



Practical synthesis of 2,5-disubstituted 1,3-dioxolane-4-ones and highly diastereoselective *cis*-2,5-disubstituted 1,3-dioxolane-4-ones from α -hydroxy acids catalyzed by *N*-triflylphosphoramidate



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ABSTRACT

N-triflylphosphoramidate (NTPA) was found to be an efficient Brønsted acid catalyst for the practical synthesis of 2,5-disubstituted 1,3-dioxolane-4-ones. Racemic and optically pure mandelic acid and lactic acid could be protected using several aldehydes in high selectivity and moderate yield in the presence of NTPA without azeotropic distillation or use of a dehydrating reagent.

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Introduction

Optically active α -hydroxy acids are useful intermediates in the synthesis of pharmaceuticals and fine chemicals.¹ Additionally they are valuable starting materials for the asymmetric synthesis of natural products which makes the protection of α -hydroxy acids an important reaction in many organic synthetic methods.² Various *cis*-1,3-dioxolane-4-ones (also known as Seebach and Fráter's chiral templates), obtained from the condensation reaction of α -hydroxy acids with an aldehyde, have found use in numerous stereocontrolled reactions.³ Seebach and co-workers have described two important reactions, namely the alkylation and aldol reactions of chiral lithium enolate acetals to generate an additional chiral center, which is known as self-reproduction of chirality.⁴ This concept has been applied to the syntheses of natural products and medicinally important targets.⁵ Additionally, the syntheses of gamma-lactams,⁶ 1,4-diketones,⁷ and 1,3-diketones⁸ by organocatalytic Michael addition, as well as beta-amino acids,⁹ glycosamino acids,¹⁰ and alpha-hydroxy esters¹¹ have been accomplished.

1,3-Dioxolane-4-ones are most often prepared using Lewis or Brønsted acid catalysts; e.g., $\text{BF}_3 \cdot \text{OEt}_2$,^{12,5a} TsOH ,^{13,5a} $\text{TsOH}/\text{H}_2\text{SO}_4$,^{12,5a} MsOH ,^{5a} TfOH .^{14,5a} Recently, Yamamoto et al. used $\text{Sc}(\text{OTf})_3$ and $\text{Sc}(\text{NTf}_2)_3$ as efficient catalysts for the diastereoselective

preparation of 1,3-dioxolanones.^{2b} Banik and co-workers have also reported the molecular iodine-catalyzed protection of α -hydroxy acids.¹⁵ Similarly, the protection of α -hydroxy acids with aldehydes using $(\text{MeO})_3\text{CH}$ has been reported by Tanabe et al.¹⁶ Finally, Dunach et al. have synthesized substituted 1,3-dioxolane-4-ones in a reaction catalyzed by $\text{Cu}(\text{OTf})_2$ and $\text{Al}(\text{OTf})_3$ which features an intramolecular cyclization of α -methylallyloxy carboxylic acids.¹⁷ Success in most cases relies on the azeotropic removal of water from the reaction medium or addition of a dehydrating agent. It would therefore be highly desirable if an alternative method could be employed which overcomes this disadvantage.

In our previous works, we have reported the preparation of acetals from carbonyl compounds in the presence of Montmorillonite K-10.¹⁸ In order to explore the protection of α -hydroxy acids, we have examined the potential of *N*-triflylphosphoramidate (phosphoramidic acid) (NTPA) as a catalyst. To the best of our knowledge, there is no report of protection of α -hydroxy acids using *N*-triflylphosphoramidate as the catalyst (Fig. 1). As seen from recent reports, achiral, 'super-acidic' organic Brønsted acids have been described with similar or higher reactivities than those of either Lewis or inorganic Brønsted acids.¹⁹ Additionally, Brønsted acids, as compared to Lewis acids, can be easily handled, are generally stable toward oxidizing media or moisture, and can be stored over long periods of time.²⁰

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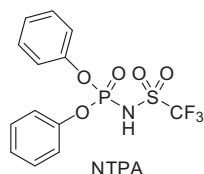
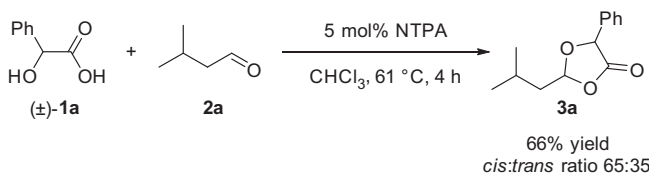


Figure 1. Structure of *N*-triflylphosphoramidate (NTPA).



Scheme 1. Model cyclocondensation of (±)-mandelic acid with *iso*-valeraldehyde.

