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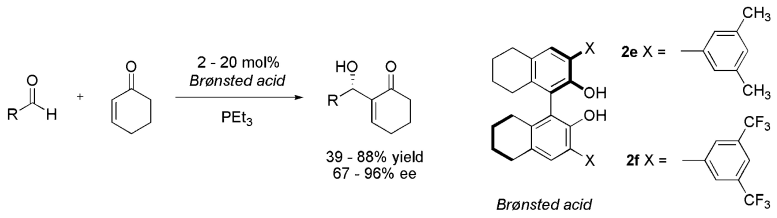

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Asymmetric Morita−Baylis−Hillman Reactions Catalyzed by Chiral Brønsted Acids

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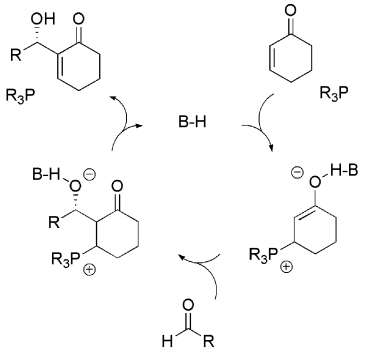
The Morita−Baylis−Hillman reaction[1] is the reaction of electron-deficient alkenes with aldehydes, catalyzed by nucleophilic amines or phosphines.[2] The products of Morita−Baylis−Hillman (MBH) reactions are highly functionalized allylic alcohols which, in enantioenriched form, could be valuable chiral building blocks for synthesis.[3] However, the identification of an asymmetric MBH reaction has been a challenge for organic chemistry. To date, efforts toward this goal have focused on the addition of acrylates to aldehydes. Notable developments include the use of chiral sultam auxiliaries,[4] quinidine-derived chiral nucleophilic amine catalysts,[5] and chiral lanthanide Lewis acids for the tertiary amine-promoted addition of acrylates to aldehydes.[6] Herein, we report the first example of a highly enantioselective asymmetric MBH reaction of cyclohexenone with aldehydes using a chiral Brønsted acid as the catalyst and triethylphosphine as the nucleophilic promoter.

Recent experiments demonstrated that the inclusion of mild Brønsted acids such as phenol and BINOL in the tri-*n*-butylphosphine-promoted MBH reaction of cyclic enones with aldehydes resulted in a significant increase in the overall rate of reaction.[7] Although (*R*)-BINOL was found not to be optimal for the MBH reaction, we postulated that the identification of a suitable chiral Brønsted acid could be used in an asymmetric reaction. In this case, the Brønsted acid may serve to promote the conjugate addition step of the reaction, and then remain hydrogen-bonded to the resulting enolate in the enantioselectivity-determining aldehyde addition step (Scheme 1). Presumably, the chiral Brønsted-acid-stabilized enolate formed after addition of the trialkylphosphine would act as the nucleophile in the addition reaction.[7]

Scheme 1. Proposed Catalytic Cycle for the Brønsted-Acid-Catalyzed Morita−Baylis−Hillman Reaction



We first conducted experiments to assess the feasibility of using chiral Brønsted acids to promote the asymmetric MBH reaction of cyclohexenone with aldehydes (Figure 1, Table 1). The reaction of cyclohexenone (1 equiv) with 3-phenylpropanal (1 equiv) using PEt_3 (0.5 equiv) in THF (1 M) yielded 5% of the desired product at 0 °C after 48 h. However, the addition of 2 mol % (*R*)-BINOL

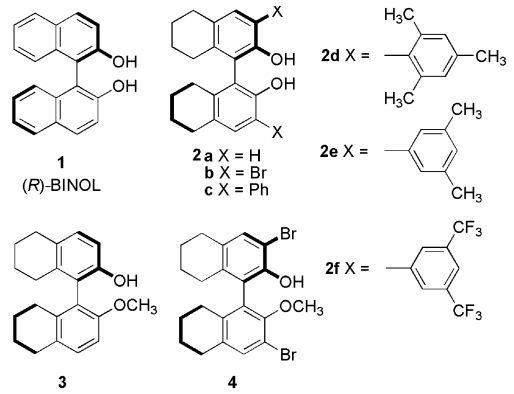
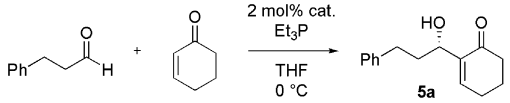


Figure 1. Binaphthol-derived Brønsted acids.

