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# Enantioselective reductive aldol reaction using tertiary amine as hydride donor

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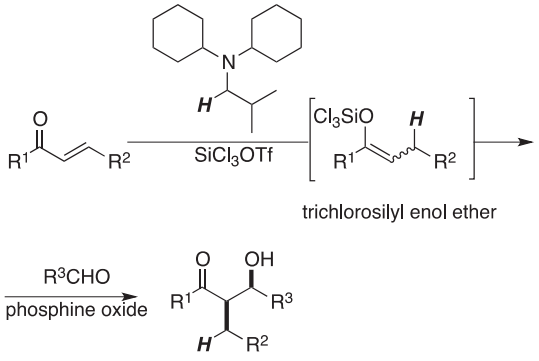
ABSTRACT

An efficient method was developed for the enantioselective reductive aldol reaction of α,β-unsaturated ketones with aldehydes in the presence of a Lewis base catalyst; conjugate reduction using a tertiary amine and trichlorosilyl triflate, followed by an aldol reaction with BINAP dioxide (BINAPO) as an organocatalyst, gave the corresponding product in high yield with high stereoselectivity.



Reductive aldol reactions comprise a sequence of conjugate reductions and aldol reactions that provide β-hydroxy carbonyl compounds directly without isolation of the enolate intermediate.[1] Reductive aldol reactions have great advantages in that they form several bonds and create contiguous stereogenic centers in one pot. To date, a number of catalysts based on metals and highly stereoselective transformations have been achieved,[2] but there was no example of organocatalyzed enantioselective reductive aldol reaction until our group demonstrated an enantioselective reductive aldol reaction with trichlorosilane catalyzed by chiral phosphine oxides as organocatalysts.[3]




**Scheme 1.** Reaction sequence of the conjugate reduction and aldol reaction.

We recently developed a trichlorosilyl triflate/tertiary amine-mediated conjugate reduction of α,β-unsaturated ketones.[4] Deuterium labeling experiments revealed that a trichlorosilyl enol ether was generated and remained intact in the reaction media.[5] This result supports the feasibility of enantioselective reductive aldol reactions if aldehydes are used as the electrophile in the presence of a Lewis base catalyst, such as phosphine oxide (Scheme 1).[6,7] Here, we report a novel type of enantioselective reductive aldol reaction of α,β-unsaturated ketones and aldehydes via a sequence of conjugate reductions with trichlorosilyl triflate/tertiary amine and aldol reactions catalyzed by a chiral phosphine oxide.

Initially, chalcone (**1a**) and benzaldehyde (**2a**) were chosen as the substrates to study a reductive aldol reaction (Table 1). After treatment of **1a** with trichlorosilyl triflate and $Cy_2N^iBu$ (2 equiv, each, Cy = cyclohexyl) in dichloromethane at −40 °C, (*S*)-BINAPO (**3**) and aldehyde **2a** were successively added to the mixture (entry 1). A small amount of the desired aldol adduct **4a** was obtained, but the major product was the reduced ketone. This result indicated that the latter aldol reaction did not proceed extensively. We suspected that acids, such as hydrogen chloride and/or trifluoromethanesulfonic acid generated adventitiously from trichlorosilyl triflate deactivated **2a** or **3**, resulting in low chemical and optical yields. Therefore, decreasing the amount of trichlorosilyl triflate (1.5 equiv) dramatically improved both the yield and stereoselectivity

