOC_6H_4$	H_2O	**4e**	>99 (95)	93:7
16	**1b**: Boc/TBS	**3b**: *o*-$MeOC_6H_4$	none	**4e**	>99 (96)	92:8
17[d]	**1b**: Boc/TBS	**3b**: *o*-$MeOC_6H_4$	H_2O	**4e**	82 (74)	88:12
18[d]	**1b**: Boc/TBS	**3b**: *o*-$MeOC_6H_4$	none	**4e**	52 (47)	88:12
19	**1b**: Boc/TBS	**3c**: *p*-$MeOC_6H_4$	H_2O	**4f**	43 (35)	88:12
20	**1b**: Boc/TBS	**3d**: *o*-ClC_6H_4	H_2O	**4g**	60 (51)	72:28
21	**1b**: Boc/TBS	**3e**: Bn	H_2O	**4h**	<10	nd
22	**1b**: Boc/TBS	**3f**: *i*-C_3H_7	H_2O	**4i**	<10	nd

[a] Unless otherwise noted, the following reaction conditions were used: pyrrole **1** (1.0 equiv., 0.4 mmol), aldehyde **2a** (1.0 equiv.), amine **3** (1.0 equiv.), reaction medium (100 equiv.), at 30±2 °C for 10 h under 59 KHz ultrasonic irradiation.
[b] Determined by ^{1}H NMR analysis of the crude reaction products; values in parentheses refer to combined yields of isolated products.
[c] Determined by ^{1}H NMR analysis of the reaction crude; nd = not determined.
[d] At room temperature, under magnetic stirring (400 rpm), no sonication used.
[e] Reaction time, 24 h.
[f] 10 equiv. water were used.
[g] 1.0 equiv. water was used.

quantities of the corresponding γ-aldol addition by-product. Application of ultrasonic irradiation was equally disappointing, resulting in moderate production of **4a** and substantial recovery of the hydrolyzed *N*-Boc-pyrrolinone product (entry 2). We assumed that these unfavourable results were mainly due to competition of the aldol reaction and, especially, to the lability of the delicate TMS-pyrrole **1a** to water. Therefore, we turned our attention to more robust *N*-Boc-protected TBS-pyrrole **1b** (entry 3).

After 10 h sonication at 30 °C, we were pleased to find that the crude material solely consisted of the expected Mannich product **4a**, which was isolated in 82% yield (94% conversion), as a 92:8 mixture of *anti*- and *syn*-configured isomers.

Evaluation of other pyrrole candidates bearing different nitrogen and silicon substituents resulted in decreased performance (entries 4–8), while variation of the reaction time led to no significant improvement (entry 9). In comparison, uncatalyzed VMMnR in anhydrous CH_2Cl_2 or toluene proved scantily productive, giving rise to aminated lactam **4a** in only moderate yield with *ca.* 70:30 *anti*:*syn* diastereomeric ratio (entries 10 and 11).

Actually, water appeared to be an important ingredient for the reaction to occur; thus, the next experiments focused on evaluating the effect of the water content within the three-component reactant mixture. Diminishing the water content from 100 mol equiv. to 10 mol equiv. did not prove detrimental, and further reduction to 1.0 mol equiv. did not cause significant erosion of the good reaction performance displayed with 100 mol equiv. water (entries 12 and 13 *vs.* entry 3).

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At this juncture, we opted to abolish water all together (entry 14) and, rather unexpectedly, by simply irradiating a mixture of 1.0 equiv. each of pyrrole **1b**, isovaleraldehyde (**2a**), and aniline (**3a**) at 30 °C for 10 h, adduct **4a** formed in high yield and with an excellent 93:7 *dr* in favour of the *anti*-isomer.

