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One-pot synthesis of α-diazo-β-hydroxyesters under phase-transfer catalysis and application to the catalytic asymmetric aldol reaction

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Abstract—The one-pot (three steps) synthesis of α-diazo-β-hydroxyesters from tosyl chloride under phase-transfer catalysis is described. The catalytic asymmetric aldol reaction between a diazoester and aldehydes was also investigated and gave moderate to good enantioselectivity.

Since its discovery, phase-transfer catalysis (PTC) has been an attractive tool in organic synthesis because it is an environmentally benign, economical and simple operation.[1] Quaternary ammonium salts, which are readily available from tertiary amines, are some of the most common PTCs, and the application of chiral ammonium salts to asymmetric synthesis has been investigated.[2] We report here an efficient one-pot (three steps) synthesis of α-diazo-β-hydroxyesters from sodium azide via azidation, diazo transfer and aldol reaction under PTC conditions. The results of an asymmetric aldol reaction using chiral PTC are also presented.

Wang and co-workers reported that α-diazoesters are acidic enough to undergo condensation with various aldehydes and imines in the presence of a catalytic amount of DBU to give the corresponding aldol adducts.[3,4] The starting diazoesters can be prepared from the corresponding β-ketoesters[5] under PTC conditions, which can be obtained from tosyl azide prepared by reacting sodium azide and tosyl chloride with PTC.[6] According to these reports, we planned the PTC-promoted one-pot synthesis of α-diazo-β-hydroxyesters from NaN_3 under aqueous basic conditions without the isolation or purification of explosive intermediates. Initially, we tried a three-step reaction using 10 mol % of tetrahexylammonium bromide (THAB) with TsCl, *tert*-butyl acetoacetate **1a** and benzaldehyde **2a**. The azidation reaction in CH_2Cl_2 was found to be proceeded smoothly and quantitatively under mild conditions to give the TsN_3, however subsequent diazo transfer with 25% aq NaOH at rt was slow and the desired aldol product **3a** was obtained in only 38% yield even after 100 h, as shown in entry 1 (Table 1). To avoid hydrolysis of the diazoester or ketoester, less basic conditions were investigated, as shown in entry 2. Azidation and diazo transfer processes proceeded successfully and the subsequent aldol reaction with 5 equiv of **2a** gave **3a** in 70% yield. On the other hand, ethyl ester **1b** was found to be quite an effective substrate, and the diazo transfer process was complete within 9 h to give **4a** in 87% yield under similar conditions (entry 3). Moreover, diethylether was also an effective solvent in the diazo-transfer step: the reaction was complete within 1.5 h and gave **4a** in 82% yield (entry 4).[7]

Encouraged by these results, we next examined various aldehydes under optimized conditions (Table 2). As expected, both aromatic and aliphatic aldehydes were smoothly converted into the corresponding aldols. For example, aromatic aldehydes such as **2b** and **2c** were transformed to **4b** and **4c** in respective yields of 73% and 80% in the presence of 10 mol % of THAB (entries 1 and 2). Moreover, primary and secondary aldehydes such as **2d**–**g** also gave the desired product in good to high yields without any self-condensation of **2** (entries 3–6). However, the reaction of **2h** was quite slow due to steric hindrance, and gave **4h** in 73% yield after 18 h (entry 7).

Thus, we have developed an efficient synthesis of α-diazo-β-hydroxyesters under PTC conditions via a one-pot process. Next, a catalytic asymmetric carbon–carbon

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Keywords: Aldol reaction; Ammonium salt; Asymmetric synthesis; Diazoester; Phase transfer.

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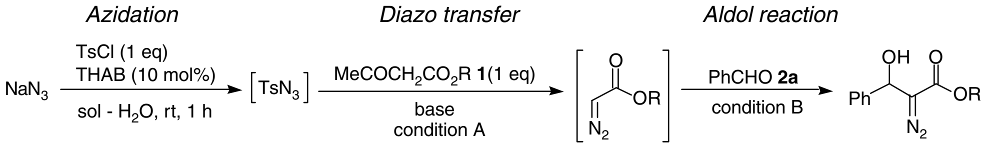
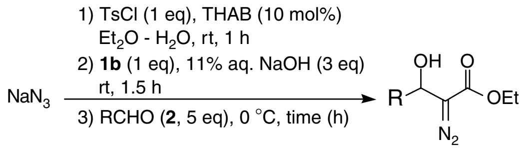
Table 1. One-pot synthesis of α-diazo-β-hydroxyesters under PTC conditions



3 or **4**

Entry	**1**	Solvent	Base (equiv)	Condition A	**2a** (equiv)	Condition B	Yield (%)
1	**1a**: R = *t*-Bu	CH_2Cl_2	25% NaOH (5)	rt, 100 h	1.2	rt, 40 h	**3a**: 38
2	**1a**: R = *t*-Bu	CH_2Cl_2	11% NaOH (3)	rt, 85 h	5	0 °C, 3 h	**3a**: 70
3	**1b**: R = Et	CH_2Cl_2	11% NaOH (3)	rt, 9 h	5	0 °C, 3 h	**4a**: 87
4	**1b**: R = Et	Et_2O	11% NaOH (3)	rt, 1.5 h	5	0 °C, 7 h	**4a**: 82

