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Boron-Catalyzed Direct Aldol Reactions of Pyruvic Acids

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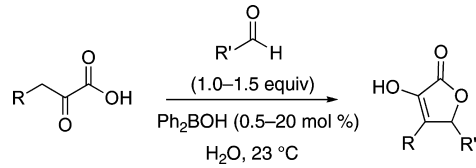
ABSTRACT



Interactions between pyruvic acids and diphenylborinic acid form the basis of an efficient, direct, boron-catalyzed aldol reaction that takes place in water at room temperature with low catalyst loadings. Both boronic and borinic acids function as catalysts, with the latter demonstrating particularly high activity. A wide range of aldehydes, including enolizable species, may be employed, delivering useful isotetronic acid derivatives in high yields.

The unique opportunities and challenges presented by water as a reaction medium have motivated intensive research efforts aimed at exploring chemistry in and "on" water.[1] While the extent to which water constitutes a "green" solvent for organic chemistry is dependent on numerous factors,[2] it is clear that mechanisms for rate acceleration[3] and stereoselectivity[4] in water may differ dramatically from those operative in organic solvents. The development of catalytic, carbon−carbon bond-forming reactions in water is an area of particular interest,[5] and progress has been achieved through the use of metal-based species and organocatalysts.

In this paper, we demonstrate that borinic acids are remarkably efficient catalysts for the direct aldol reaction of pyruvic acids and aldehydes in aqueous suspension at 23 °C. Near-equimolar quantities of aldol donor and acceptor are employed, with low catalyst loadings (as low as 0.5 mol %); highly enolizable aldehydes such as acetaldehyde and unbranched aliphatic aldehydes are tolerated. Underlying this process is the stabilization of the enol tautomer of pyruvic acids by organoboron species, a well-precedented interaction in molecular recognition and chemical sensing that has not previously been exploited in synthesis.

The development of "direct" aldol reactions, in which enolates or enolate equivalents are generated in catalytic amounts, is a major ongoing area of research. Success has been realized through two strategies: amine-catalyzed reactions proceeding through enamine intermediates;[6] and processes based on "soft" enolization with complexes of nickel(II),[7] copper(II),[8] magnesium(II),[9] and zinc(II).[10]

Although protocols based on the use of stoichiometric quantities of boron reagents remain methods of choice for aldol reactions used in complex molecule synthesis,[11] boron-*catalyzed* aldol reactions have been an elusive goal, despite

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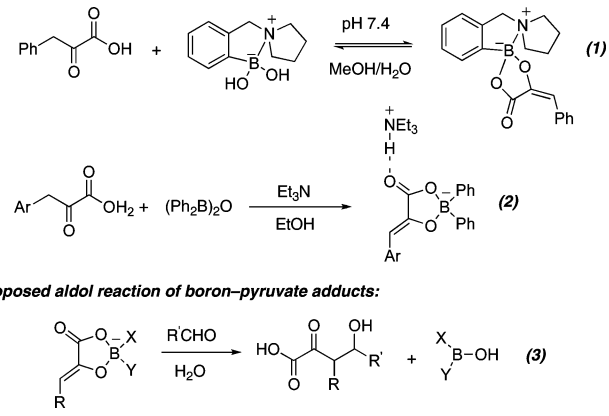
the low cost, low toxicity, and functional-group tolerance of organoboron compounds. Kobayashi and co-workers developed the first strategy for catalytic generation of boron enolates, employing diphenylborinic acid to accelerate reactions of silyl enol ethers.[12] Recently, Whiting and co-workers achieved the first *direct*, boron-catalyzed aldol reactions using the "ate" complex of a bifunctional benzimidazolylphenylboronic acid to promote aldol reactions of acetone and hydroxyacetone with aldehydes.[13] While the latter report represents a conceptually fascinating mode of reactivity and a significant step toward efficient boron-based catalysis of the aldol reaction, practical limitations include the requirement for a large excess of aldol donor and the high catalyst loadings used (20 mol %).