With both aqueous and solvent-free reaction alternatives almost equally viable, our further scrutiny involved the applicability of these VMMnR procedures with respect to the amine component, again employing pyrrole **1b** and aldehyde **1a**. Success was attained with *o*-anisidine (**3b**), with the solvent-free protocol performing equally well as compared to the corresponding aqueous counterpart (entries 15 *vs.* 16).[11] Also, *p*-anisidine (**3c**) and *o*-chloroaniline (**3d**) were tolerated, albeit with inferior results (entries 19 and 20). Interestingly, aliphatic candidates such as benzylamine (**3e**) and isopropylamine (**3f**) proved ineffective (entries 21 and 22), highlighting the unique role displayed by anilines in these uncatalyzed transformations. Collectively, these data suggest that the combination of Boc and TBS substituents within the pyrrole donor **1** provided the optimum balance between reactivity, selectivity, and stability, with *o*-anisidine preferred as the amine component.[12] Not only is *o*-anisidine less toxic than aniline itself and relatively inexpensive, it is also easy to remove when the Mannich products have to be advanced to further synthetic manipulation.[13] Also, the *ortho*-substitution provided by 2-anisidine, in conjunction with the presence of water, might concur to activate the imine *via* an H-bridge bond in the setting of a chelate with the methoxy group.

Following on from these primary screening studies and capitalizing on the above findings, we went on to investigate the scope of the present VMMnR in terms of the aldehyde component. Although it may well be that specific optimization would be necessary for each aldehyde to optimize both the efficiency and selectivity of the processes, all VMMnR were carried out using *N*-Boc-TBS-substituted pyrrole **1b** and *o*-anisidine (**3b**) under the conditions optimized for aldehyde **2a** (see entries 15 and 16 in Table 1). As can be seen, in addition to isovaleraldehyde (**2a**) used in the initial investigation, which furnished adduct **4e**, both lipophilic and hydrophilic aldehydes were scrutinized. Aqueous (W) and solvent-free (SF) protocols were adopted in parallel and the results are grouped in Table 2.

The palette of scrutinized aldehydes encompassed aliphatic aldehydes **2a–2d**, aromatic representatives **2e–2h**, suitably protected α-alkoxy aldehydes **2i** and **2j**, as well as hydrophilic candidates **2k–2n**. All the lipophilic aliphatic aldehydes (entries 1–4) reacted with almost equal ease when both aqueous (plain entries) and solvent-free (primed entries) methodologies were applied, and delivered the expected Mannich products **4e**, **5b–5d** in good to excellent isolated yields, with virtually complete γ-site selectivity and no side products. Consistent preference for the *anti*-configured adducts was attained, with *dr* values ranging from 91:9 to 98:2. Neutral, electron-rich, and electron-poor aromatic aldehydes also proved to be pertinent substrates (entries 5–8), which furnished the expected Mannich adducts in good isolated yields for both W and SF reaction conditions. However, with these aldehydes the diastereoselectivity was markedly lower than that obtained with aliphatic counterparts. W and SF protocols were particularly suited for protected alkoxy aldehydes (entries 9 and 10), leading to the products with promising yields and complete γ-site selectivities. Remarkably, with protected (*R*)-glyceraldehyde **2j** three stereoisomers were obtained, the major product being the 5,1′-*anti*:1′,2′-*anti*-configured isomer **5j**, which was accompanied by the 5,1′-*anti*:1′,2′-*syn* isomer **5j′** and the 5,1′-*syn*:1′2′-*syn* isomer **5j″** with 3/2.8/1 (W) and 2/1.6/1 (SF) diastereomeric ratios for the three candidates. In this special case the magnitude of the simple diastereoselection favouring the 5,1′-*anti* isomers is maintained (*anti*:*syn*=85:15 and 78:22 for the W and SF protocols, respectively), whereas the facial selectivity at the aldehyde carbonyl is low in both cases (1′,2′-*syn*:*anti* ratio = 56:44), demonstrating that the presence of the chiral α-alkoxy group is not a prerequisite for determining the sense of the diastereofacial selectivity of these reactions.