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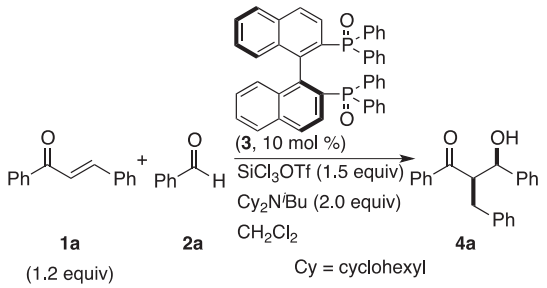
**Table 1**
Optimization of the reaction conditions for the reductive aldol reaction of chalcone (**1a**) and benzaldehyde (**2a**) catalyzed by BINAPO (**3**) [a]




| Entry | Temp., °C | Time, h | Yield[b], % | *syn*/*anti*[c] | ee (*syn*) [d], % |
|---|---|---|---|---|---|
| 1[e] | −40 | 24 | 30 | 17/83 | 5 |
| 2 | −40 | 1 | 83 | 95/5 | 95 |
| 3[f] | −40 | 1 | 85 | 97/3 | 89 |
| 4[g] | −40 | 1 | 32 | 95/5 | 93 |
| 5 | −60 | 18 | 87 | 97/3 | 93 |
| 6 | −78 | 24 | 22 | 90/10 | 84 |

[a] Unless otherwise noted, the reactions were conducted using **2a** (0.5 mmol), **1a** (1.2 equiv), $Cy_2N^iBu$ (2.0 equiv), $SiCl_3OTf$ (1.5 equiv), and **3** (10 mol %) in $CH_2Cl_2$ (5 mL).
[b] Isolated yield.
[c] Determined by $^1H$ NMR analysis.
[d] Determined by HPLC analysis.
[e] $SiCl_3OTf$ (2.0 equiv).
[f] $^iPr_2N^iBu$ (2.0 equiv) was used in place of $Cy_2N^iBu$.
[g] $^iPr_2NEt$ (2.0 equiv) was used in place of $Cy_2N^iBu$.

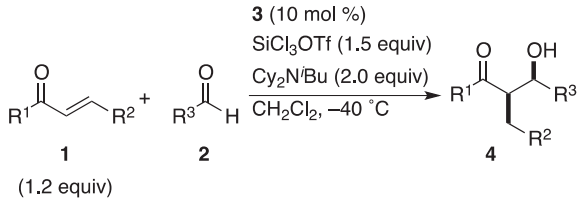
(entry 2).[8] Varying the size of amines proved to have a large effect on the reaction (entries 2–4). The enantioselection of the reaction involving $^iPr_2N^iBu$ was similar to that involving $Cy_2N^iBu$ (entry 3), although $^iPr_2NEt$ provided reduced product yields (entry 4). Lowering the temperature slightly improved the product yield but prolonged the reaction time (entries 5 and 6).

With the optimal conditions in hand, reductive aldol reactions of benzaldehyde (**2a**) with various types of α,β-unsaturated ketones **1** were performed (Table 2).[9] All reactions with the chalcone derivatives **1a–g** proceeded smoothly to give the corresponding products in good yields with high diastereo- and enantioselectivities (entries 2–7). Isopropyl ketone **1h** provided the aldol product in high yield and selectivity (entry 8), whereas the stereoselectivity of the reaction with cyclopropyl ketone **1i** was found to decrease (entry 9).[10]

Next, reductive aldol reactions between various aldehydes **2** and chalcone (**1a**) were conducted (entries 10–15). The aromatic aldehydes tended to give the aldol adducts **4j–l** with good yields and high stereoselectivities (entries 10–12). The conjugate aldehyde **2e**, which provided a lower selectivity in the reductive aldol reaction with trichlorosilane,[3b] furnished the product **4m** in high yield with high selectivity (entry 13). Strikingly, the aliphatic aldehydes **2f** and **2g**, which were generally less reactive in Lewis base-catalyzed reactions,[7,11] gave the corresponding aldol adducts in good yields with high diastereoselectivities (entries 14 and 15).

