# Diastereo- and Enantioselective Direct Henry Reaction of Pyruvates Mediated by Chiral P-Spiro Tetraaminophosphonium Salts

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The stereoselective direct Henry reaction of pyruvates mediated by chiral P-spiro tetraaminophosphonium salts is described. High levels of diastereo- and enantioselectivities have been achieved by the use of L-valine-derived (*P*,*S*)-**2e** bearing *para*-chlorophenyl groups as a precatalyst.

Chiral $\beta$-nitroalkanols are a versatile intermediate for the stereoselective construction of biologically important, polyfunctional molecular frameworks, such as 1,2-amino alcohols and $\alpha$-hydroxy acids.[1] The catalytic enantioselective direct Henry reaction[2] is undoubtedly the most efficient and straightforward method to produce this class of compounds, and hence it has been extensively studied since Shibasaki's pioneering work using a powerful heterobimetallic catalyst.[3] Despite the elaborations of structurally diverse catalyst families that accommodate a range of aldehydes as an electrophile, the development of the reaction with ketones has met with limited success even with highly activated substrates.[4–6] Although effective catalyst systems have emerged for the enantioselective addition of nitromethane to $\alpha$-keto esters[4] and trifluoromethylketones,[5] there has been only one report on addressing the stereochemical issues associated with the generation of two adjoining chiral centers in the reaction of substituted nitroalkanes with $\alpha$-keto esters.[4f]

Recently, we reported a catalytic, highly anti- and enantioselective direct Henry reaction of aldehydes.[7a] The key to achieving high stereoselectivity was the development of a chiral P-spiro tetraaminophosphonium salt (*M*,*S*)-**1** (Figure 1) as a conjugate acid of the actual organic base catalyst, chiral triaminoiminophosphorane.[7] The cationic moiety of **1** was expected to form a structured chiral organic ion pair with nitronate anion via double hydrogen-bonding, being responsible for rigorous stereocontrol in the addition to aldehyde. Here, we demonstrate further potential of this type of tetraaminophosphonium salt as a catalytic stereocontroller for establishing highly diastereo- and enantioselective Henry reactions of $\alpha$-keto esters.

An initial trial was conducted by applying (*M*,*S*)-**1a**–**1c**, which were previously found to be effective for the Henry reaction of aldehydes,[7a] to the reaction of nitroethane with ethyl pyruvate (Table 1, Entries 1–3). Bond formation proceeded smoothly at $-78\,^{\circ}C$ to give the desired Henry adduct **3a** in good yield with moderate syn- and enantioselectivities.[8] Fortunately, the use of partially yet selectively N-methylated aminophosphonium salt (*P*,*S*)-**2a** (Figure 1), originally developed for a direct Mannich-type reaction of azlactones,[9] improved diastereoselectivity without sacrificing enantioselectivity (Entry 4). Interestingly, while the spiro-chirality of (*P*,*S*)-**2** is opposite to that of (*M*,*S*)-**1**, preferential formation of the configurationally identical syn isomer was observed. Next, the effect of the aromatic substituent on the diazaphosphacycles of (*P*,*S*)-**2** was investigated. The introduction of the *para*-tolyl group [(*P*,*S*)-**2b**] led to improvement of diastereoselectivity albeit with certain rate retardation (Entry 5). Although aminophosphonium salt (*P*,*S*)-**2c**, which possesses highly electron-deficient *para*-trifluoromethylphenyl substituents, showed essentially no catalytic activity (Entry 6), the use of (*P*,*S*)-**2d** or -**2e**, both of which bear the moderately electron-withdrawing *para*-halophenyl moiety, resulted in notable enhancement of enantioselectivity (Entries 7 and 8). Throughout this optimization, however, dimerization of pyruvate appeared to be a problematic side reaction.[10] In order to suppress the undesired dimerization, 20 equiv of nitroethane were added, which as we assumed, allowed for the isolation of **3a** at a synthetically useful chemical yield (Entry 9). Unfortunately, further increase in the amount of nitroethane to 30 equiv negatively affected the stereochemical control by (*P*,*S*)-**2e**, probably due to the influence of the polarity of the reaction medium (Entry 10).