Highly hydrophilic substrates, namely formaldehyde (**2k**) (37% formalin), dimethoxyacetaldehyde (**2l**) (60% in water), and chloroacetaldehyde (**2m**) (55% in water), which are commercially available as solutions in water, were obviously assayed with the W protocol only (entries 11–13). To our delight, the Mannich products could be acquired smoothly in excellent yields, with virtually complete γ-selectivity and favourable *dr* values in favour of *anti*-isomers. Perhaps most notable, protecting group-free, racemic glyceraldehyde **2n** reacted efficiently (entry 14), and again we were happy to see that the expected vinylogous Mannich compounds **5n**, **5n′** and **5n″** still formed in satisfactory 61% combined yield, to which 5,1′-*anti*:1′,2′-*syn*, 5,1′-*anti*:1′,2′-*anti*-, and 5,1′-*syn*:1′,2′-*syn*-configurations were assigned, respectively, based on chemical correlation to the enantiopure materials previously obtained with protected (*R*)-glyceraldehyde **2j** (entry 14 *vs.* 10).

The relative configuration within isovaleraldehyde-derived adduct *anti*-**4e** and the relative (hence absolute) configuration within glyceraldehyde-derived compounds **5j′** (*via* its saturated counterpart **6**) and **5j″** were unambiguously established by single crystal X-ray diffraction analyses (Figure 1), whilst the structures of the remaining Mannich adducts were as-

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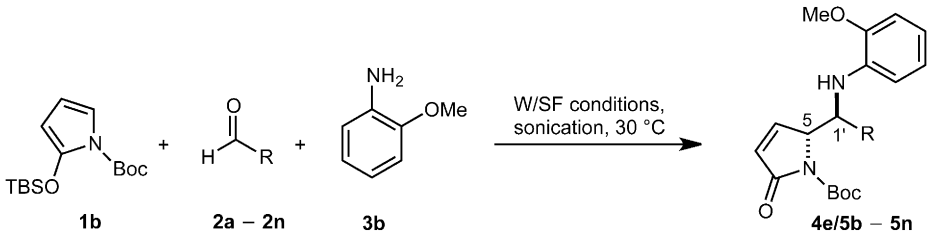
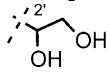
Table 2. Scope of aldehydes for the uncatalyzed three-component VMMnR under aqueous (W) and solvent-free (SF) conditions.[a]



Entry	**2**: R	Conditions	Time [h]	Product	Yield [%][b]	*dr* (*anti*:*syn*)[c]
1	**2a**: *i*-Bu	W	9	**4e**	95	93:7
1′		SF	8		96	92:8
2	**2b**: *i*-Pr	W	9	**5b**	82	94:6
2′		SF	7		99	93:7
3	**2c**: *c*-hexyl	W	7	**5c**	96	98:2
3′		SF	6		99	96:4
4	**2d**: *n*-heptyl	W	8	**5d**	83	93:7
4′		SF	6		95	91:9
5	**2e**: C_6H_5	W	7	**5e**	82	67:33
5′		SF	7		71	67:33
6	**2f**: *p*-$MeOC_6H_4$	W	7	**5f**	91	61:39
6′		SF	9		87	57:43
7	**2g**: *p*-BrC_6H_4	W	9	**5g**	94	65:35
7′		SF	8		78	61:39
8	**2h**: *p*-$NO_2C_6H_4$	W	20	**5h**	60	73:27
8′		SF	8		83	62:38
9	**2i**: $-CH_2OTBS$	W	21	**5i**	72	99:1
9′		SF	13		91	98:2
10	**2j**: 	W	14	**5j**	95	85:15[d]
10′		SF	8		96	78:22[e]
11	**2k**: H	W	5	**5k**	99	-
12	**2 L**: $-CH(OMe)_2$	W	13	**5l**	92	91:9
13	**2m**: $-CH_2Cl$	W	7	**5m**	91	91:9
14	**2n**: 	W	15	**5n**	61	90:10[f]

[a] Unless otherwise noted, the following reaction conditions were used: pyrrole **1b** (1.0 equiv., 0.4 mmol), aldehyde **2a–2n** (1.0 equiv.), amine **3b** (1.0 equiv.), H_2O (100 equiv.) (labelled as W) or neat (labelled as SF), at 30±2 °C under 59 KHz ultrasonic irradiation.

[b] Combined yield of isolated products.

[c] Determined by ^1H NMR analysis of the reaction crude. Relative configurations *anti*:*syn* refer to the stereodisposition of the newly formed C-5 and C-1′ stereocenters.

