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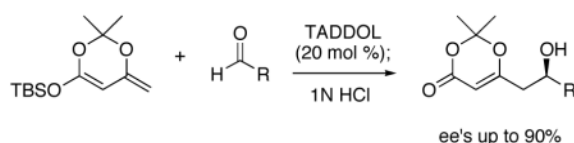
Org Lett. 2005 December 8; 7(25): 5657–5660. doi:10.1021/ol052301p.

Hydrogen Bond Catalyzed Enantioselective Vinylogous Mukaiyama Aldol Reaction

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Abstract



The concept of hydrogen bonding catalysis was extended to the vinylogous Mukaiyama aldol reaction, which gives rapid access to polyketide derivatives. The reaction of the silyldienol ether shown and a range of aldehydes catalyzed by TADDOL proceeds regiospecifically to produce the addition products in good yields and enantiomeric excesses.

Nature uses hydrogen bonding as a central force for the promotion of enzyme-catalyzed reactions. Yet, only recently have organic chemists begun to use this non-covalent interaction to catalyze chemical reactions of interest.^{1,2,3} We have previously demonstrated the successful use of hydrogen bond activation for the promotion of highly enantioselective Diels-Alder and Hetero-Diels-Alder reactions.⁴ Motivated by these results, we sought to expand this metal-free activation concept to other broadly useful classes of reactions. Herein we describe the first examples of hydrogen bond catalyzed enantioselective vinylogous Mukaiyama aldol (VMA) reactions.

The VMA reaction has proven to be a powerful method for complex molecule synthesis, as it provides rapid access to polyketide derivatives such as δ -hydroxy- β -ketoesters and α,β -unsaturated δ -hydroxy carbonyl compounds (Scheme 1).⁵ Further transformation of these compounds can be accomplished with good diastereoselectivity⁶ and paves the way to polyol units, a motif common to many natural products. Given the usefulness of the VMA reactions, considerable effort has been expended on the development of chiral catalysts for these reactions. Most of the reported catalysts are based on Lewis acidic metals, such as boron-,⁷ titanium-,⁸ copper-,⁹ chromium-,¹⁰ and promote the reaction by activating the electrophilic carbonyl group. Catalysts that promote the reaction by activating the nucleophilic component have also been shown to be effective.^{9c,11,12} Our objective was to promote the VMA reaction by activating the electrophile under metal-free conditions.

To the extent that hydrogen bonding represents a subset of Lewis acid activation, then a variety of chiral hydrogen bond donors should be capable of promoting asymmetric reactions. For the present study, we examined the effectiveness of several common chiral alkaloids and diols (Figure 1), as catalysts for the VMA reaction of trimethylsilyldienol ether of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1a**) and 2-nitrobenzaldehyde (Table 1). These studies revealed

that although many compounds promote the VMA reaction with varying levels of enantioselectivity, the best results were obtained using the TADDOL (α,α',α' -tetraaryl-1,3-dioxolane-4,5-dimethanol) family of diols (Table 1, entries 13–15).

The optimization of reaction conditions was accomplished using the commercially available 1-naphthyl-TADDOL (**7**) as the catalyst and ethyl glyoxalate as the aldehyde partner (Table 2). When the reaction was carried out at $-40\text{ }^{\circ}\text{C}$ with 20 mol % of the catalyst, the VMA product was formed in 61% ee (Table 2, entry 1). The ee improved significantly upon lowering the reaction temperature to $-80\text{ }^{\circ}\text{C}$ (entry 2). In order to scavenge adventitious water or acidic species that might enhance the racemic background reaction, various additives were investigated, with Hunig's base providing the greatest improvement in enantioselectivity (entries 3–6). The silyl substituent on the nucleophile was found to have a small but measurable effect on enantioselectivity, and optimum results were obtained with the TBS group (entry 9). It is noteworthy that the reactions between silyldienol ethers and glyoxalate **2b** are generally very rapid, showing >90% conversion within 10 minutes.

The hydrogen bond catalyzed VMA reaction was applied to a variety of reactive aldehydes (Table 3). The use of Hunig's base, which decreases the rate of the reaction, was omitted for the reaction with aldehydes other than glyoxalates. In order to facilitate purification and analysis, the products were isolated as the free alcohols following a 1N HCl quench. As can be seen from these results, glyoxalate esters, α,β -unsaturated aldehydes, oxazole aldehydes, thiazole aldehydes, as well as electron-poor aromatic aldehydes can be used in this process, providing vinylogous aldol products in moderate to good ee's (entries 1–9). Surprisingly, 4-nitrobenzaldehyde (entry 10) proved much less reactive than 2-nitrobenzaldehyde (entry 6) under otherwise identical conditions. Aliphatic aldehydes were less reactive and yielded products with low ee's (entries 11 and 12). It should be noted that all these reactions showed excellent γ -selectivity, as the regioisomer resulting from attack at the α position of the silyldienol ether was not detected.