As previous reports for phosphine oxide-catalyzed aldol reaction,[3b,7] the production of a *syn*-isomer indicated that the conjugate reduction of the chalcone derivatives predominantly produced (*Z*)-trichlorosilyl enol ether. To confirm the generation of (*Z*)-trichlorosilyl enol ether, the conjugate reduction of ketone **1f** was examined in a NOESY experiment. A NOESY correlation was observed between the two hydrogen atoms, as shown in Figure 1 (the spectrum is provided in the Supplementary data). This

**Table 2**
Enantioselective reductive aldol reaction of α,β-unsaturated ketones **1** and aldehydes **2** catalyzed by BINAPO[a]




**1a**: $R^1 = R^2 = Ph$
**1b**: $R^1 = Ph$, $R^2 = p\text{-}MeOC_6H_4$
**1c**: $R^1 = Ph$, $R^2 = p\text{-}BrC_6H_4$
**1d**: $R^1 = Ph$, $R^2 = C_6H_5C{\equiv}C$
**1e**: $R^1 = p\text{-}MeOC_6H_4$, $R^2 = Ph$
**1f**: $R^1 = p\text{-}BrC_6H_4$, $R^2 = Ph$
**1g**: $R^1 = C_6H_5C{\equiv}C$, $R^2 = Ph$
**1h**: $R^1 = {}^iPr$, $R^2 = Ph$
**1i**: $R^1 = {}^cPr$, $R^2 = Ph$

**2a**: $R^3 = Ph$
**2b**: $R^3 = p\text{-}MeOC_6H_4$
**2c**: $R^3 = p\text{-}BrC_6H_4$
**2d**: $R^3$ = 2-furyl
**2e**: $R^3 = PhCH{=}CH$
**2f**: $R^3 = PhCH_2CH_2$
**2g**: $R^3 = Cy$

| Entry | 1 | 2 | Time, h | 4 | Yield[b], % | *syn*/*anti*[c] | ee[d] (*syn*), % |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 1 | **4a** | 83 | 95/5 | 95 |
| 2 | **1b** | **2a** | 1 | **4b** | 84 | 97/3 | 93 |
| 3 | **1c** | **2a** | 1.5 | **4c** | 86 | 96/4 | 93 |
| 4 | **1d** | **2a** | 1 | **4d** | 82 | 95/5 | 80 |
| 5 | **1e** | **2a** | 1.5 | **4e** | 69 | 74/26 | 81 |
| 6 | **1f** | **2a** | 1 | **4f** | 83 | 97/3 | 88 |
| 7 | **1g** | **2a** | 1.5 | **4g** | 56 | 89/11 | 84 |
| 8 | **1h** | **2a** | 4 | **4h** | 73 | 94/6 | 89 |
| 9 | **1i** | **2a** | 4 | **4i** | 79 | 70/30 | 32 |
| 10 | **1a** | **2b** | 0.5 | **4j** | 81 | 96/4 | 90 |
| 11 | **1a** | **2c** | 2 | **4k** | 87 | 95/5 | 95 |
| 12 | **1a** | **2d** | 0.25 | **4l** | 57 | 97/3 | 90 |
| 13 | **1a** | **2e** | 1 | **4m** | 83 | 97/3 | 84 |
| 14[e] | **1a** | **2f** | 1 | **4n** | 50 | 96/4 | 89 |
| 15[e] | **1a** | **2g** | 1 | 4o | 68 | 99/1 | 70 |

[a] Unless otherwise noted, the reactions were conducted in the presence of **2** (0.5 mmol), **1** (1.2 equiv), $Cy_2N^iBu$ (2.0 equiv), $SiCl_3OTf$ (1.5 equiv), and **3** (10 mol %) in $CH_2Cl_2$ (5 mL).
[b] Isolated yield.
[c] Determined by $^1H$ NMR analysis.
[d] Determined by HPLC analysis.
[e] The reaction was conducted with ketone **1** (1.0 equiv), aldehyde **2** (1.5 equiv), and $SiCl_3OTf$ (1.2 equiv).