Table 1
Cyclocondensation of (±)-mandelic acid with *iso*-valeraldehyde under different conditions^a

Entry	NTPA amount (mol %)	Solvent	Temp (°C)	Yield ^b (%)	Ratio ^c <i>cis/trans</i>
1	5	CHCl ₃	61	66	65:35
2	10	CHCl ₃	61	72	68:32
3	15	CHCl ₃	61	73	70:30
4	20	CHCl ₃	61	75	71:29
5	10	CH ₃ CN	81	55	75:25
6	10	Toluene	111	81	54:46
7	10	Toluene	40 ^d	65	63:37
8	10	THF	66	49	60:40
9	10	CH ₂ Cl ₂	40	85	79:21

^a Reactions were heated at reflux. Molar ratio of (±)-mandelic acid/*iso*-valeraldehyde was 1.0:1.2.

^b Isolated yield.

^c Diastereomeric ratio was determined by ¹H NMR analysis of the crude product.

^d Reaction was heated at 40 °C. Molar ratio of (±)-mandelic acid/*iso*-valeraldehyde was 1.0:1.5.

In this Letter, we describe the practical synthesis of 1,3-dioxolane-4-ones from α -hydroxy acids with aldehydes using NTPA.²¹ We started our investigation with the model reaction of racemic

mandelic acid (±)-**1a** with *iso*-valeraldehyde **2a** in the presence of 5 mol % *N*-triflylphosphoramidate (NTPA) in chloroform (Scheme 1). The reaction was heated at reflux without azeotropic water distillation and was found to proceed to completion in 4 h to give 2-(*iso*-butyl)-5-phenyl-1,3-dioxolan-4-one **3a** in 66% yield and a *cis/trans* ratio of 65:35.

In order to further improve the reaction, we examined the effect of different solvents and catalyst loadings which are summarized in Table 1. Firstly, the reaction was examined using different amounts of catalyst (entries 1–4). Although the highest yield was observed using 20 mol % of NTPA (entry 4), we also obtained a fairly good yield using 10 mol % NTPA (entry 2). Having established the optimal catalyst loading (entry 2, 10 mol % NTPA), we then proceeded to examine the solvents, which revealed dichloromethane to give the greatest yield (85%) and diastereomeric ratio (*cis/trans* ratio: 79:21) (entry 9).

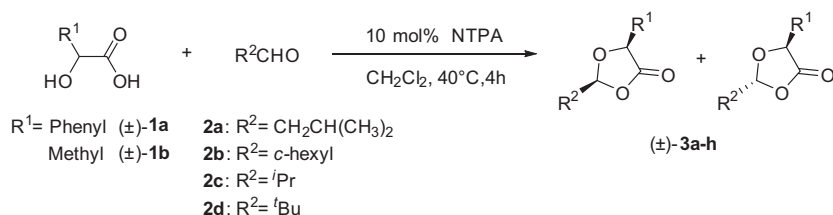
After optimization of the reaction conditions, we decided to explore the generality of the NTPA-catalyzed acetalization reaction using a variety of substrates. The reaction was examined with racemic mandelic acid (±)-**1a** and racemic lactic acid (±)-**1b**, and a variety of aldehydes **2a–d**. It can be seen from Table 2 that racemic mandelic acid and racemic lactic acid both reacted in moderate yield to give the corresponding cyclization products (±)-**3a–h**. The high catalytic activity of NTPA was demonstrated by acetalization with primary aldehydes and also sterically hindered secondary or tertiary aldehydes.

After the successful development of this methodology for the protection of α -hydroxy acids, the process was extended to the synthesis of diastereomeric 2,5-disubstituted 1,3-dioxolane-4-ones (Table 3). A mixture of *cis* and *trans* dioxolanones **4a–h** were obtained with high diastereoselectivity and high yields by the NTPA-catalyzed acetalization of (*S*)-mandelic acid (*S*)-**1a** and (*S*)-lactic acid (*S*)-**1b** with several aldehydes.

The *cis* isomers of dioxolanones were favored^{4b,22} and the configuration of the major diastereomer of **4a–h** was assigned by comparison with published ¹H NMR data. Depending upon the aldehyde and α -hydroxy acids used, the *cis/trans* ratios ranged from 81:19 to 95:5 as determined by ¹H NMR. As observed in entries 4 and 8, the *cis/trans* selectivity increased when the sterically hindered *tert*-butyl aldehyde was used. *iso*-valeraldehyde and *c*-hexyl aldehyde reacted quantitatively with (*S*)-mandelic acid (entries 1–2).

Table 2

Protection of (±)-mandelic acid and (±)-lactic acid with various aldehydes in the presence of NTPA^a



Entry	R ¹	Aldehyde	Yield ^b (%)	Ratio ^c <i>cis/trans</i>
1	Ph	2a	85	79:21
2	Ph	2b	83	83:17
3	Ph	2c	84	82:18
4	Ph	2d	79	84:16
5	CH ₃	2a	83	77:23
6	CH ₃	2b	80	78:22
7	CH ₃	2c	82	73:27
8	CH ₃	2d	80	77:23

^a Reactions were heated at 40 °C. Molar ratio of (±)- α -hydroxy acid/aldehyde was 1.0:1.2.

^b Isolated yield.

^c Diastereomeric ratio was determined by ¹H NMR analysis of the crude product.

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