Table 1. Asymmetric Morita−Baylis−Hillman Reactions Catalyzed by Binaphthol-Derived Brønsted Acids[a]



entry	catalyst	% yield[b]	% ee[c]
1		5	
2	**1**	74	32
3	**2a**	73	48
4	**2b**	73	79
5	**2c**	69	86
6	**2d**	9	31
7	**2e**	70	88
8	**2f**	84	86
9	**3**	43	3
10	**4**	15	3

[a] Reactions were run with 1 mmol of 3-phenylpropanal, 1 mmol of cyclohexenone, 0.5 mmol of PEt_3, and 2 mol % catalyst in THF (1 M) at 0 °C for 36 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

1 to the reaction mixture afforded the MBH product **5a** in 74% isolated yield and 32% ee (entry 2, Table 1).

Encouraged by these results, we evaluated other BINOL-derived Brønsted acids in the reaction (Figure 1). During our investigation, two structural features of the catalyst were found to be important for achieving high enantioselectivity: saturation of the BINOL derivative[8] (entry 3, Table 1) and substitution at the 3,3′-positions (entries 4−8). When (*R*)-3,3′-diphenyl-H_8-BINOL **2c**[9] was used as the catalyst in the MBH reaction, **5a** was produced in 86% ee and 69% yield (entry 5). However, when mesityl-catalyst **2d**[10] was used, the product was formed in low yield and correspondingly low enantioselectivity (entry 6). We reasoned that the mesityl substituent restricted rotation about the biaryl bond of the 3-substituent, a structural prerequisite for catalysis. The highest levels of enantioselectivity were achieved using (*R*)-3,3′-(3,5-dimethylphenyl)-H_8-

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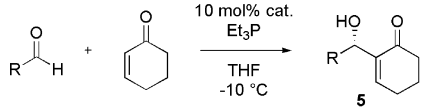
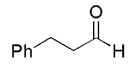
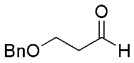
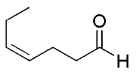
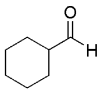
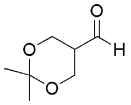
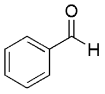
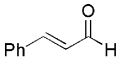
Table 2. Brønsted-Acid-Catalyzed Asymmetric Morita−Baylis−Hillman Reactions[a]



entry	aldehyde	catalyst	yield (%)[b]	% ee[c]
a		**2f**	**5a** (88)	90
b		**2f**[d]	**5b** (74)	82
c		**2e**	**5c** (72)	96
d		**2e**	**5d** (71)	96
e		**2e**	**5e** (82)	95
f		**2e**[d]	**5f** (70)	92
g		**2f**	**5g** (40)	67
h		**2e**	**5h** (39)	81

[a] Reactions were run with 1 mmol of aldehyde, 2 mmol of cyclohexenone, 2 mmol of PEt_3, and 10 mol % catalyst in THF (1 M) at −10 °C for 48 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 20 mol % catalyst.

BINOL **2e** as the catalyst (88% ee, entry 7), and employing 3,3′-[3,5-bis(trifluoromethyl)phenyl]-catalyst **2f** resulted in the greatest levels of conversion (84% yield, entry 8).

It is interesting to note that removal of one Brønsted-acid equivalent from the BINOL-derived catalyst, as is the case for catalysts **3** and **4**, resulted in diminished catalytic activity and no enantioselectivity in the production of **5a** (entries 9 and 10). Finally, using trialkylphosphines such as PMe_3 or $P(n\text{-}Bu)_3$ in the reaction afforded **5a** in yields similar to that of PEt_3, but lower enantioselectivities (50% and 64% ee, respectively).

Optimization of the reaction resulted in the identification of a set of conditions that proved to work for a variety of aldehydes. In general, the conditions that favored the production of **5** in high yields and enantioselectivities were 2 equiv of PEt_3 and cyclohexenone, and only 10−20 mol % of the chiral Brønsted acid **2e** or **2f** at −10 °C in THF. Optimal results were obtained using catalyst **2f** in the MBH reaction of aliphatic aldehydes (Table 2, entries a, b), while catalyst **2e** afforded the best results with more hindered aldehydes (entries d−f). The MBH reaction of conjugated aldehydes such as benzaldehyde and cinnamaldehyde (entries g and h) resulted in low yields and low enantioselectivities.

In summary, we have developed a highly enantioselective asymmetric Morita−Baylis−Hillman reaction involving the addition of cyclohexenone to aldehydes. The asymmetric reaction is catalyzed by a chiral BINOL-derived Brønsted acid. The use of small organic molecules as catalysts to promote asymmetric reactions is a new frontier in reaction methodology development.[11] Asymmetric Brønsted acid catalysis is a recent addition to this emerging field.[12] Further development of the asymmetric MBH reaction and elucidation of the mechanism through which the reaction proceeds will facilitate understanding of the chemical principles which govern this new area of catalysis. Experiments are ongoing and will be described in due course.

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Supporting Information Available: Experimental procedures, characterization of all new compounds, and HPLC separations for compounds **5a**−**5h** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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