[d] 3/2.8/1 *dr* for the 5,1′-*anti*:1′,2′-*anti*-, 5,1′-*anti*:1′,2′-*syn*-, and 5,1′-*syn*:1′,2′-*syn*-configured isomers **5j**, **5j′**, and **5j″**.

[e] 2/1.6/1 *dr* for the 5,1′-*anti*:1′,2′-*anti*-, 5,1′-*anti*:1′,2′-*syn*-, and 5,1′-*syn*:1′,2′-*syn*-configured isomers **5j**, **5j′**, and **5j″**.

[f] 5.6/3/1 *dr* for the 5,1′-*anti*:1′,2′-*syn*-, 5,1′-*anti*:1′,2′-*anti*-, and 5,1′-*syn*:1′,2′-*syn*-configured isomers **5n**, **5n′**, and **5n″**.

signed by analogy or by comparison with known substances (see the Supporting Information for details).

Encouraged by the success of the aqueous protocol with highly hydrophilic candidates, we finally wondered to see whether protecting group-free aldose sugars could even be pertinent substrates in these VMMnR trasformations. Remarkably, as was the case with prototypical protecting group-free glyceraldehyde **2n**, direct exposure of commercial grade D-(−)-arabinose (**7**) to pyrrole **1b** and *o*-anisidine (**3b**) in the presence of 100 mol equiv. water under ultrasonic irradiation did produce the expected *C*-glycosylated lactam adducts in acceptable yield and diastereoselectivity (Scheme 1).

However, due to difficult purification of the crude water-soluble material by chromatography, peracetylation was necessary to arrive at pure pyrrolinone tetraacetate **8**, which was delivered in 38% yield after

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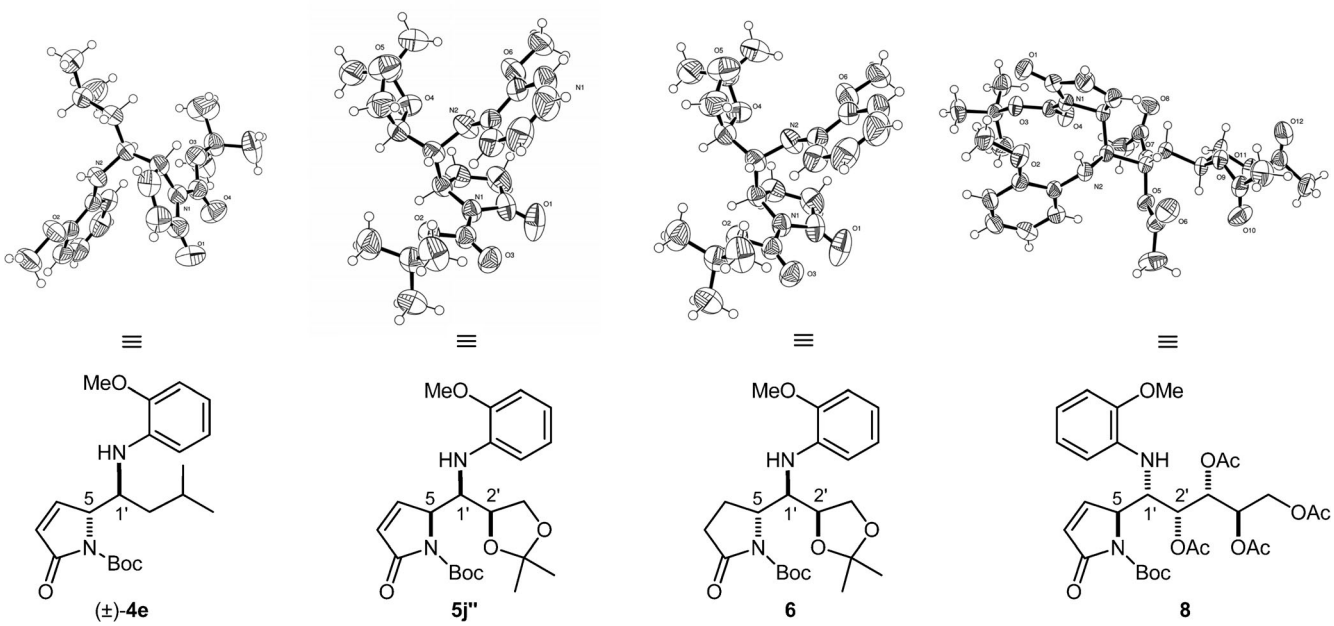
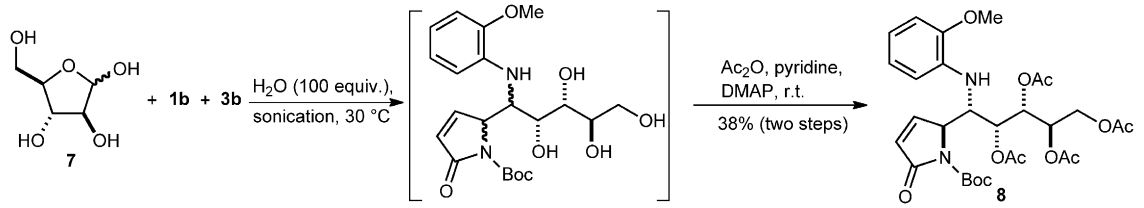


