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Rate enhancement by water in a $TiCl_4$-mediated stereoselective vinylogous Mukaiyama aldol reaction

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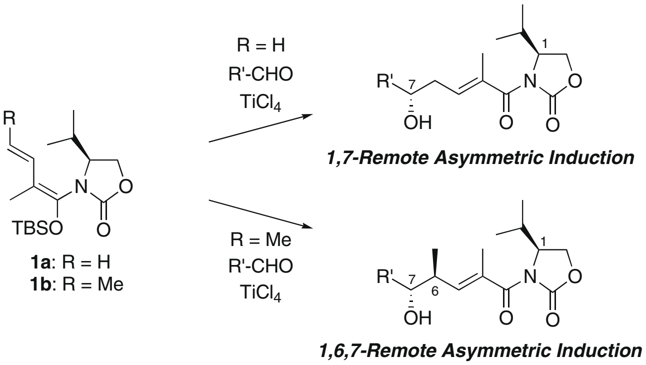
ABSTRACT

A remarkable enhancement in the rate of a $TiCl_4$-mediated stereoselective vinylogous Mukaiyama aldol reaction (VMAR) using vinylketene silyl *N*,*O*-acetal **1** was observed in the presence of water.

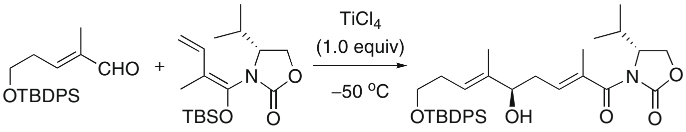
We previously developed a highly stereoselective vinylogous Mukaiyama aldol reaction (VMAR) using vinylketene silyl *N*,*O*-acetal **1** (Scheme 1),[1,2] which provides a unique and remarkable entry to a remote asymmetric induction. From a synthetic point of view the VMAR affords a δ-hydroxy-α-methyl- or δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl unit in one step with high diastereoselectivity. Because this unit is common to many natural products, VMAR has been efficiently utilized in the total synthesis of several important biologically active compounds by many groups including us.[3] However, VMAR involving conjugated aldehydes generally require a prolonged reaction time at low temperature,[3a] whereas such VMAR conducted at higher temperatures (between −40 °C and −35 °C) gives only modest yields.[1a,3k] In this context, an improvement of VMAR, particularly involving enals, is strongly needed.

During our synthetic study of fomitellic acid B, we observed a remarkable increase in the reaction rate in VMAR of enal **2** with vinylketene silyl *N*,*O*-acetal *ent*-**1a** by the addition of a catalytic amount of water (Scheme 2).[4] Herein, we report the rate enhancement by water in $TiCl_4$-mediated stereoselective VMAR using vinylketene silyl *N*,*O*-acetal **1**[5] in detail.



Scheme 1. Remote asymmetric induction.

Table 1
VMAR of enal **2** with *ent*-**1a**



2 (2.0 equiv) *ent*-**1a** **3** dr >20:1

Entry	Solvent (M)[b]	Additive (mol %)	Time (h)	Yield[a] (%)
1	CH_2Cl_2 (0.1)	–	7	43
2	Toluene (0.1)	–	23	51
3	Toluene (0.5)	–	77	77
4	Toluene (0.5)	H_2O (5)	55	76
5	Toluene (0.5)	H_2O (10)	40	74
6	Toluene (0.5)	H_2O (20)	26	69

[a] Isolated yield.
[b] For *ent*-**1a**.

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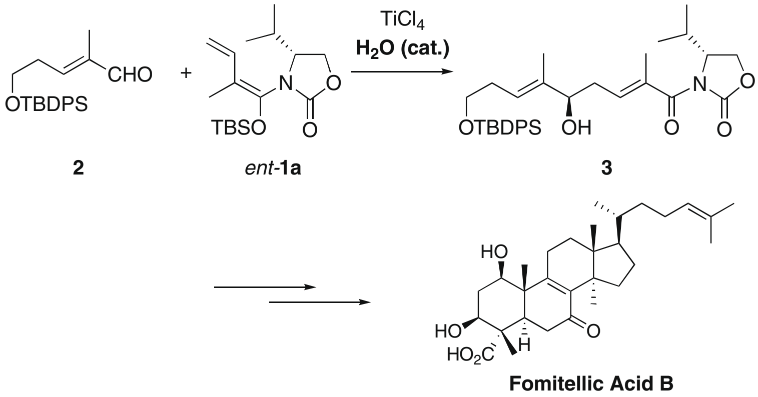


Scheme 2.