Our strategy for the development of a boron-catalyzed aldol reaction is based on the known reactivity of organoboron compounds with pyruvic acids to furnish dioxoborolanones (Scheme 1). Such reactions were first observed almost

Scheme 1. Boron−Pyruvate Interactions as the Basis for a Direct, Catalytic Aldol Reaction



a century ago and form the basis of methods for the quantitative analysis of pyruvic acids.[14] We were particularly intrigued by the observations of Anslyn and co-workers, who found that dioxoborolanones are rapidly generated from amine-substituted boronic acids and pyruvic acids in aqueous buffer at room temperature (Scheme 1, eq 1).[15] The facile formation of a stable, well-defined boron enolate in water seemed ideally suited as the basis for a catalytic reaction. Analogous dioxoborolanones derived from borinic acids have also been studied and characterized by X-ray crystallography (Scheme 1, eq 2).[16]

We thus sought to determine whether catalytically generated dioxoborolanones could engage in aldol reactions with aldehydes (Scheme 1, eq 3). Given that enzyme-catalyzed additions of pyruvic acids and their derivatives to aldehydes are key steps in carbohydrate biosynthesis and metabolism,[17] acceleration of this reaction by synthetic catalysts is worthy of study.[18] Whereas boron−carboxylate interactions have been exploited extensively in the context of boron-catalyzed acyl transfer reactions,[19] their application in catalysis of carbon−carbon bond-forming reactions is restricted to the boron-catalyzed Diels−Alder reactions of α,β-unsaturated carboxylic acids reported recently by Hall and co-workers.[20]

Screening experiments established that organoboron compounds are indeed able to catalyze aldol reactions of pyruvic acids: a variety of boronic and borinic acid derivatives promoted the addition of phenylpyruvic acid to benzaldehyde, yielding isotetronic acid derivative **3a** by aldol addition and in situ lactonization (Table 1). Arylborinic acids proved to be more efficient catalysts than arylboronic acids. Triphenylborane was also a competent promoter of the reaction: we ascribe this behavior to rapid protonolysis of a C−B bond by pyruvic acid under the reaction conditions, yielding a borinic acid derivative.[21] Brønsted acids and Lewis acidic metal salts did not efficiently catalyze the reaction under these conditions.[22]

Several electronically distinct arylborinic acids were tested using anisaldehyde as the electrophile (entries 7−10): its attenuated reactivity provided a more challenging testing ground for these active catalysts. No trend in their reactivity is evident; given the heterogeneous nature of the reaction mixture (see below), the factors underlying catalyst activity may be more complex than might be expected based on simple electronic effects. Diphenylborinic acid is the optimal catalyst, both in terms of its activity and its availability from inexpensive **2b**.

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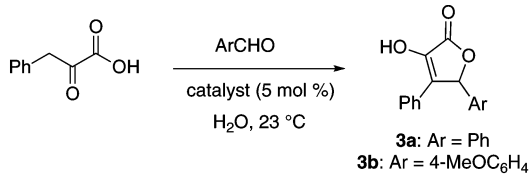
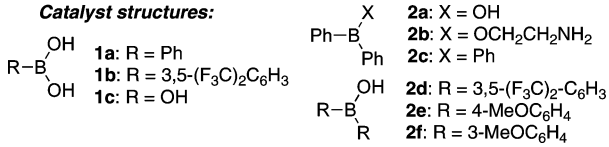
(22) Catalysts tested include *p*-toluenesulfonic acid, benzoic acid, magnesium(II) triflate, zinc(II) triflate, and copper(II) triflate.

Table 1. Evaluation of Organoboron Catalysts for Aldol Reaction of Phenylpyruvic Acid and Benzaldehyde



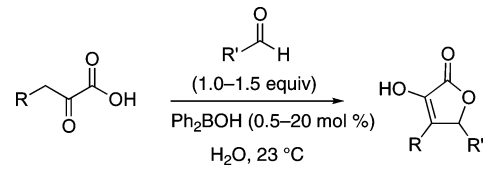
Catalyst structures:



entry	Ar	catalyst	yield[a] (%)
1	Ph	**1a**	19
2	Ph	**1b**	40
3	Ph	**1c**	8
4	Ph	**2a**	90
5	Ph	**2b**	83
6	Ph	**2c**	87
7	4-$MeOC_6H_4$	**2a**	68[b]
8	4-$MeOC_6H_4$	**2d**	42[b]
9	4-$MeOC_6H_4$	**2e**	22[b]
10	4-$MeOC_6H_4$	**2f**	66[b]

[a] Yield (0.2 mmol scale) as determined by NMR with 4,4′-di-*tert*-butylbiphenyl as a quantitative internal standard. [b] 20 mol % of catalyst used.