With the optimized conditions in hand, the substrate profile was evaluated (Table 2).[11] With regard to the ester substituent,

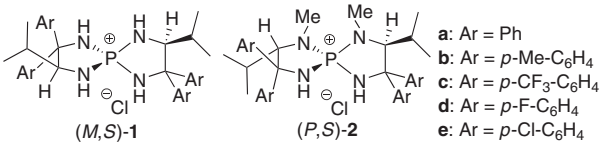
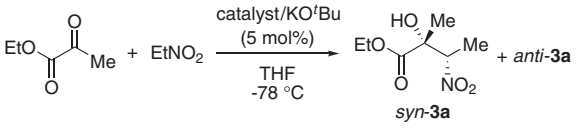



**Figure 1.** Structures of chiral P-spiro tetraaminophosphonium chlorides.

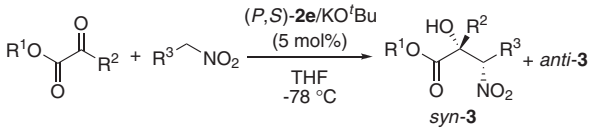
**Table 1.** Effect of catalyst structure on stereoselectivity




| Entry | Catalyst | $EtNO_2$ (equiv) | Time/h | Yield[a] /% | dr[b] (syn/anti) | ee[c] /% |
|---|---|---|---|---|---|---|
| 1 | (*M*,*S*)-**1a** | 10 | 2 | 84 | 3:1 | 68 |
| 2 | (*M*,*S*)-**1b** | 10 | 2.5 | 80 | 3:1 | 73 |
| 3 | (*M*,*S*)-**1c** | 10 | 2.5 | 68 | 3:1 | 76 |
| 4 | (*P*,*S*)-**2a** | 10 | 4.5 | 70 | 6:1 | 71 |
| 5 | (*P*,*S*)-**2b** | 10 | 12 | 70 | 9:1 | 76 |
| 6 | (*P*,*S*)-**2c** | 10 | 24 | 8[d] | 5:1 | 79 |
| 7 | (*P*,*S*)-**2d** | 10 | 24 | 63 | 7:1 | 86 |
| 8 | (*P*,*S*)-**2e** | 10 | 24 | 52 | 10:1 | 86 |
| 9 | (*P*,*S*)-**2e** | 20 | 20 | 76 | 10:1 | 86 |
| 10 | (*P*,*S*)-**2e** | 30 | 12 | 84 | 5:1 | 78 |

[a]Isolated yield. [b]Determined by $^1H$ NMR (500 MHz) analysis of crude aliquot. [c]Enantiomeric excesses of major syn isomer were analyzed by chiral stationary phase HPLC using TCI Chiral CH-S with hexane/2-propanol = 10:1 as eluent. [d]Not all conversion.

**Table 2.** Substrate scope




| Entry | $R^1$ | $R^2$ | $R^3$ | Time/h | Yield[a] /% | dr[b] (syn/anti) | ee[c] /% |
|---|---|---|---|---|---|---|---|
| 1 | Me | Me | Me | 21 | 75 | 6:1 | 72 |
| 2 | $^t$Bu | Me | Me | 24 | Trace | — | — |
| 3 | Et | Me | H | 15 | 98 | — | 76 (R)[e] |
| 4 | Et | Me | Et | 24 | 50[d] | 9:1 | 90 |
| 5 | Et | Et | Me | 24 | 55[d] | 9:1 | 92 |

