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Hydrogen Bond Catalyzed Enantioselective Vinylogous Mukaiyama Aldol Reaction

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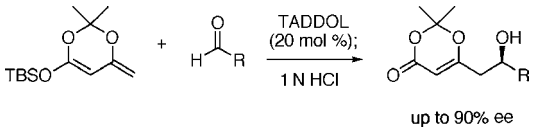
ABSTRACT

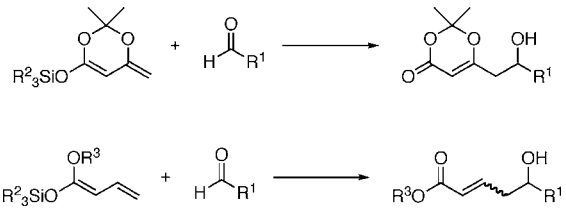


The concept of hydrogen bonding catalysis was extended to the vinylogous Mukaiyama aldol reaction, which gives rapid access to polyketide derivatives. The reaction of the silyldienol ether shown and a range of aldehydes catalyzed by TADDOL proceeds regiospecifically to produce the addition products in 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 noncovalent interaction to catalyze chemical reactions of interest.[1−3] 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

Scheme 1. Vinylogous Mukaiyama Aldol Reactions



accomplished with good diastereoselectivity[6] and paves the way to polyol units, a motif common to many natural products. Given the usefulness of the VMA reactions,

(1) *An Introduction to Hydrogen Bonding*; Jeffrey, G. A., Ed.; Oxford University Press: New York, 1997; p 272.

(2) For recent reviews, see: (a) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

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(4) (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (c) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

(5) (a) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319. For recent reviews, see: (b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

(6) For example, see: (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (b) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

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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] and 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

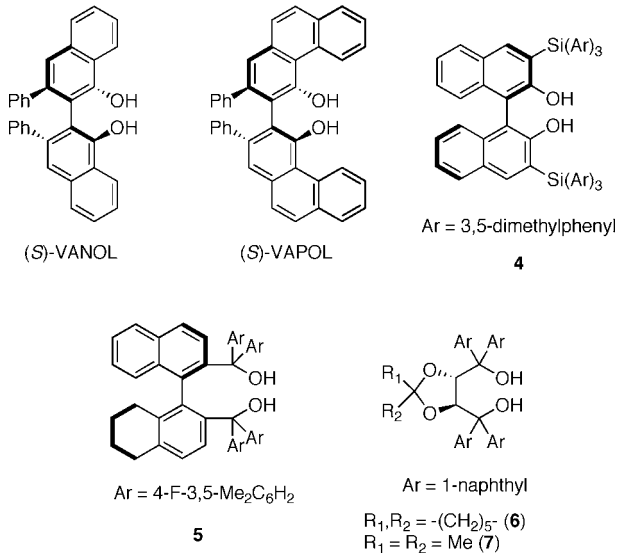
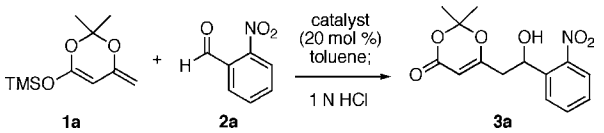


Figure 1. Diol catalysts used for the hydrogen bond catalyzed VMA reaction.

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 with the TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) family of diols (Table 1, entries 13−15).

Table 1. Exploration of Various Hydrogen Bond Donors as Catalysts for the VMA Reaction[a]



1a 2a 3a

entry	catalyst	temp (°C)	time (h)	conv (%)[b]	ee (%)[c]
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

[a] 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. [b] Determined by ^{1}H NMR of the crude reaction mixture. Numbers in parentheses indicate the isolated yield. [c] Detemined by chiral HPLC analysis.

The optimization of reaction conditions was accomplished by 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 °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 °C (entry 2). 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. To facilitate purification and analysis, the products were isolated as the free alcohols following a 1 N 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 values (entries 1−9). Surprisingly, 4-nitrobenzaldehyde (entry 10) proved much less reactive

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(8) (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360. (c) De Rosa, M.; Acocella, M. R.; Villano, R.; Soriente, A.; Scettri, A. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2499 and references therein.

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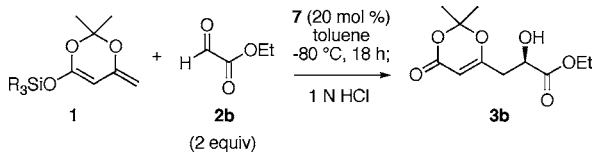
(10) Shimada, Y.; Matsuoka, Y.; Irie, R.; Katsuki, T. *Synlett* **2004**, 57.

(11) (a) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774.

(12) Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, *66*, 4293.

