Communication

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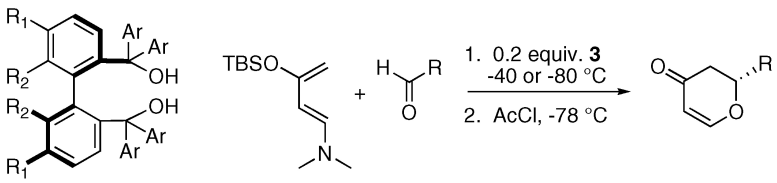

3: BAMOL **1** **4**

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Axially Chiral Biaryl Diols Catalyze Highly Enantioselective Hetero-Diels−Alder Reactions through Hydrogen Bonding

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The bare hydrogen nucleus, a proton, functioning in the Brønsted-Lowry sense, is the most commonly used catalyst for promoting chemical reactions. In contrast, the Lewis acid property of the hydrogen atom, most evident in hydrogen bonds,[1] has been little utilized for catalysis. In contemporary organic synthesis, especially for asymmetric reactions, the field of Lewis acid catalysis has become synonymous with metal-based catalysis.[2] Despite its central importance as an organizational force in large biomolecules, the hydrogen bond is recognized as a weak interaction, and, perhaps for this reason, only a handful of reports describe its successful use for nonenzymatic asymmetric catalysis.[3,4] Exploration of hydrogen bond-based catalysts would improve our fundamental understanding of this important type of catalysis and uncover unique facets of chemical reactivity. We report here a new hydrogen bonding catalyst for highly enantioselective hetero-Diels−Alder (HDA) reactions.

In a recent communication, we had reported that hydrogen bonding solvents greatly accelerate the HDA reaction[5] between 1-amino-3-siloxybutadiene[6] (**1**) and unactivated aldehydes[7] and ketones.[8] The cycloadducts are transformed, upon workup, into the corresponding dihydropyranones, which are useful precursors to natural products.[9] Significantly, it was discovered that a chiral alcohol, TADDOL, through hydrogen bonding, can catalyze the HDA reactions of aldehydes, as well as the DA reaction of acroleins, to afford the expected adducts in good yields and excellent ee's.[10] In advancement of this novel form of asymmetric catalysis, we have found the axially chiral 1,1′-biaryl-2,2′-dimethanol (**3**, BAMOL) scaffold to be highly effective for the catalysis of the HDA reactions of a wide range of aliphatic and aromatic aldehydes. The new scaffold shares with TADDOLs the bis(diarylhydroxymethyl) functionality, in which the steric and electronic properties are readily tunable. Moreover, the axial chirality in BAMOL provides further opportunity for tweaking the chiral environment.[11]

A variety of BAMOL catalysts can be accessed from commercially available 2,2′-biphenols through a convenient, three-step sequence.[12] Palladium-mediated carbonylation of the bistriflates in the presence of an alcohol delivered the diesters (**2**), which in turn can then be reacted with a variety of aryllithiums to give the desired diols (**3**) in good overall yields, with no loss in enantiopurity (Scheme 1).[13]

A survey of different BAMOLs revealed that diols **3a** and **3b**, possessing the 4-fluoro-3,5-dimethylphenyl and 4-fluoro-3,5-diethylphenyl groups, respectively, delivered the best combination of yield and ee for the cycloaddition of **1** and various aldehydes. These two diols were then examined as catalysts for the HDA reactions of a diverse group of aldehydes. The cycloadditions were carried out in toluene at either −40 or −80 °C, in the presence of 20 mol % of the indicated catalyst (Table 1).

BAMOLs **3a** and **3b**, functioning strictly through hydrogen bond-based activation, catalyze the enantioselective cycloadditions of both aromatic and aliphatic aldehydes. Perusal of the results shows that

Scheme 1. Preparation of Chiral Diols **3**

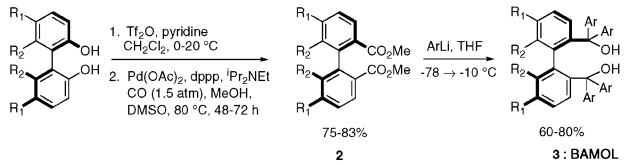
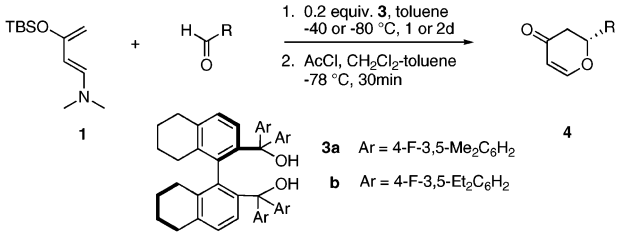


Table 1. Asymmetric Hetero-Diels−Alder Reaction Catalyzed by BAMOLs[a]



entry	product	R	catalyst[b]	yield (%)[c]	ee (%)[d]
1	**4a**	Me	**3b**	75	97[e]
2	**4b**	*n*-propyl	**3a**	76	94
3	**4c**	$Ph(CH_2)_2$	**3a**	95	95
4	**4d**	$PhS(CH_2)_2$	**3a**	76	94[e]
5	**4e**	$Phth(CH_2)_3$[f]	**3a**	67	92[e]
6	**4f**	1-propynyl	**3a**	42	98[e]
7	**4g**	*i*-butyl	**3a**	79	90[e]
8	**4h**	*c*-hexyl	**3a**	99	84
9	**4i**	Ph	**3b**	84	98
10	**4j**	3-(MeO)-C_6H_4	**3b**	86	98[e]
11	**4k**	2-(NO_2)-C_6H_4	**3b**	93	98[e]
12	**4l**	1-naphthyl	**3b**	67	97[e]
13	**4m**	2-furyl	**3b**	96	>99