Figure 1. ORTEP representation of the X-ray crystal structures of (±)-*anti*-**4e** (CCDC 834892), **5j″** (CCDC 834893), **6** (CCDC 834894), and **8** (CCDC 834895) (see the Supporting Information for details). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.



Scheme 1. Water-assisted, three-component VMMnR as applied to protecting group-free D-arabinose **7**.

chromatography (two steps). To this compound a 5,1′-*anti*:1′,2′-*syn*-configuration (D-*glycero*-D-*gulo*) was assigned based on single crystal X-ray analysis (Figure 1).

Coming back to the role of water in the present three-component vinylogous Mannich transformation, one may question as to whether and how water is considered an active, indispensable reaction ingredient in these transformations.

In truth, water is present even in reactions carried out under neat conditions (1.0 equiv., that is, the aldehyde-amine condensation by-product), and only subtle variation of yield and selectivity is observed when passing from aqueous to solvent-free experiments.

To exclude water completely, we assayed a two-component VMMnR using a preformed, pure imine, keeping the environment as anhydrous as possible. When pyrrole **1b** was exposed to the imine derived from aldehyde **2a** and amine **3b** under an argon atmosphere, no reaction occurred at all, and complete recovery of the starting reactants was attained. Conversely, addition of as little as 1.0 mol equiv. of water propelled the reaction well, paralleling the results of the corresponding three-component reactions almost exactly (see entries 1, 1′ in Table 2). Thus, water seems to be a crucial element in both water and solvent-free reactions and its role is manifold.

Even though a full rationale of the present VMMnR is hard to formulate, we can hypothesize that water acts as both proton donor, to activate the *in situ*-generated imine component, and silicon scavenger, to sequestrate the silicon ion into an inactive R_3SiOH species, which is actually the sole by-product in these transformations. Other peculiar functions of water as transition state stabilizer or ion species-solvating agent cannot in principle be ruled out, while the often invoked paradigm of the hydrophobic effect or cohesive pressure effect exerted by water under water conditions[14] hardly applies in this special case, owing to the close parallelism observed for both aqueous and solvent-free experimentations.[15]

In conclusion, we have developed an unprecedented three-component vinylogous Mukaiyama–Man-

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nich-type methodology amenable to work equally well under both aqueous and solvent-free environments. No catalysts, salts, organic solvents, co-solvents, surfactants, or metal adjuvants are required.[16] Thanks to its operational simplicity and practicality, this unique transformation allows the expedient formation of a repertoire of valuable vicinal aminolactam structures in high isolated yields, with virtually complete γ-site selectivities, good diastereoselectivities in favour of the *anti*-configured adducts, and no aldol by-products. A varied palette of lipophilic aldehyde substrates carrying diverse aliphatic and aromatic substituents is well suited, as are highly hydrophilic candidates which are available solely as solutions in water. The power of this technology is particularly evident when applied to protecting group-free, sugar-related carbonyls, which paves the way to the construction of a rare progeny of chiral non-racemic pyrrolinone *C*-glycoside frameworks with good stereocontrol.