Table 2. One-pot reaction using various aldehydes



4

Entry	**2**: aldehyde	Time (h)	Yield (%)
1	**2b**: R = 4-MeO–Ph	2	**4b**: 73
2	**2c**: R = 1-naphthyl	3	**4c**: 80
3	**2d**: R = $Ph(CH_2)_2$	3	**4d**: 86[a]
4	**2e**: R = *i*-Bu	20	**4e**: 82
5	**2f**: R = *i*-Pr	3	**4f**: 75
6	**2g**: R = *c*-Hex	4	**4g**: 75
7	**2h**: R = *t*-Bu	18	**4h**: 73

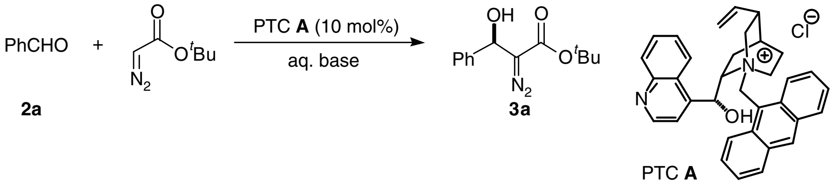
[a] Three equivalents of **2d** was used.

bond-forming reaction using a chiral PTC was investigated (Table 3).[8] Initially, we examined the reaction using a readily available quaternary salt (PTC **A**),[9,10] diazoester and benzaldehyde **2a**, as shown in Table 3. The reaction was carried out in the presence of 10 mol% of PTC **A** with *tert*-butyl diazoacetate, and gave the desired product **3a** at −20 °C with 32% ee. To optimize the conditions, the solvent and base were surveyed. With a strong base such as 50% aq RbOH, the reaction proceeded smoothly in toluene even at −40 °C, and gave **3a** in excellent yield with 56% ee (entry 4).[11,12] The absolute stereochemistry was determined to be *R* based on a comparison of the optical rotation to that of the corresponding β-hydroxyester after treatment of **3a** with Pd/H_2.[13]

The results described above indicate that PTC **A** plays an important role in creating a chiral stereocentre. We next investigated the scope and limitations of this reaction using various aldehydes under similar conditions (Table 4). Surprisingly, the substituents on the benzene ring in aldehydes strongly influenced the enantioselectivity. For example, a methyl group at the 4 position decreased the ee value to 39% and a more strong electron-donating group such as methoxy resulted in a racemate of **3b** (entries 1 and 2). On the other hand, an electron-withdrawing group such as 4-CF_3 dramatically increased the ee with good yield (entry 3). Furthermore, 1-naphthaldehyde **2c**, which contains a highly conjugated plane, seems to be quite effective, and gave the corresponding aldol in 79% ee (entry 4). Next, we turned to investigate the aliphatic aldehydes. In case of α-monosubstituted aliphatic aldehydes (**2d**–**e**), their enantioselectivity was quite lower with up to 31% ee (entries 5 and 6), however the bulkier substituents such as isopropyl and cyclohexyl groups gave better results (entries 7 and 8) and pivalaldehyde **2h** was converted into **3h** in good yield with 78% ee (entry 9). These results are summarized in Table 4.

The aldol reaction between diazoacetates and aldehydes under basic conditions is known to be an equilibrium process,[4b] and we next investigated the reaction profile.

Table 3. Catalytic asymmetric aldol reaction of **2a** using PTC **A**

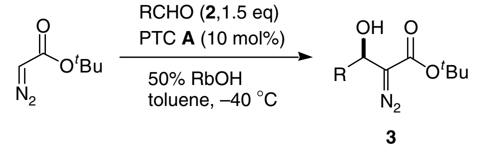


2a **3a** PTC **A**

Entry	Solvent	Base	**2a** (equiv)	Conditions	Yield (%)	Ee (%)[a]
1	Et_2O	11% NaOH	5	−20 °C, 30 h	59	32
2	Et_2O	11% NaOH	5	−40 °C, 5 h	74	39
3	Toluene	50% KOH	5	−40 °C, 5 h	66	44
4	Toluene	50% RbOH	1.5	−40 °C, 12 h	91	56

[a] Determined by chiral HPLC analysis using Daicel Chiralcel OD.