[a] Reactions were run with 1 mmol aldehyde, 0.5 mmol diene, and 0.1 mmol catalyst in 0.5 mL of toluene under an atmosphere of argon. Following workup with 1 mmol AcCl, products were isolated by flash column chromatography on silica gel. [b] Reactions with **3a** were run at −40 °C for 1 day and with **3b** at −80 °C for 2 days. [c] Isolated yields. [d] Determined by chiral HPLC analysis. [e] Absolute stereochemistry undetermined. [f] Phth = phthalimide.

straight-chain aliphatic aldehydes afford the cycloadducts in uniformly good yields and excellent enantiomeric excesses (entries 2−5). On the other hand, aldehydes possessing branched chains gave adducts with lower ee's (entries 7, 8). Aliphatic aldehydes containing Lewis basic heteroatoms were tolerated quite well and afforded yields and ee's comparable to that obtained for butyraldehyde (entries 4, 5). The high ee's observed for acetaldehyde and 2-butynal (entries 1, 6), each with a small substituent attached to the aldehyde carbonyl, are noteworthy and consistent with the above general trend of higher enantioselectivity for aldehydes having a small α-substituent.

The BAMOL-catalyzed HDA reactions of aromatic aldehydes were uniformly highly enantioselective. Although both catalysts afforded adducts in good yield, catalyst **3b** provided better

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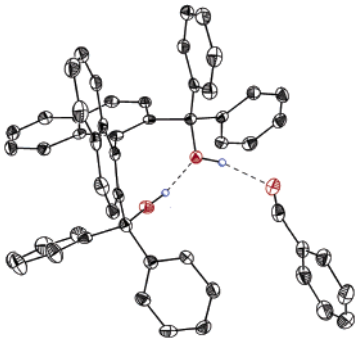

Figure 1. X-ray structure of catalyst **5**−PhCHO complex.

enantioselectivity. Electron-rich and electron-poor aldehydes gave comparable results to benzaldehyde (entries 9−11). In the case of *o*-nitrobenzaldehyde, both yield and ee were excellent despite the steric bulk of an ortho substituent, Lewis basicity of the nitro group, or competition from background reaction associated with electron deficient aldehydes. On the other hand, it would appear that sterics compromised the yield, but not the enantioselectivity, of 1-naphthaldehyde (entry 12). The HDA cycloaddition of furfural proceeded in excellent yield and ee (>99%, entry 13). To the extent that the furyl group is sterically less demanding than a phenyl group, then the superior selectivity observed here mirrors the trend seen with aliphatic aldehydes.

In an effort to shed light on the factors responsible for asymmetric induction, we have attempted to obtain complexes between the biaryldiol catalysts and aldehydes. To date, we have succeeded in obtaining an X-ray structure of an inclusion complex of 2,2′-bis-(diphenylhydroxymethyl)binaphthylene (**5**),[14] a simple member of the BAMOL family of catalysts, and benzaldehyde (Figure 1).[15] The structure not only shows a 1:1 association between BAMOL **5** and benzaldehyde, but also reveals the presence of an *intra*molecular hydrogen bond between the two hydroxyls and an *inter*molecular hydrogen bond to the carbonyl oxygen of benzaldehyde.[16,17] The above complex suggests that carbonyl activation is through a single-point hydrogen bond, as was postulated for TADDOL catalysis.[10b,17]

The above results illustrate that axially chiral diols of the BAMOL family are highly effective catalysts for enantioselective HDA reactions between aminosiloxydiene **1** and a wide variety of unactivated aldehydes. The reactions proceed in useful yields and excellent enantioselectivities. The diols function in the same capacity as Lewis acids, by activating the aldehyde carbonyl group through hydrogen bonding. The present work also represents the first successful use of the axially chiral biaryldimethanol scaffold and points to its potential use in other catalytic asymmetric reactions, whether through hydrogen bonding or metal-based Lewis acid catalysis.

Acknowledgment. This work is dedicated to Professor Iwao Ojima, SUNY, Stony Brook, on the occasion of his 60th birthday. The X-ray structure was solved by Dr. Ian Steele (The University of Chicago). V.H.R. (CHE-0316803) and H.Y. (CHE-0412060) thank the National Science Foundation for generous financial support of this work.

Supporting Information Available: Experimental procedures, spectral characterization of catalyst and dihydropyranones, and HPLC separations of dihydropyranones (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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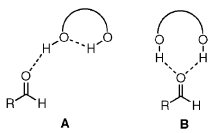
(16) The location of the H atoms in the hydrogen bonds is based on the residual electron density peaks in the difference Fourier map. In the absence of atoms heavier than O, these small residual peaks become more significant and are comparable in magnitude to that observed for the aromatic hydrogens, the positions of which are more certain.
(17) The single-point activation (**A**) proposed here differs from two-point activation (**B**). The latter is the subject of the review in ref 3a.



A **B**

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