Experimental Section

Representative Experimental Procedure W (Aqueous Conditions): Preparation of Lactam *anti*-4e

N-(*tert*-Butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (TBSOP, **1b**) (114.3 mg, 0.384 mmol) was added to the heterogeneous mixture of isovaleraldehyde (**2a**) (41 μL, 0.384 mmol), *o*-anisidine (**3b**) (43 μL, 0.384 mmol) and water (692 μL, 38.4 mmol) and kept under sonication in an open-air vessel. The resulting heterogeneous reaction mixture was kept in the ultrasound bath at *ca.* 30 °C and monitored by TLC (hexane/EtOAc 70/30) to check the complete disappearance of the reactants. After 9 h, the reaction was judged complete and the reaction mixture was extracted with EtOAc (3 × 1 mL). The organic layers were collected, dried with $MgSO_4$, filtered, and concentrated under vacuum to give a mixture of *anti/syn*-**4e**. The *anti/syn* diastereomeric ratio of the products was determined to be 93:7 by ^{1}H NMR analysis of the crude reaction residue. The residue was then purified by silica gel flash chromatography (hexane/EtOAc 70/30) affording *anti*-**4e** (yield: 127 mg) as a white solid and *syn*-**4e** (yield: 9.6 mg) as a colourless oil in a 95% combined yield. Characterization data and crystal data are given in the Supporting Information.

Representative Experimental Procedure SF (Solvent-Free Conditions): Preparation of Lactam *anti*-4e

Pyrrole **1b** (114.3 mg, 0.384 mmol) was added to the mixture of isovaleraldehyde (**2a**) (41 μL, 0.384 mmol), and *o*-anisidine (**3b**) (43 μL, 0.384 mmol) in an open-air vessel kept under sonication. The reaction was sonicated at *ca.* 30 °C and monitored by TLC (hexane/EtOAc 70/30) to check the complete disappearance of the reactants. The reaction was judged complete after 8 h and the reaction mixture was concentrated under reduced pressure to remove volatile by-products (e.g., TBSOH) obtaining a mixture of *anti/syn*-**4e**. The *anti/syn* diastereomeric ratio of the products was determined to be 92:8 by ^{1}H NMR analysis of the crude reaction residue. The crude residue was then purified by silica gel flash chromatography (hexane/EtOAc 70/30) affording *anti*-**4e** (yield: 127 mg) as a white solid and *syn*-**4e** (<ield: 11 mg) as a colourless oil in a 96% combined yield.

Supporting Information

Description of experimental procedures, characterization data, crystal data for compounds (±)-*anti*-**4e**, **5j″**, **6**, and **8**, transition state models, and NMR spectra of new compounds are available as Supporting Information.

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[12] Three-component VMMnR additions to iminium ions formed *in situ* from aldehydes and secondary amines were also investigated under both aqueous and solvent-free conditions. In the absence of any catalyst, reaction between **1b**, **2a**, and *N*-methylaniline provided the respective addition products in modest yields and reduced diastereoselectivities (55% yield, 83:27 *dr*, and 18% yield, 67:33 *dr* for aqueous and solvent-free conditions, respectively). In comparison, non-aromatic representatives such as morpholine and dibenzylamine proved totally reluctant to react.

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[15] Due to *Z*/*E* geometric equilibration, imines can adopt *syn*- or *anti*-disposed arrangements in the transition states, and this renders a precise mechanistic rationale accounting for the observed diastereoselection hard to formulate. Nevertheless, based on several precedents in this field, plausible transition states for the present *anti*-selective VMMnR of *N*-arylimines to silyloxypirroles are visualized in Figure S1 in the Supporting Information.

[16] As a genuinely green option, products of entries 1, 1′, 2′, 3, 3′, 4′, 9′, and 11 in Table 2 can be isolated directly by high vacuum treatment of the reaction crudes, thus avoiding organic solvent intervention. However, for the data to be consistent, standard protocols involving organic solvents and chromatography were adopted in all experiments.

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