In addition to providing access to polyketide derivatives, the products can be easily transformed into the formal products of an aldol reaction with acetone, as shown in Scheme 2. Refluxing the VMA adducts **3b** and **3d** in a toluene/water mixture cleanly provides the desired product **8b** and **8d** respectively.^{8a} The absolute configuration of VMA products **3k** and **3l** were determined by comparison of their optical rotations with the reported values,^{9a,13} whereas that of **8b** was assigned by correlation with a known derivative (see Supporting Information).¹⁴

The asymmetric induction observed in the formation of **3b** can be rationalized using the general model (Figure 2) that we had developed for other TADDOL-catalyzed reactions.⁴ The TADDOL catalyst is expected to exist in a well-defined, internally hydrogen-bonded arrangement.¹⁵ The free hydrogen atom on the catalyst, which is expected to be more acidic than a normal OH, can hydrogen bond with the aldehyde oxygen, thereby lowering its lowest unoccupied molecular orbital energy. Stabilization of the hydrogen-bonded aldehyde through a postulated $\pi-\pi^*$ donor-acceptor interaction between the electron-rich proximal equatorial 1-naphthyl ring and the electron-deficient aldehyde carbonyl should further stabilize the hydrogen-bonded carbonyl, leaving its *Re-face* accessible to attack by the nucleophile.^{4b} The above model correctly predicts the observed absolute stereochemistry in the product.

In conclusion, we have demonstrated the successful use of hydrogen bonding catalysis in enantioselective vinylogous Mukaiyama aldol reactions. The reactions are most effective with highly reactive aldehydes and give the expected products in good to excellent yields and ee's as high as 90%. We are currently investigating the use of other types of nucleophiles in order to expand the scope of this reaction. We are also examining a wider range of hydrogen bond

donors, particularly those in which the proton acidity can be readily tuned, so as to catalyze a broader range of transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the National Science Foundation and the National Institutes of Health for financial support. M.G. gratefully acknowledges the Natural Sciences and Engineering Research Council of Canada for a postdoctoral fellowship. We thank Professor William D. Wulff (Michigan State University) for samples of (S)-VANOL and (S)-VAPOL, and Professor Hisashi Yamamoto (University of Chicago) for a sample of catalyst **4**.

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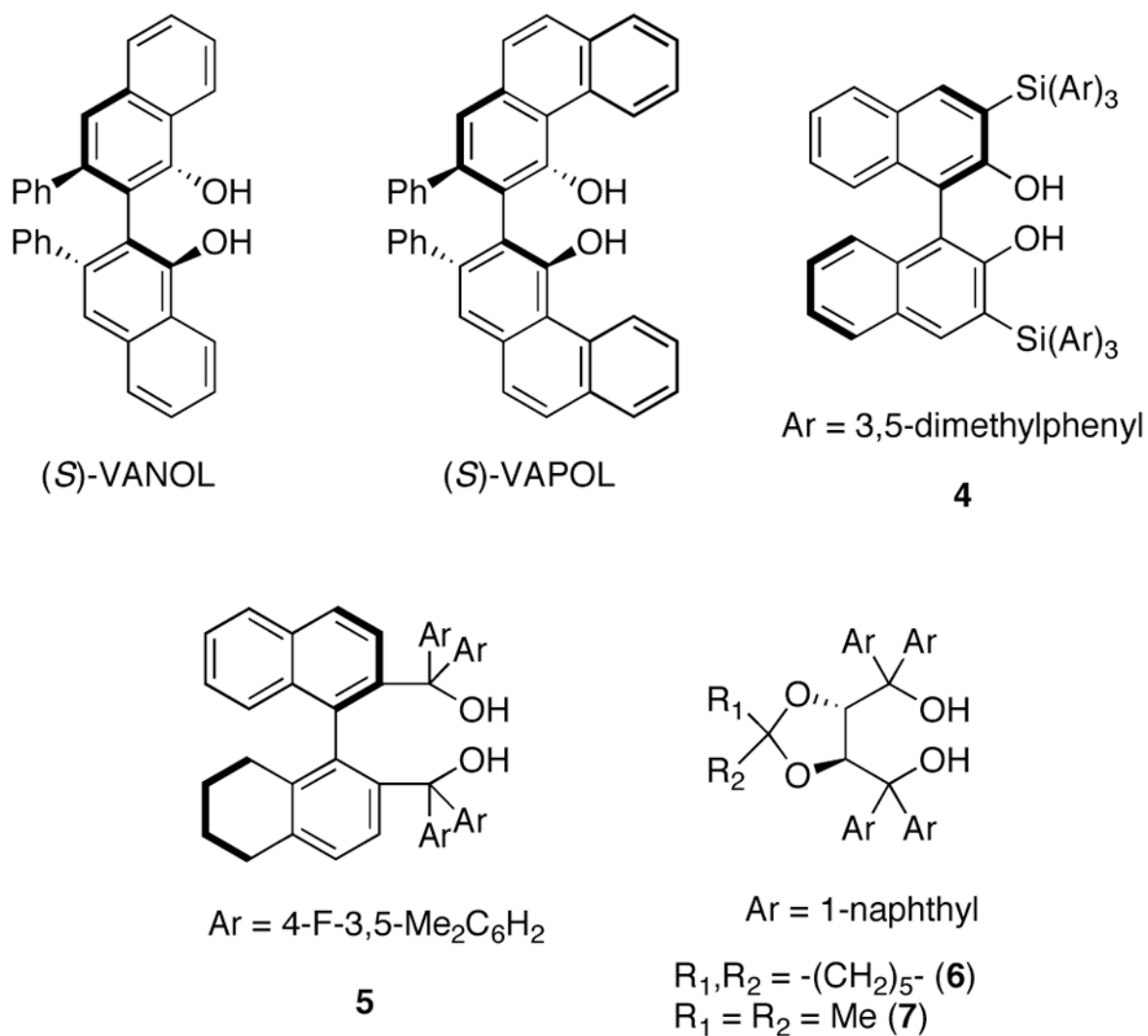