Table 2. Scope of Diphenylborinic Acid-catalyzed Aldol Reaction of Pyruvic Acids



entry	R	R′	product	catalyst (mol %)	yield[a] (%)
1	Ph	Ph	**3a**	0.5	90
2	Ph	4-$MeOC_6H_4$	**3b**	20	70
3	Ph	4-$F_3CC_6H_4$	**3c**	5	81
4	Ph	2-thienyl	**3d**	5	82
5	Ph	2-furyl	**3e**	5	89
6	Ph	n-C_5H_{11}	**3f**	1	90[b]
7	Ph	cyclohexyl	**3g**	5	84
8	Ph	CH_3	**3h**	10	55[b,c]
9	Ph	CH(Me)Ph	**3i**	5	81 (68)[d]
10	4-HOC_6H_4	n-C_5H_{11}	**3j**	5	80
11	2-$O_2NC_6H_4$	n-C_5H_{11}	**3k**	5	89
12	CH_3	Ph	**3l**	5	71[c,e]
13	CH_3	n-C_5H_{11}	**3m**	5	56[c,e]

[a] Isolated yield of pure product by recrystallization. [b] Isolated yield of *O*-silylated isotetronic acid, purified by column chromatography. [c] 5 equiv of acetaldehyde was used. [d] Diastereoselectivity was 4.8:1 in favor of the *syn* adduct: the relative stereochemistry was elucidated by X-ray crystallography. Yield in parentheses represents the isolated yield of diastereomerically enriched material (>20:1 dr) after recrystallization. [e] 3.0 equiv of ketobutyric acid was used.

Solvent effects in the borinic acid-catalyzed aldol reaction are dramatic. The reactions are most effective when carried out in aqueous suspension or "on water":[3b] lower reactivity was observed when organic solvents (protic or nonprotic) were employed.[21] The addition of surfactants, or the use of saturated sodium chloride instead of distilled water, did not measurably accelerate the reaction. We note that the two previously developed boron-catalyzed aldol reactions also make use of aqueous conditions:[12a,13] while a mechanistic explanation for this feature is not apparent, it is clear that boron catalysis offers considerable potential as a strategy for carbon−carbon bond-forming reactions under aqueous conditions.

Variation of both the aldehyde and pyruvic acid component revealed that this method is useful for the preparation of a broad range of isotetronic acid derivatives (Table 2). The isotetronic acid motif is found in a number of bioactive natural products, including compounds with antitumor[23] and aldose reductase inhibitory[24] activities. Isotetronic acids are also useful building blocks for the preparation of butenolide- and polyketide-based natural products.[25] Under the conditions described here, sterically and electronically diverse aliphatic and aromatic aldehydes react efficiently. While a catalyst loading of 5 mol % was generally employed, in certain instances as little as 0.5−1 mol % of diphenylborinic acid was sufficient (entries 1 and 6).

The use of a chiral electrophile, 2-phenylpropionaldehyde, resulted in moderate selectivity (4.8:1 dr) for the diastereomer predicted by the Felkin−Anh model (entry 9). The yields presented in Table 2 were obtained by recrystallization,without resort to column chromatography: indeed, isotetronic acids have been found to be unstable toward chromatography.[18a,d,e] In cases where recrystallization was not feasible, the isotetronic acids were *O*-silylated and isolated by column chromatography.

A noteworthy aspect of the reactions described here is the ability to use near-equimolar ratios of pyruvic acid and aldehyde (generally 1.1 equiv of aldehyde is used), even when the latter is prone to enolization. Selective, direct, cross-aldol reactions of two enolizable species remains a challenge: generally, an excess of one component (usually the ketone) or slow addition protocols are used.[26] The ability to achieve a direct aldol reaction of acetaldehyde as an acceptor (Table 2, entry 8) illustrates the ability of the boron catalyst to promote the selective enolization of pyruvic acids. This is a remarkable result, given the high propensity of acetaldehyde to serve as the aldol donor in conventional amine- or metal-catalyzed direct aldol reactions.

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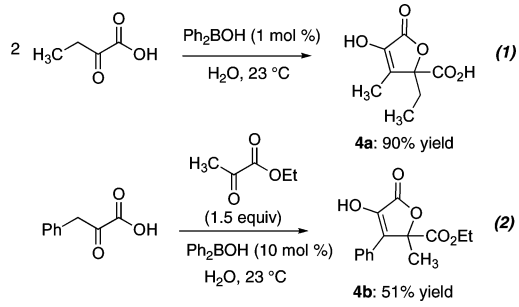
(25) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565.