Table 4. Catalytic asymmetric aldol reaction with various aldehydes



Entry	R	Time (h)	Yield (%)	Ee (%)
1	**2i**: 4-Me–Ph	66	**3i**: 66	39
2	**2b**: 4-MeO–Ph	120	**3b**: 56	0
3	**2j**: 4-CF_3–Ph	140	**3j**: 81	73
4	**2c**: 1-naphthyl	94	**3c**: 86	79
5	**2d**: $Ph(CH_2)_2$	72	**3d**: 32	31
6	**2e**: *i*-Bu	72	**3e**: 85	20
7	**2f**: *i*-Pr	20	**3f**: 45	40
8	**2g**: *c*-Hex	10	**3g**: 88	33
9	**2h**: *t*-Bu	72	**3h**: 83	78

As shown in Figure 1, the chemical yield of **3a** gradually increased as the reaction proceeded and reached to equilibrium after 5 h at 90% yield. The enantioselectivity was also not constant but rather similar to the chemical yield, increased during the early phase step (0–3 h) and reached around 60% ee after 3 h. **(±)-3a** was subjected to similar conditions. As expected both *tert*-butyl diazoacetate and **2a** were observed even at −40 °C and **3a** was recovered in only 3% ee (72% yield), which shows that the kinetic resolution of racemic **3a** does not play a role in this reaction (Scheme 1). These results suggest that the asymmetric induction of **3a** is achieved via not only C–C bond formation but also a retroaldol step.[14]

In conclusion, we have realized a phase-transfer-catalyzed one-pot process to give α-diazo-β-hydroxyesters under mild conditions and have applied chiral PTC to asymmetric induction to give aldol adducts (up to 79% ee). We assume that enantiomeric enrichment by the retroaldol reaction of racemic **3a** is also important for the observed asymmetric induction. However, the overall asymmetric induction is still unclear. Further studies on the mechanism of this reaction and optimization of the catalyst structure are in progress.

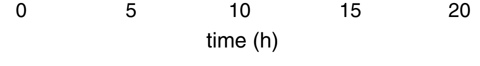
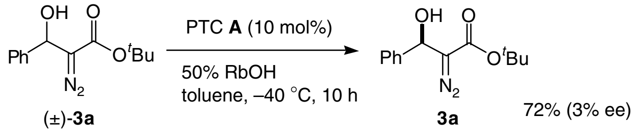


Figure 1. Reaction profile of **3a**.



Scheme 1. Retroaldol reaction of (±)-**3a** with PTC **A**.

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7. Typical experimental procedure for one-pot synthesis of **4a** (Table 1, entry 4): To a solution of TsCl (200 mg, 1.05 mmol) and THAB (46 mg, 0.1 mmol, 10 mol%) in diethylether (5.3 mL) was added NaN_3 (70.0 mg, 1.05 mmol) and water (0.3 mL) at room temperature. The mixture was stirred for 1 h and was added **1b** (0.14 mL, 1.05 mmol) and 3 N NaOH (1166 mg, 3.15 mmol), subsequently stirring was contributed for additional 1.5 h. After disappearance of α-diazo-β-keto-ester, benzaldehyde **2a** (0.53 mL, 5.25 mmol) was added at rt and the mixture was stirred for 7 h at 0 °C. The mixture was extracted with AcOEt (10 mL × 3) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Subsequent flash column chromatography (hexane–AcOEt 10:1) gave the desired product **4a** as a yellow oil (190 mg. 0.86 mmol, 82%).
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10. According to the modified Corey's procedure, PTC **A** was prepared as follows: The suspension of cinchonidine (1.15 g, 5.1 mmol) and anthracenylmethyl chloride (1.5 g, 5.1 mmol) in toluene (26 mL) was treated under reflux conditions. After stirring for 2 h, the solvent was removed under vacuum and the resulting yellow solid was washed with benzene and recrystallized from hot MeOH (30 mL). Filtration and washing with MeOH gave the desired

quaternary ammonium salt as yellow crystal [1.5 g, 2.8 mmol, 56%, $[\alpha]_D^{22}$ −438° (*c* 1.05, $CHCl_3$), mp: 169–171 °C].[9c] Commercially available PTC **A** [from Aldrich, $[\alpha]_D^{23}$ −350° (*c* 0.99, $CHCl_3$), mp:165–168 °C] gave **3a** in 69% yield with 42% ee under similar conditions. Recrystallization from hot MeOH improved the value of $[\alpha]_D$ and mp of quaternary salt as described above, and ee of **3a**.

11. Other PTCs such as O-protected or *N*-4-CF_3 benzyl derivatives resulted in much lower ee.
12. Typical experimental procedure for asymmetric aldol reaction, synthesis of **3a** using PTC **A** (Table 3, entry 4): To a solution of benzaldehyde **2a** (56 μL, 0.53 mmol), *tert*-butyl diazoacetate (50 mg, 0.35 mmol) and PTC **A** (17 mg, 0.035 mmol, 10 mol %) in toluene (1.8 mL) was added 50% RbOH (78 mg, 0.7 mmol) at −40 °C. The mixture was stirred for 12 h and partitioned between AcOEt and water. The resulted residue was extracted with AcOEt (5 mL × 3) and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Following flash column chromatography (hexane–AcOEt 15:1) gave the desired aldol product **3a** as a yellow oil (79 mg, 0.31 mmol, 91%).
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