Figure 1.
Diol catalysts used for the hydrogen bond catalyzed VMA reaction

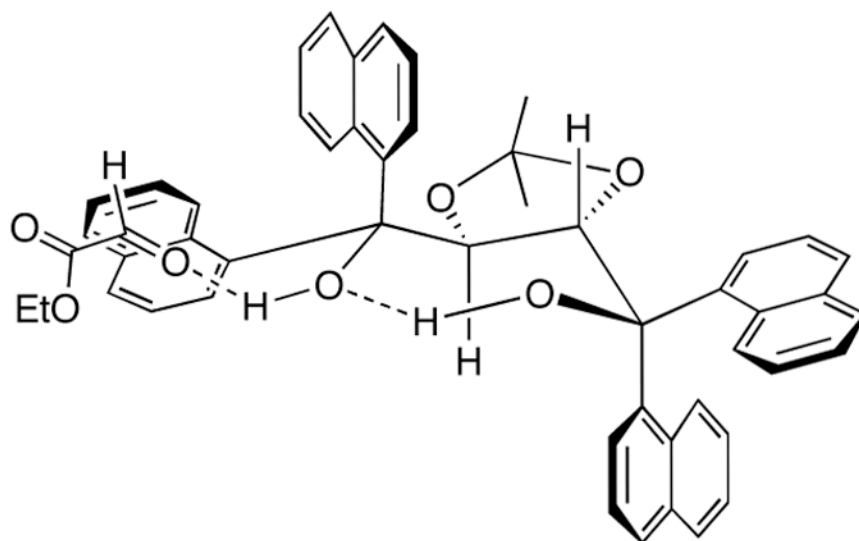
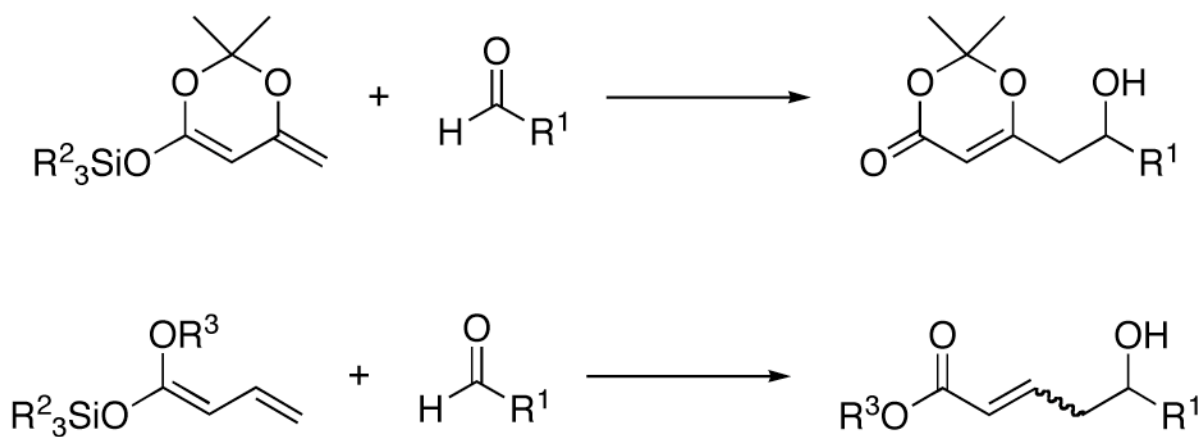
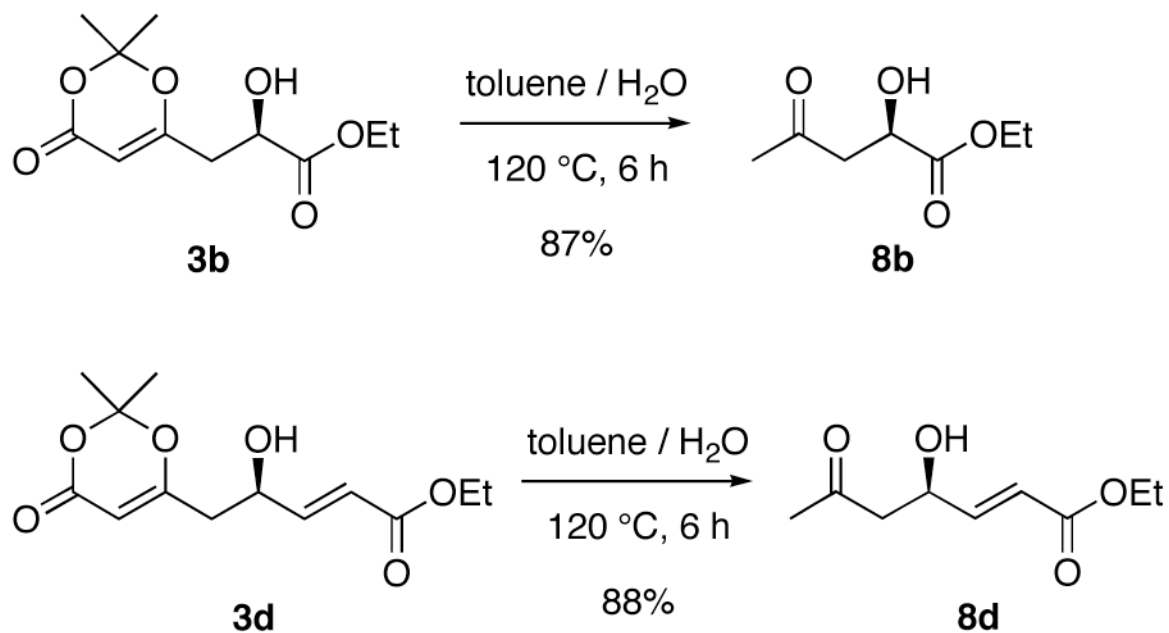


Figure 2.
Proposed model for the hydrogen bond catalyzed VMA reaction.



Scheme 1.
Vinylogous Mukaiyama Aldol Reactions



Scheme 2.
Further Transformations of VMA Products

Table 1
Exploration of Various Hydrogen Bond Donors as Catalysts for the VMA Reaction

entry	catalyst	temp. (°C)	time (h)	conversion (%) ^a	ee (%) ^b
1	(-)-ephedrine	-80	13	10	7
2	(+)-N-methylephedrine	-80	13	9	20
3	cinchonidine	-80	13	7	33
4	quinine	-80	13	17	35
5	Quinine-TFA	-80	10	0	-
6	Quinine-TfOH	-80	10	0	-
7	Quinine-AcOH	-80	10	27	24
8	(S)-BINOL	20	3	(50)	4
9	(S)-VANOL	-40	114	(30)	3
10	(S)-VAPOL	-40	114	(24)	2
11	4	-40	114	(42)	30
12	5	20	14	(46)	19
13	6	20	6	(72)	37
14	6	-40	60	(48)	63
15	7	-40	60	(60)	59

All the reactions were run at a 0.2 M concentration of the limiting reagent. For entries 1 to 7, 2 equiv of aldehyde was used. For entries 8 to 14, 3 equiv of silyldienol ether was used.

^a Determined by ¹H NMR of the crude reaction mixture. Numbers in parentheses indicate the isolated yield.

^b Determined by chiral HPLC analysis.

