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Expanding the Scope of the Direct Regiospecific Asymmetric Aldol Reaction to Enones and Dienones Catalyzed by a BINOL-Derived Brønsted Acid

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Chiral phosphoric acid (*R*)-**1a** has been shown to be an efficient Brønsted acid catalyst for the useful asymmetric synthesis of various acyclic and endo- and exocyclic β-hydroxyenones through a regiospecific aldol reaction between α,β-unsaturated ketones and ethyl glyoxalate. Moreover, two unprecedented examples involving sensitive dienones are reported.

Introduction

The aldol reaction is a venerable chemical transformation that is still stimulating intense research despite a very long history. This useful reaction, carried out under acidic or basic conditions, enables the rapid formation of β-hydroxy ketones or aldehydes with potentially two new stereocenters. Control of their relative and absolute stereochemistries has focused the attention of chemists for the last 40 years.[1] This has been achieved by using chiral auxiliaries and stoichiometric or catalytic amounts of enantiopure organometallic complexes and organocatalysts.[2] Nowadays, one of the current challenges is to carry out the aldol reaction in a direct catalytic diastereo- and enantioselective manner.[3] The direct use of a simple carbonyl nucleophile for this reaction is relevant if one considers the instability and tedious handling of silyl enol ethers required for Mukaiyama aldol reactions[4] and because of an increasing demand for environmentally benign processes. The direct asymmetric aldol reaction has been achieved early on by using enzymes as catalysts with, however, a limited substrate scope.[5] Other important contributions include the use of bifunctional chiral metal complexes for the catalysis of direct aldol reactions.[6] In the last decade, since the seminal publication of List, Lerner, and Barbas,[7] organocatalysis and in particular aminocatalysis has solved this problem partially.[8] Indeed, proline and all subsequent organocatalysts bearing primary or secondary amino groups are able to catalyze the direct aldol reaction more or less by using the same mode of nucleophilic activation, via an enamine intermediate. However, despite its synthetic potential, enamine catalysis does not operate properly with several types of ketones.

On the basis of this observation and the long history of the aldol reaction, we recently developed the first direct Brønsted acid organocatalyzed aldol reaction[9] by using BINOL-derived phosphoric acid **1a**[10] prepared conveniently in only four steps from (*R*)-BINOL according to an improved methodology developed in our laboratory.[11] We focused our attention mostly on compounds that have not been described in amino-catalyzed aldol reactions. In this respect, only two simple enones (2-cyclohexenone or 3-penten-2-one) were tested.

Before our work, only two reports have described the direct asymmetric aldol reaction of enones catalyzed by zinc or rhodium complexes with good selectivities but variable yields.[12] However, the main limitation of these previous reports is the limited number of enones used. For example, Trost used only methyl vinyl ketone in his report, whereas Nishiyama has shown that only cyclic enones were suitable substrates for their metal-catalyzed direct aldol (Scheme 1). Since then a recent publication described the α′ position activation of enones by deprotonation with the use of cinchona alkaloid derivatives (two enones tested).[13] Therefore, expanding the scope of this largely unexplored reaction is highly valuable, especially regarding the enone partner, as the resulting hydroxy enones are useful synthetic intermediates due to their highly functionalized nature.[14] The objective was to expand the reaction to a wide variety of compounds including unstable enones carrying an acid-sensitive moiety to show the full potential of our methodology.

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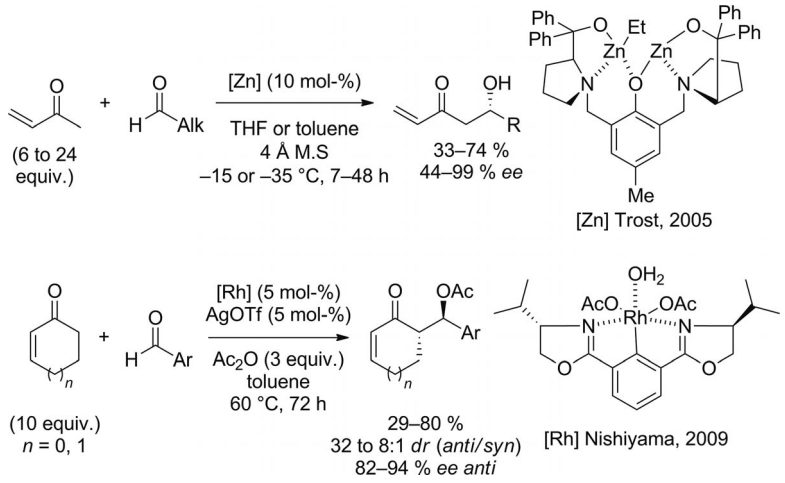
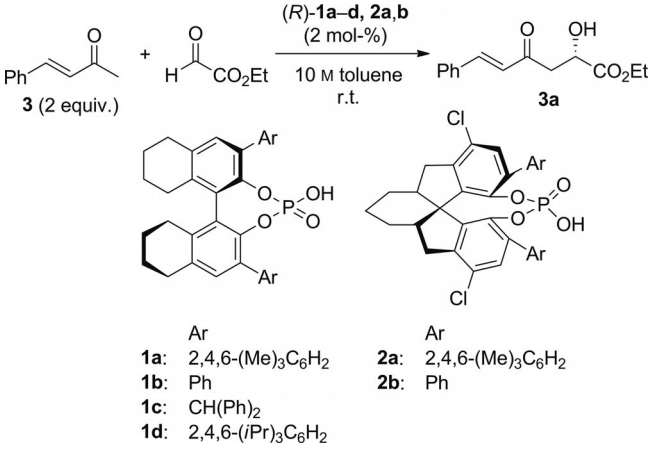


Scheme 1. Previous direct asymmetric aldol reactions with enones.

