Asymmetric Catalysis

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Highly Diastereo- and Enantioselective Mukaiyama Aldol Reactions Catalyzed by Hydrogen Bonding**

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Although still in its infancy, the area of asymmetric catalysis promoted by hydrogen bonds has seen explosive growth in the past few years.[1–5] Reports from several research groups have demonstrated that many asymmetric reactions that had previously been the domain of metal-based Lewis acids, can now be catalyzed by organic compounds capable of donating a hydrogen bond. However, unlike traditional Lewis acids, which catalyze a diverse range of reactions with useful levels of enantioselectivity (>90% *ee*), hydrogen-bond catalysts have been shown to be efficacious for relatively few reactions, such as the Diels–Alder, aza-Henry, Mannich, Michael, Morita–Baylis–Hillman, and Strecker reactions.[2–4] In connection with our interest in hydrogen-bond-promoted reactions, we have examined the application of this mode of catalysis to the Mukaiyama aldol.

The Mukaiyama aldol reaction has proven to be one of the most powerful transformations for the controlled assembly of β-hydroxycarbonyl units, a structural motif found in numerous natural products.[6] The reaction involves the C–C bond coupling of two fragments, with the formation of up to two new stereogenic centers. Much effort has been directed to asymmetric catalysis of this reaction, and the vast majority of the successes have been recorded with metal-based chiral Lewis acids.[7] Among the few metal-free methods that have been developed, the most successful have involved the use of chiral phosphoramides as Lewis bases.[8] Despite its central importance in the synthesis of complex molecules, there is, to date, only a single report of the Mukaiyama aldol reaction catalyzed by hydrogen bonding (3 examples, 30–56% *ee*).[5,9] We now report that simple, chiral hydrogen-bond donors are effective as metal-free catalysts for the promotion of highly diastereo- and enantioselective Mukaiyama aldol reactions.

Among the many permutations of Mukaiyama aldol reactions, we focused our efforts on the reaction of silylated enolates of amides, since the presence of the enamine unit was

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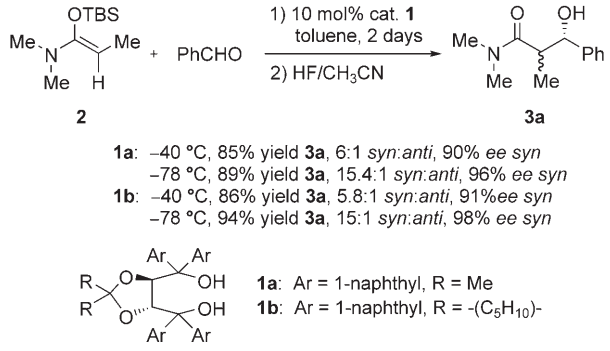
expected to render these compounds highly nucleophilic. Indeed, Myers and Widdowson have reported that such *O*-silyl-*N*,*O*-ketene acetals react with aldehydes at ambient temperature to yield the expected aldol products as a mixture of diastereomers.[10] We began our investigation with the expectation that if the reaction were carried out in the presence of a chiral hydrogen-bond donor, then the two prochiral faces of the aldehyde could be differentiated on complexation, and enantiomerically enriched aldol products would be formed. Previous work from our research group has shown that simple diols of the taddol family are highly effective catalysts for enantioselective reactions (taddol = α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol).[2a,b,d] In initial trials, *O*-silyl-*N*,*O*-acetal **2** was treated with benzaldehyde in the presence of 10 mol% of commercially available tetra-1-naphthyl-taddol (**1a**) at −40 °C in toluene. The reaction proceeded rapidly at this temperature, with complete consumption of **2** within 4 h, to give the aldol adducts in 83% yield, as a 6:1 mixture of *syn* and *anti* diastereomers, with *ee* values of 90 and 77%, respectively (Scheme 1). Crude β-hydroxyamide product **3a** was isolated after stirring the reaction mixture in the presence of HF (1–2 h), with no observed erosion in the diastereomeric ratio.

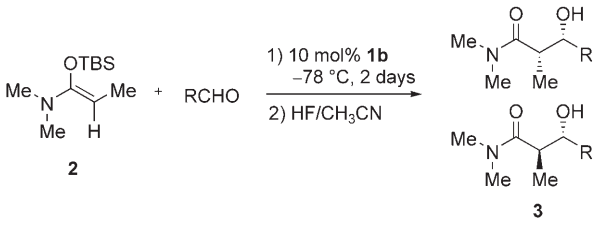


Scheme 1. Initial discovery of taddol-catalyzed aldol reaction of **2**. **1a**: tetra-1-naphthyl-taddol, **1b**: cyclohexylidene-taddol, TBS = *tert*-butyldimethylsilyl.