(26) For example, see: Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

While the catalyst system presented here mediates aldol reactions of pyruvic acids that do not bear an aryl substituent (Table 2, entries 12 and 13), these reactions are less broad in scope than those involving arylpyruvic acids. This limitation is due to efficient boron-catalyzed aldol dimerizations of sterically unhindered pyruvic acids (Scheme 2, eq 1). Pyruvic acid undergoes rapid homoaldol reaction under these conditions, such that cross-aldol reactions with aldehydes do not occur in useful yields.[27] The cross-aldol reaction of phenylpyruvic acid and ethyl pyruvate is also possible (Scheme 2, eq 2). The latter represents an interesting example of a direct, catalytic cross-aldol reaction of two enolizable ketone partners.

Scheme 2. Borinic Acid-Catalyzed Direct Homo- and Cross-Aldol Reactions of Pyruvates



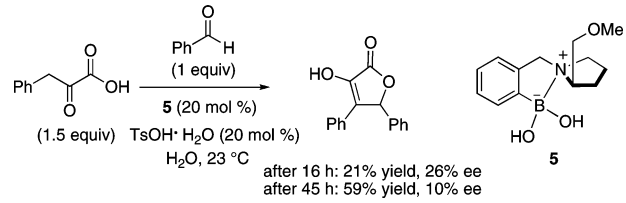
A detailed mechanistic study of this new reaction will likely be challenging given the heterogeneous nature of the reaction mixture. Nonetheless, ^{11}B NMR experiments (see the Supporting Information), as well as previously reported results,[14,15] are consistent with the facile formation of a tetracoordinate boron species from boronic or borinic acids and phenylpyruvic acid in a variety of solvents. This observation suggests that dioxoborolanone intermediates (Scheme 1) are indeed accessible under the reaction conditions. Since these species are tetracoordinate at boron, closed transition states involving activation of the aldehyde by Lewis acidic boron, as are invoked in conventional boron-based aldol reactions, seem unlikely. The aldol reactions shown in Table 2 are inhibited by bases, including 2,6-di-*tert*-butyl-4-methylpyridine and potassium carbonate, suggesting that the aldehyde may be activated by acid catalysis. Computational studies aimed at addressing this issue are underway.

The lactonization step of the initially generated hydroxy acid may be catalyzed by the borinic acid, given the extensive precedent for borinic acid-catalyzed acyl transfer reactions of carboxylic acids.[19] Simple Brønsted acid catalysis of related lactonizations has, however, been observed in previous studies.[18c,d] In any case, this lactonization step may play a role in facilitating catalyst turnover, since the carboxylate group is no longer available for binding to boron.

(27) Uncatalyzed homoaldol reaction of pyruvic acid in water is rapid, yielding a mixture of dimer and other oligomers. Selective dimerization is achieved by diphenylborinic acid catalysis in cyclohexane solvent.

To investigate the feasibility of developing an enantioselective variant of this reaction, we explored the chiral amine−boronate receptors employed by Anslyn and coworkers for recognition of α-hydroxy acids (Scheme 3).[15]

Scheme 3. Chiral Amine Boronate-Catalyzed Aldol Reaction



Receptor **5** alone did not catalyze the direct aldol reaction, but its activity was restored upon adding Brønsted acids (presumably protonation at nitrogen destabilizes a N−B bond or an amine-stabilized B−O bond).[28] While neither the yield nor the enantioselectivity of this process are synthetically useful, we note that receptor **5** was developed for a purpose distinct from asymmetric catalysis, and it differs profoundly from the diarylborinic acids that show optimal catalytic activity for this aldol reaction.[29]

The ability of organoboron compounds to activate pyruvic acids in a selective fashion under aqueous conditions has thus enabled the development of highly efficient boron-catalyzed direct aldol reactions. The use of water as reaction medium, the isolation of the products by recrystallization, and the low loadings of inexpensive catalyst all contribute to the practicality of this method. Employing boron-based receptors as an inspiration for new reactivity represents an unconventional strategy for developing catalysts that operate under aqueous conditions. Efforts to apply boron-pyruvate and related interactions in the context of other useful carbon−carbon bond-forming reactions, and to devise efficient chiral variants thereof, are the focus of our ongoing research efforts.

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Supporting Information Available: Complete experimental procedures and characterization data; X-ray data for **3i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) The decrease in enantiomeric excess over time may reflect changing catalyst composition or a pathway for product racemization under these conditions.