Results and Discussion

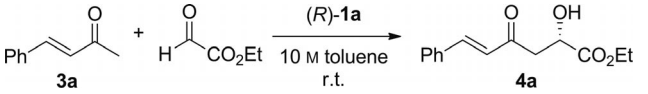
Initially, on the basis of the promising results obtained previously with phosphoric acid **1a**, we reconsidered the reaction parameters to define the best conditions compatible with the acid-sensitive enones by using (*E*)-4-phenylbut-3-en-2-one (**3a**) as a model substrate with ethyl glyoxalate.[15] Stoichiometry of the reagents, amount of catalyst, concentration, and temperature were the main parameters evaluated in the first part of this work. The main guidelines to optimize the reaction conditions were to avoid the use of an excess amount of the ketone, as is often done in organocatalysis, and to keep the amount of catalyst as low as possible while retaining good product selectivity and reaction rate. Initial screening of the catalysts identified (*R*)-**1a** as the most promising in terms of reactivity and selectivity: experiments have shown that with 5 mol-% catalyst, (*R*)-**1a** delivered 63%*ee*, whereas more sterically hindered (*R*)-**1d** led to only 50%*ee*; (*R*)-**1b** and (*R*)-**1c** gave even lower selectivities (Scheme 2). Surprisingly, spirobiindane-derived phosphoric acids, which have shown great promise for other enantioselective reactions,[16] led to lower selectivities. Under similar conditions, (*R*)-**2a** afforded 61%*ee* and (*R*)-**2b** only 52%*ee*.[17] Therefore, catalyst (*R*)-**1a** was selected for the optimization of the reaction conditions.

A test reaction using an excess amount of ketone **3a** at room temperature in the absence of acid yielded a trace amount of product **4a**, whereas with (*R*)-**1a** (5 mol-%), a 67% yield of **4a** was isolated, attesting the importance of the catalyst for the reaction (Table 1, Entries 1 & 2). In our previous report, a ketone/glyoxalate ratio of 10:1 was optimized to maintain high reactivity and selectivity.[9] However, decreasing the amount of ketone was considered necessary to make the chemistry more appealing in the case of a valuable ketone substrate. Consequently, we investigated the impact of various ketone/glyoxalate ratios on the yield and selectivity of the reaction. When an equimolar ratio of both substrates was used the reaction became sluggish, affording a low 46% yield (Table 1, Entry 4). More interestingly, the use of an excess amount of inexpensive ethyl gly-



Scheme 2. Catalysts screened in this study.

Table 1. Optimization of the aldol reaction involving (*E*)-4-phenylbut-3-en-2-one.



Entry	(*R*)-**1** [mol-%]	Ratio **3**/glyoxalate	Time [d]	Yield [%][a]	*ee* [%][b]
1	0	10:1	4	2	–
2	5	10:1	4	67	61
3	5	2:1	5	73	63
4	5	1:1	5	46	63
5	5	1:2	5	70	64
6	5	1:5	2	78	66
7	4	1:2	2	64	68[c]
8	2	1:2	2	50	67[c]
9	1	1:2	4	53	62
10	0.5	1:2	1	42	58[d]
11	2	1:2	5	73	63
12	10	1:2	5	79	71[e]
13	1	1:2	14	70	75[e]

[a] Isolated product. [b] Determined by chiral HPLC. [c] Concentration 1 M. [d] Run at 45 °C. [e] Run at 0 °C.

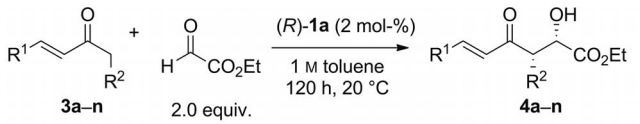
oxalate led to improved reaction rates (Table 1, Entries 5 and 6). The use of a fivefold excess gave slightly higher yield and selectivity, and a twofold excess was retained to simplify the purification process and to maintain an atom economic process. Next we probed the minimal amount of catalyst necessary. Although 0.5 mol-% of (*R*)-**1a** was found to be still effective at 45 °C, a significant erosion of the enantioselectivity was noticed (Table 1, Entry 10). Regarding the various results obtained with 5, 4, 2, 1, and 0.5 mol-%, a catalyst loading of 2 mol-% was retained as a good compromise between yield and selectivity (Table 1, compare Entries 6–10).