Through a brief study, where nearly a dozen readily prepared taddol catalysts were screened, it was determined that the cyclohexylidene-taddol derivative **1b** gave the best combination of diastereo- and enantioselectivity for the aldol reaction of **2** with benzaldehyde. Catalysts bearing various alkyl- and alkoxy-substituted phenyl rings gave products with diminished d.r. and *ee* values. The selectivities increased significantly when the reaction was carried out at −78 °C. Optimal conditions for the reaction of **2** with benzaldehyde were realized using 10 mol% of **1b** and 2 equivalents of benzaldehyde in toluene at −78 °C for 2 days, which gave **3a** in 94% yield with a 15:1 *syn*:*anti* ratio and 98% *ee* for the major diastereomer (84% *ee* minor diastereomer).

The scope of the Mukaiyama aldol reaction of **2** with a range of aldehydes was examined under optimized conditions using taddol **1b** as the catalyst (Table 1). Examination of the results shows that the aldol products are generally formed in good yields with high to excellent diastereo- and enantioselectivities. For the sake of consistency, most of the reactions were performed for 2 days, although comparable results were obtained with shorter reaction times: quenching the reactions after 16 and 20 h gave the expected products in good yield and high selectivity (Table 1, entries 2 and 5). The reaction of **2** with *para*-substituted aromatic aldehydes possessing either electron-withdrawing or weakly electron-donating functionalities in the presence of **1b** gave superior results (Table 1, entries 3–6). Substrates containing a strong electron-donating group *para* to the aldehyde were found to be less reactive. For example, the reaction of *p*-anisaldehyde proceeded sluggishly at −78 °C. At higher temperature (−40 °C), the reaction progressed to afford **3i** in modest yield (47%), but with lower d.r. and *ee* values (Table 1, entry 10). *Meta* substitution is tolerated well and affords products in reasonable diastereoselectivity and with high *ee* values (Table 1, entries 7, 8 and 11). Substrates with a substituent *ortho* to the aldehyde, such as *o*-anisaldehyde and 1-naphthaldehyde (Table 1, entries 12 and 13), gave diminished diastereoselectivity, although still with high enantioselectivity. Heteroaromatic aldehydes are also good Mukaiyama aldol partners, as demonstrated by the reaction of 2-thiophenecarboxaldehyde (Table 1, entry 15). Although we have not fully explored the taddol-catalyzed aldol reactions of aliphatic aldehydes, a preliminary study

Table 1: Asymmetric Mukaiyama aldol reaction catalyzed by a taddol derivative.[a]



Entry	Product	R	Yield [%][b]	d.r.[c]	*ee syn* [%] (*anti*)[d]
1	**3a**[e]	Ph	94	15:1	98 (84)
2	**3a**[f]	Ph	88	14:1	98
3	**3b**	4-(NO_2)-C_6H_4	93	13:1	94 (82)
4	**3c**	4-Cl-C_6H_4	86	20:1	97
5[g]	**3d**	4-(CF_3)-C_6H_4	84	>25:1	96
6	**3e**	4-(CH_3)-C_6H_4	77	16:1	97
7	**3f**	3-(CH_3)-C_6H_4	77	9:1	96 (73)
8	**3g**	3-Br-C_6H_4	84	9:1	95 (67)
9	**3h**	3,4-(Cl)$_2$-C_6H_3	71	9:1	94 (58)
10	**3i**	4-(MeO)-C_6H_4[h]	47	5:1	87 (72)
11	**3j**	3-(MeO)-C_6H_4	81	13:1	97
12	**3k**	2-(MeO)-C_6H_4	50	8:1	91 (58)
13	**3l**	1-naphthyl	80	2:1	90 (86)
14	**3m**	2-naphthyl	50	10:1	97
15	**3n**	2-thiophene	88	10:1	95 (48)
16	**3o**	*n*-propyl	47	9:1	91

[a] Reactions were performed using 1 equiv ketene acetal **2**, 2 equiv aldehyde, and 0.1 equiv catalyst **1b** in 0.5 mL of toluene for 2 days in an argon atmosphere. Following workup with 5 mmol aq HF, the products were isolated by flash column chromatography on silica gel. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture prior to separation by column chromatography. [d] Determined by chiral HPLC analysis. [e] 1*S*,2*S* absolute configuration.[11] [f] Reaction time was 16 h. [g] Reaction time was 20 h. [h] Reaction run at −40 °C for 2 days.

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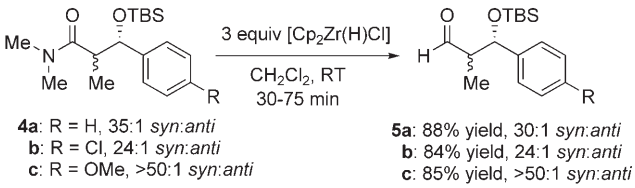
with butyraldehyde showed that the reaction proceeded with good diastereoselectivity and high enantioselectivity (Table 1, entry 16).