Table 2. Optimization of the Hydrogen Bond Catalyzed VMA Reaction[a]



entry	SiR_3	additive (10 mol %)	conv (%)[b]	ee (%)[c]
1[d]	TMS (**1a**)		98	61
2	TMS (**1a**)		82	81
3	TMS (**1a**)	4 Å MS[e]	95	63
4	TMS (**1a**)	$HC(OMe)_3$	98	84
5	TMS (**1a**)	2,6-di-*tert*-butylpyridine	99	83
6	TMS (**1a**)	$(i\text{-Pr})_2NEt$	95	85
7	TES (**1b**)	$(i\text{-Pr})_2NEt$	90	85
8	TIPS (**1c**)	$(i\text{-Pr})_2NEt$	95	85
9	TBS (**1d**)	$(i\text{-Pr})_2NEt$	93	87
10	TBDPS (**1e**)	$(i\text{-Pr})_2NEt$	74	54

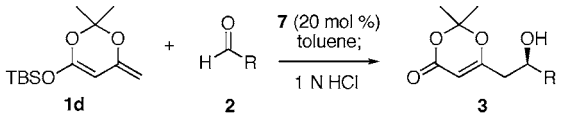
[a] All the reactions were run at a 0.2 M concentration of silyldienol ether. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Detemined by chiral HPLC analysis. [d] Reaction run at −40 °C (bath). [e] 100 mg used (0.2 mmol of **1**).

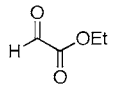
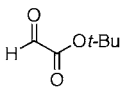
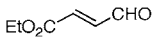
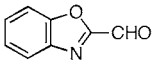
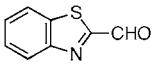
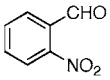
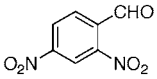
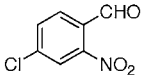
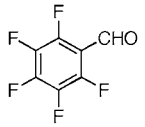
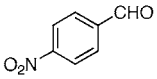
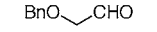
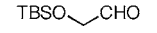
than 2-nitrobenzaldehyde (entry 6) under otherwise identical conditions. Aliphatic aldehydes were less reactive and yielded products with low ee values (entries 11 and 12). It should be noted that all these reactions showed excellent γ-selectivity, as the regioisomer resulting from attack at the α position 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 configurations 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

Table 3. Hydrogen Bond Catalyzed VMA Reaction with Various Aldehydes[c]

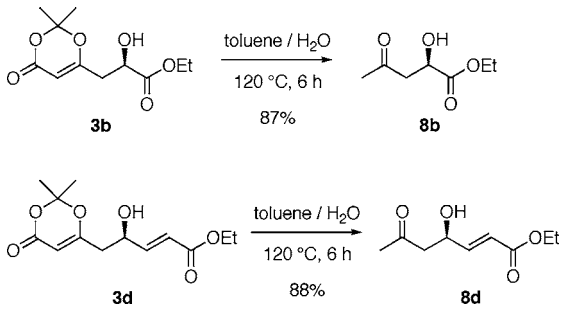


entry	aldehyde	temp (°C)	time (h)	product	yield (%)	ee (%)[a]
1[b]		-80	1	**3b**	60	87
2[b]		-80	1	**3c**	54	84
3		-60	120	**3d**	66	71
4		-80	66	**3e**	55	83
5		-80	98	**3f**	73	90
6		-60	130	**3a**	58	75
7		-60	96	**3g**	40	62
8		-60	120	**3h**	25	62
9		-60	120	**3i**	57	67
10		-60	96	**3j**	0	-
11		-40	72	**3k**	54	22
12		-40	72	**3l**	23	27

[a] Determined by chiral HPLC analysis. [b] 10 mol % of $(i\text{-Pr})_2NEt$ was added. [c] See Supporting Information for experimental details.

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]

Scheme 2. Further Transformations of VMA Products



(13) Sugita, Y.; Sakaki, J.-i.; Sato, M.; Kaneko, C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2855.

(14) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1991**, *32*, 3527.

(15) (a) Beck, A. K.; Bastani, B.; Plattner, D. A.; Petter, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vecchia, L.*Chimia* **1991**, *45*, 238. (b) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.

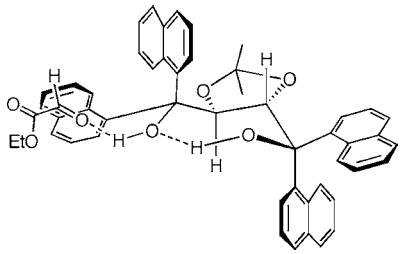


Figure 2. Proposed model for the hydrogen bond catalyzed VMA reaction.

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 values as high as 90%. We are currently investigating the use of other types of nucleophiles 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.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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