In parallel we observed a moderate effect of dilution: more diluted reactions afforded slightly higher selectivities at the expenses of yields (Table 1, compare Entries 5/7 and 8/11). Thus, a 1 M concentration was selected and the reaction time was increased (5 days) to preserve the high conversion of ketone **3**. Finally, the reaction conducted at 0 °C afforded higher selectivity but led to an unacceptable long reaction time of 14 d (Table 1, Entry 13) with a low catalyst loading. Noteworthy, no elimination product was observed during the optimization process even at higher temperature, witnessing the very mild conditions of the reaction. A possible intramolecular acid-catalyzed oxa-Michael reaction was not detected either,[17] probably due to the low nucleophilic character of the hydroxy group adjacent to an ester in aldol products **4**.

Having set the optimized parameters, the scope of the reaction was explored to broaden the utility of the organocatalyzed aldol reaction (Table 2). Methyl vinyl ketones β-substituted by an aryl or heteroaryl moiety behaved similarly, regardless of the electronic nature of the aromatic substituents (Table 2, products **4a**–**h**). Interestingly, acid-sensitive furan and thiophene β-substituted vinyl ketones **3f** and **3g** afforded **4f** and **4g** in 67 and 71% yield, respectively. When cyclic enones were used, the regioselective adduct corresponding again to the α′-aldol reaction (no reaction on the γ position is detected) was obtained in 66–80% yield with higher enantioselectivities for the exocyclic enones adducts **4j** and **4k** but with no diastereoselectivity (Table 2). Methyl vinyl ketones α′-substituted by a methyl reacted slowly and led to **4l** in a moderate 48% yield, probably due to a hindered enol intermediate.

Intrigued by the unique reactivity of catalyst (*R*)-**1a** we decided to test dienones. Such substrates are unexplored in aldol reactions, probably because of their limited stability under either basic or acidic conditions. Considering those substrates as a good challenge for our mild reaction conditions, we submitted ketones **5a** and **5b** to the same conditions as defined previously, that is, a twofold excess of ethyl

Table 2. Aldol reactions with enones and ynone derivatives.



	4a	4b
Yield [%][a]	72	68
ee [%][b]	66	68

	4c	4d
Yield [%][a]	67	66
ee (*syn*) [%][b]	68	66

	4e	4f
Yield [%][a]	70[c]	67
ee (*syn*) [%][b]	70	64

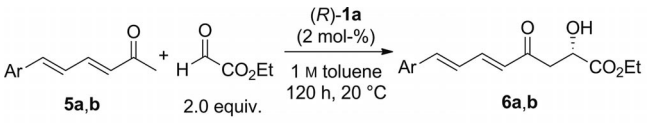
	4g	4h
Yield [%][a]	71	67
ee (*syn*) [%][b]	70	52

	4i	4j
Yield [%][a]	66	72
dr (*syn*/*anti*)[c]	70:30	50:50
ee (*syn*) [%][b]	68	82

	4k	4l
Yield [%][a]	80	48
dr (*syn*/*anti*)[c]	55:45	70:30
ee (*syn*) [%][b]	82	58

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Run at 10 °C.

Table 3. Aldol reactions with dienones derivatives.



	6a	6b
Yield [%][a]	66	71
ee [%][b]	64	68

[a] Isolated yields. [b] Determined by chiral HPLC.

glyoxylate at room temperature in the presence of 2 mol-% of catalyst (*R*)-**1a** (Table 3).

Gratifyingly, good yields of both adducts **6a** and **6b** were obtained, whereas no elimination product was detected. As with monovinyl ketone products, no intramolecular oxa-Michael compound was detected.[18] The observed enantioselectivities (≈60%*ee*) are in the same range as that reported earlier, but to the best of our knowledge those results are the first examples of asymmetric direct aldol reactions involving dienones.

Conclusions

In conclusion, we have extended the direct asymmetric aldol reaction catalyzed by Brønsted acids to challenging enones that have never been used. The very mild conditions notably optimized for this study are compatible with a large variety of enones, including acyclic and endo- or exocyclic enones, and dienones. Moreover, the results presented above were obtained by using low catalyst loadings and reasonable stoichiometries of the reagents, which make this chemistry very practical for synthetic applications and compatible with atom-efficient processes. We believe this reaction could serve as a benchmark for the development of new chiral acid catalysts owing to the chemical challenge offered by the substrates involved. In its current state, the reaction should be quite useful due to the complex molecular structures obtained in a straightforward manner and is a an important step forward complementing aminocatalysis in the field of organocatalyzed aldol reactions.

Experimental Section

Representative Procedure for the Acid-Catalyzed Aldol Reaction: A glass tube equipped with a septum was charged with ketone **3a** (59 mg, 0.4 mmol), catalyst (*R*)-**1a** (5 mg, 0.008 mmol, 2 mol-%), and a solution of ethyl glyoxylate in toluene (50% w/w, 164 mg, 0.8 mmol). The reaction was stirred for 120 h at room temperature and deposed on silica. Column chromatography of the crude mixture (cyclohexane/EtOAc, 7:3 to 6:4) yielded **4a** (72 mg, 72% yield, 66%*ee*) as a colorless solid.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization of the products.

Acknowledgments

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