To render the above method more broadly applicable to the synthesis of complex molecules, we examined methods for the transformation of the amide functionality into an aldehyde group. Provided this conversion could be accomplished without eroding the high diastereo- and enantioselectivities, then the outcome would correspond to the products of crossed-aldol reactions of aldehydes. After a brief examination of aluminum-based reducing agents,[12] we directed out attention to the use of Schwartz's reagent. Georg and co-workers showed previously the direct reduction of achiral *N*,*N*-dialkylamides to the corresponding aldehydes using this reagent.[13] Subjecting amide **4a** to the conditions reported by Georg and co-workers produced the desired aldehyde product, but with considerable diminution in the diastereomeric ratio. This erosion in diastereoselectivity can be understood by considering the suggested mechanism for the reduction, wherein the proposed iminium intermediate can isomerize to an enamine, with loss of stereochemistry at the carbon atom α to the carbonyl group. Consistent with this rationale is the observation that the diastereoselectivity decreases with longer reaction times. Examination of the reaction parameters showed that the reduction proceeded rapidly in CH_2Cl_2 and gave the desired aldol product in high yield. Under optimized conditions (using three equivalents of Schwartz's reagent in CH_2Cl_2) the amide aldol products **4** were converted into the corresponding chiral aldehydes **5** in high yields with limited or no epimerization of the α stereocenter (Scheme 2).



4a: R = H, 35:1 *syn*:*anti*
b: R = Cl, 24:1 *syn*:*anti*
c: R = OMe, >50:1 *syn*:*anti*

5a: 88% yield, 30:1 *syn*:*anti*
b: 84% yield, 24:1 *syn*:*anti*
c: 85% yield, >50:1 *syn*:*anti*

Scheme 2. Reduction of chiral amides to aldehydes under mild conditions. Cp = cyclopentadienyl

The high enantioselectivity observed in the above reactions implies the intermediacy of a highly ordered transition state, generated by hydrogen bonding between the chiral diol and the aldehyde. In our study of taddol-catalyzed Diels–Alder reactions, we presented a hypothesis based on the X-ray structures of uncomplexed taddols to rationalize the observed enantioselectivities.[2b,14a] We have now succeeded in obtaining the first crystal structure of a complex between a taddol (racemic **1a**) and an aldehyde (Figure 1).[14b] The X-ray structure clearly supports some of the basic tenets of our hypothesis by showing the presence of an intramolecular hydrogen bond between the two hydroxy groups of the catalyst and an intermolecular hydrogen bond to the carbonyl oxygen atom of *p*-anisaldehyde. This complex is consistent with the suggested mode of activation of the carbonyl group through a single-point hydrogen bond to a preorganized

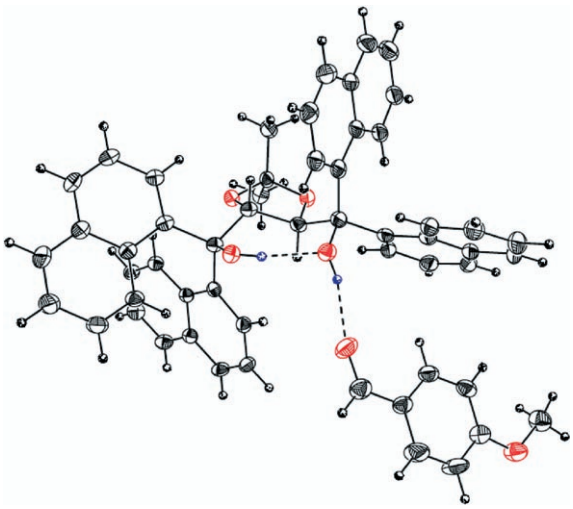


Figure 1. X-ray structure of the complex formed between the catalyst *rac*-**1a** and *p*-anisaldehyde. Red = oxygen atom, blue = hydrogen atom involved in hydrogen bonding.

catalyst. Since hydrogen bonding is a subset of the Lewis acid type of interaction, the present mode of activation represents a form of Lewis acid assisted Lewis acid catalysis.[1c]

In this report, we have described the catalysis of highly diastereo- and enantioselective Mukaiyama aldol reactions of *O*-silyl-*N*,*O*-ketene acetals mediated solely through activation by hydrogen bonding. The catalyzed reaction was effective for a range of aldehydes, and gave products in synthetically useful yields and selectivities. The mild conversion of the amide aldol products into the corresponding aldehydes using Schwartz's reagent, with little or no erosion in diastereoselectivity, renders this reaction useful for further synthetic applications. The crystal structure of the taddol–aldehyde complex clearly shows coordination of the aldehyde carbonyl group through a single-point hydrogen-bonding interaction. This mode of activation is likely critical for the Mukaiyama aldol reaction presented here as well as for the cycloaddition reactions that we reported previously. [2]

A desired characteristic of any highly useful catalyst is the capacity to effect a broad range of reactions. The results presented herein when taken in conjunction with our previous studies shows that taddol may well be considered a "privileged" scaffold for asymmetric catalysis mediated by hydrogen bonding.[15,16] Further investigation of taddol ligands as chiral hydrogen-bond donors should provide exciting new developments in asymmetric catalysis.

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