[a]Isolated yield. [b]Determined by $^1$H NMR (500 MHz) analysis of crude residue. [c]Enantiomeric excesses of major diastereomer were analyzed by chiral stationary phase HPLC. [d]Not all conversion. [e]Absolute configuration was determined by comparison of its HPLC retention time with literature data.[4d,4e]

similar reactivity and selectivity were observed with methyl pyruvate, but *tert*-butyl pyruvate gave only a trace amount of the product upon being reacted with nitroethane (Entries 1 and 2). As a nucleophile, nitromethane added to ethyl pyruvate at a faster rate to furnish the $\beta$-nitro alcohol **3** almost quantitatively with comparable enantioselectivity (Entry 3), and its absolute stereochemistry was determined to be R on the basis of literature data.[4d,4e] Nitropropane also appeared to be a good candidate in terms of stereoselectivity (Entry 4). Further, the reaction of ethyl 2-oxobutanoate with nitroethane was found to proceed with high levels of both relative and absolute stereocontrol (Entry 5).

In conclusion, we have demonstrated that chiral tetraaminophosphonium chloride (*P*,*S*)-**2e** can function as an effective, catalytic stereocontroller for realizing highly syn- and enantioselective direct Henry reaction of pyruvates. This study underscores the importance of the combination of the spiro-chirality and the central chirality of the catalyst as well as its appropriate structural modifications.

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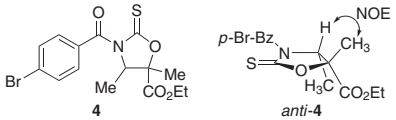
8 Relative stereochemistry was assigned by NOESY experiment of both diastereomers after derivatization to the corresponding *N*-(*p*-bromobenzoyl)thiocarbamate *syn*- and *anti*-**4** in 4 steps.[4f]

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10 About 10–20% of pyruvate dimer was observed in the reactions for Entries 7 and 8 in Table 1.

11 **General procedure:** To a solution of (*P*,*S*)-**2e** (8.11 mg, 0.011 mmol) and nitroethane (0.29 mL, 4.0 mmol) in THF (2.0 mL) was introduced a 1.0 M THF solution of KO$^t$Bu (0.01 mL, 0.01 mmol) at $-78$ °C and the mixture was stirred there for 30 min. Ethyl pyruvate (0.02 mL, 0.20 mmol) was then added and stirring was continued at $-78$ °C for 20 h. The reaction was quenched by addition of a 0.5 M toluene solution of trifluoroacetic acid (0.1 mL) at $-78$ °C and the whole mixture was poured into saturated aqueous $NH_4Cl$ solution. After extractive workup with ethyl acetate and evaporation of solvents, the crude residue was analyzed by $^1$H NMR (500 MHz) to determine the diastereoselectivity (syn/anti = 10:1), and subsequent purification by silica gel column chromatography (hexane/ethyl acetate = 4:1 as eluent) afforded the adduct **3a** in 76% yield (86% ee for syn isomer). $^1$H NMR (500 MHz, $CDCl_3$) for *syn*-**3a**: $\delta$ 4.91 (1H, q, $J = 7.0$ Hz), 4.33 (1H, q, $J = 7.0$ Hz), 4.30 (1H, q, $J = 7.0$ Hz), 1.66 (3H, d, $J = 7.0$ Hz), 1.42 (3H, s), 1.32 (3H, t, $J = 7.0$ Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) for *syn*-**3a**: $\delta$ 174.2, 86.8, 74.8, 62.9, 23.4, 14.0, 12.7; IR (liq. film): 3492, 2987, 1736, 1555, 1448, 1390, 1261, 1184, 1101, 1016 cm$^{-1}$; HRMS (ESI-TOF) *m*/*z*: Calcd for $C_7H_{13}NO_5Na^+$ ($[M + Na]^+$): 214.0686. Found: 214.0695; HPLC (TCI Chiral CH-S): hexane/2-propanol = 10:1, flow rate = 0.5 mL min$^{-1}$, $\lambda = 210$ nm, 8.9 min (minor anti isomer), 9.3 min (minor syn isomer), 10.3 min (major syn isomer), 11.6 min (major anti isomer).

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