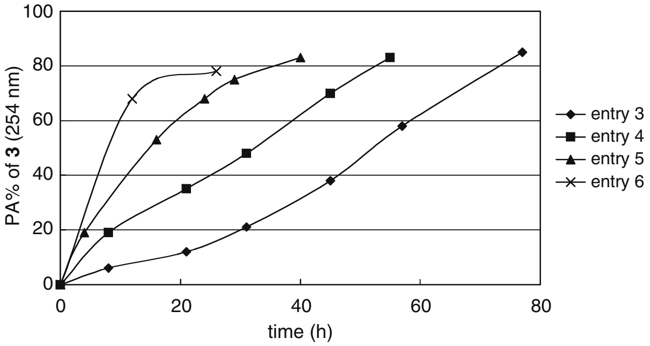
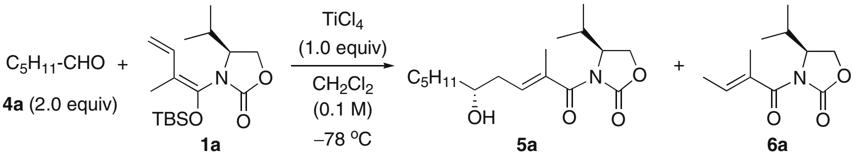


Figure 1. Reaction progress of the VMAR of enal **2** with *ent*-**1a**.

The results of VMAR of enal **2** with *ent*-**1a** are shown in Table 1. Initial attempts under standard conditions, previously established in our laboratory,[1] afforded aldol adduct **3** in only 43% yield (entry 1). A remarkable increase in yield was observed by using toluene as a solvent in higher concentration (entry 3), although the reaction was extremely slow and not very reproducible. To our surprise, addition of a catalytic amount of water accelerated the reaction in a reproducible manner without decreasing the yield and diastereoselectivity[6] of the product. Moreover, the reaction rate was found to increase as a function of the increasing amount of water (entries 4–6) up to a certain threshold value. Addition of 20 mol % of water resulted in a lower yield because of the competing hydrolysis of *ent*-**1a** (entry 6). Reaction progress of the VMAR was monitored by taking a small aliquot of the mixture and analyzing by HPLC.[7] Figure 1 shows a plot of the percentage accumulation of peak area (PA) of **3** as a function of time for entries 3–6 in Table 1. PA% was calculated as [PA of **3**]/([PA of **3**] + [PA of *ent*-**1a**] + [PA of *ent*-**6a**]) × 100. Note that PA% of **3** does not correspond to the exact yield of product because the molar absorbance of each molecule is different. Nevertheless, these results clearly demonstrate the enhancement of reaction rate by the addition of water.

In order to clarify whether the rate enhancement effect of water is a general characteristic of this type of reaction, we next examined the VMAR of hexanal **4a** as a representative aldehyde under various conditions (Table 2). The reaction was carried out in CH_2Cl_2 at −78 °C without additive to afford aldol adduct **5a** in 96% yield with high diastereoselectivity in 7 h (entry 1). The acceleration effect of water was also observed in the reaction of hexanal **4a** in CH_2Cl_2 at −78 °C. The VMAR product **5a** was isolated in 98% yield as an almost single isomer after 1.5 h by the addition of 10 mol % of water (entry 2). It is also noteworthy that the addition of 10 mol % of water does not result in any significant hydrolysis of vinylketene silyl *N*,*O*-acetal **1a** into imide **6a**. Intriguingly, this remarkable enhancement in the rate of reaction was not observed in the presence of other additives

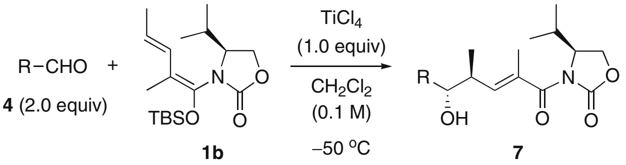
Table 2
VMAR of hexanal with **1a**



Entry	Additive (mol %)	Time (h)	HPLC PA% (254 nm)			Yield[a] (%)	dr[b]
			5a	**1a**	**6a**		
1	–	1.5	79.7	18.4	1.9	96	>20:1
		3.0	88.6	9.4	2.0		
		7.0	94.3	3.3	2.4		
2	H_2O (10)	0.75	89.9	8.5	1.6	98	>20:1
		1.5	97.0	1.4	1.6		
3	MeOH (10)	3.0	91.5	5.3	1.8	95	>20:1
		6.0	93.5	2.8	2.0		
4	*i*-PrOH (10)	3.0	85.7	10.1	2.0	–[c]	–
5	*t*-BuOH (10)	3.0	79.7	17.6	2.7	–[c]	–
6	AcOH (10)	3.0	80.1	14.0	5.9	–[c]	–

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] Not isolated.