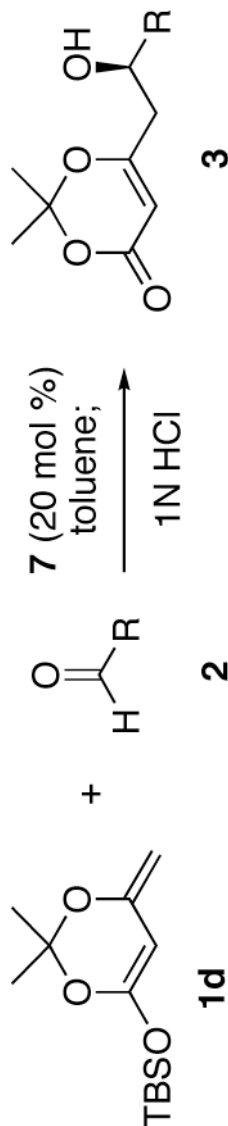


Table 2
Optimization of the Hydrogen Bond Catalyzed VMA Reaction

Reaction scheme: Silyldienol ether **1a** (2-(trimethylsilyloxy)-2-methyl-5-vinyl-2H-pyran) reacts with 2-nitrobenzaldehyde **2a** in the presence of a catalyst (20 mol %), toluene, and 1N HCl to yield product **3a** (2-(2-(2-nitrophenyl)-2-hydroxyethyl)-2-methyl-2H-pyran-5(2H)-one).

entry	SiR ₃	additive (10 mol%)	conv. (%) ^a	ee (%) ^b
1 ^c	TMS (1a)	-	98	61
2	TMS (1a)	-	82	81
3	TMS (1a)	4 Å MS ^d	95	63
4	TMS (1a)	HC(OMe) ₃	98	84
5	TMS (1a)	2,6-Di- <i>t</i> -butylpyridine	99	83
6	TMS (1a)	(<i>i</i> -Pr) ₂ NEt	95	85
7	TES (1b)	(<i>i</i> -Pr) ₂ NEt	90	85
8	TIPS (1c)	(<i>i</i> -Pr) ₂ NEt	95	85
9	TBS (1d)	(<i>i</i> -Pr) ₂ NEt	93	87
10	TBDPS (1e)	(<i>i</i> -Pr) ₂ NEt	74	54

All the reactions were run at a 0.2 M concentration of silyldienol ether.

^a Determined by ¹H NMR of the crude reaction mixture.

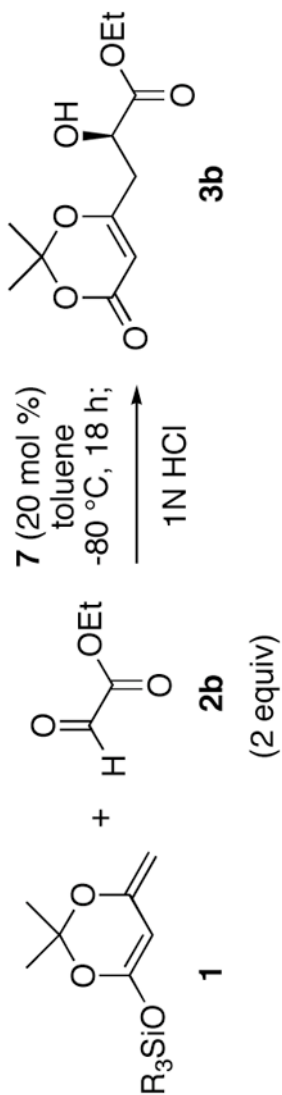
^b Determined by chiral HPLC analysis.

^c Reaction run at -40 °C (bath).

^d 100 mg used (0.2 mmol of **1**).

Table 3
Hydrogen Bond Catalyzed VMA Reaction with Various Aldehydes

entry	aldehyde	temp. (°C)	time (h)	product	yield (%)
1 ^b		-80	1	3b	60
2 ^b		-80	1	3c	54
3		-60	120	3d	66
4		-80	66	3e	55
5		-80	98	3f	73
6		-60	130	3a	58
7		-60	96	3g	40
8		-60	120	3h	25
9		-60	120	3i	57
10		-60	96	3j	0
11		-40	72	3k	54
					ee (%) ^d
					87
					84
					71
					83
					90
					75
					62
					62
					67
					-
					22



entry	aldehyde	temp. ($^{\circ}\text{C}$)	time (h)	product	yield (%)	ee (%) ^a
12	TBSO-CHO	-40	72	3l	23	27

See Supporting Information for experimental details.

^a Determined by chiral HPLC analysis.

^b 10 mol % of (*i*-Pr)₂NEt was added.