Table 3
VMAR of **1b** with aldehydes



Entry	Aldehyde	H_2O (mol %)	Time (h)	Yield[a] (%)	dr[b]
1	R = C_5H_{11}, **4a**	–	2.0	99	>20:1
2	R = C_5H_{11}, **4a**	10	0.75	99	>20:1
3	R = Ph, **4b**	–	4.5	96	20:1
4	R = Ph, **4b**	10	3.0	97	20:1
5	R = (*E*)-$CH_3CH{=}C(CH_3)$, **4c**	–	23	86	>20:1
6	R = (*E*)-$CH_3CH{=}C(CH_3)$, **4c**	10	12	85	>20:1
7	R = (*E*)-$CH_3CH{=}C(CH_3)$, **4c**	20	7	69	>20:1

[a] Isolated yield.

[b] Determined by ^1H NMR analysis.

(entries 3–6). Methanol did accelerate the VMAR slightly. However, we speculate the rate enhancement by methanol might be due to the water generated during the dimethyl acetal formation from **4a** and methanol. Indeed methylated by-product was formed in about 3% yield in addition to **5a**.

Next, the VMAR of **1b** with various aldehydes was examined in CH_2Cl_2 at −50 °C in the presence or absence of water (Table 3). The VMAR proceeded smoothly in the case of hexanal **4a** and benzaldehyde **4b**, regardless of the addition of water. However a slight enhancement effect of water was also observed (entries 1–4). On the other hand, the VMAR of **1b** with tiglic aldehyde **4c** is rather slow. The corresponding VMAR product **7c** was isolated in 86% yield after 23 h in the absence of water (entry 5). The other group also reported the VMAR of **4c** performing at −60 °C for 4 days in order to reach completion.[3a] In contrast, the addition of 10 mol % of water resulted in an enhancement of the VMAR, that is, **7c** isolated in 85% yield after 12 h (entry 6).[8] Using 20 mol % water the reaction was complete in 7 h, but the yield was only modest due to the competitive hydrolysis of **1b** (entry 7).

Although the specific role of water in the VMAR remains unclear, we tentatively propose the following two possibilities: (i) water might coordinate to $TiCl_4$ and result in partial dissociation of $TiCl_4$ aggregates, and (ii) both the proton and $TiCl_4$ of a plausible hydrated $TiCl_4$ might coordinate to the carbonyl oxygen, resulting in double activation.[9]

In summary, we have demonstrated a rate enhancement by water in $TiCl_4$-mediated stereoselective vinylogous Mukaiyama aldol reactions. It must be emphasized that the addition of water did not affect the high level of diastereoselectivity of VMAR. To the best of our knowledge, there has been no precedent for such an enhancement in reaction rate caused by the presence of water in $TiCl_4$-mediated reactions. Further investigations of the role of water as well as extension of this finding are in progress.

Acknowledgment

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5. The vinylketene silyl *N,O*-acetal **1** (**1a**, *ent*-**1a**, and **1b**) used in this study were prepared according to the method described in the literature[1a] and then purified by crystallization with 2-propanol and water.
6. Diastereomeric ratio of **3** was determined by HPLC analysis after the protection of the alcohol and removal of the chiral auxiliary (see Ref. 4).
7. HPLC conditions: L-column ODS (250 × 4.6 mm id; 5 μm, Chemicals Evaluation and Research Institute, Tokyo, Japan) (80% aq CH_3CN, 1.0 mL/min, detection at 254 nm, 40 °C).
8. *A general experimental procedure was as follows*: To a stirred solution of tiglic aldehyde **4c** (0.11 mL, 1.14 mmol) and H_2O (1.0 μL, 0.06 mmol) in CH_2Cl_2 (6 mL), $TiCl_4$ (1.0 M in CH_2Cl_2, 0.59 mL, 0.59 mmol) was added at −78 °C and then vinylketene silyl *N,O*-acetal **1b** (200 mg, 0.59 mmol) was added at the same temperature. After stirring for 12 h at −50 °C, the reaction was quenched by the addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Rochelle salt. The resulting mixture was diluted with CH_2Cl_2 and stirred at room temperature until the white slurry was dissolved. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford aldol adduct **7c** (148 mg) in 85% yield.
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