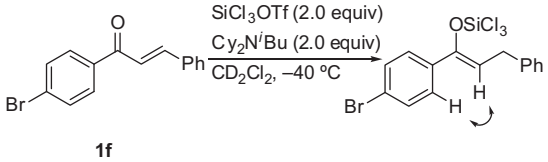
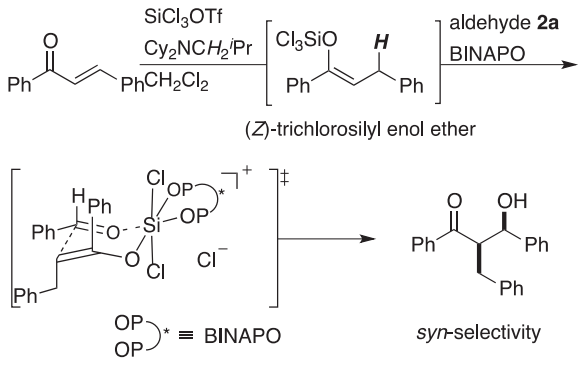



**Figure 1.** NOESY 2D experiments of the silyl enol ether derived from **1f**.

observation clearly demonstrated the generation of (*Z*)-trichlorosilyl enol ether through the stereoselective reduction of ketone **1f** and the high *syn*-selectivity in the aldol step.

Based on the above observation and our previous results,[3] we proposed the reaction mechanism, as shown in Scheme 2. The conjugate reduction of chalcone (**1a**) gave the (*Z*)-trichlorosilyl enol ether stereoselectively. The latter aldol reaction of (*Z*)-trichlorosilyl enol ether with aldehyde (**2a**) proceeded via a six-membered transition state involving hypervalent silicon species,[6a,6d] to afford the




**Scheme 2.** Stereochemistry of the reductive aldol reaction.

corresponding aldol adduct with high *syn*-diastereo- and enantioselectivities.

In conclusion, we demonstrated a novel type of the enantioselective reductive aldol reaction using a tertiary amine-mediated conjugate reduction and an organocatalyzed aldol reaction. The present reaction offered the aldol products with high diastereo- and enantioselectivities. The NOESY analysis verified the (*Z*)-selective generation of trichlorosilyl enol ethers, which ensured high *syn*-selectivity in reductive aldol reaction. This is the first example of the enantioselective sequential reaction involving a tertiary amine-mediated reduction. Efforts in our laboratory continue to extend this strategy to other asymmetric reactions.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.147.

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8. The acidic condition might diminish the activity of the Lewis base catalyst. A slight excess amount of the amine kept the reaction media basic to increase the catalyst activity, leading to high yield and stereoselectivity.
9. *Representative procedure for the reductive aldol reaction of ketone* ***1a*** *and aldehyde* ***2a****:* A solution of trichlorosilyl triflate in dichloromethane (2.0 M, 0.38 mL, 0.75 mmol, 1.5 equiv) was added dropwise to the solution of ketone **1a** (125.0 mg, 0.6 mmol, 1.2 equiv) and dicyclohexylisobutylamine (237.4 mg, 1.0 mmol, 2.0 equiv) in dichloromethane (5 mL) at −40 °C. (*S*)-BINAPO (32.7 mg, 0.05 mmol, 10 mol%) and aldehyde **2a** (0.05 mL, 0.5 mmol, 1.0 equiv) were successively added to the mixture, which was further stirred for 1 h. The reaction was quenched with sat. $NaHCO_3$ (5.0 mL) and stirred for 1 h. After filtration through celite®, the aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic layers were successively washed with 15% HCl (3 × 20 mL), water (20 mL), sat. $NaHCO_3$ (20 mL), and brine (20 mL), and dried over $Na_2SO_4$. After filtration and evaporation, the obtained crude product was purified by column chromatography (hex/EtOAc = 8:1, $SiO_2$ 10 g) to furnish the aldol product as a diastereomeric mixture. The enantiomeric excess was determined by chiral HPLC.
10. The conjugate reductions of enones bearing aliphatic substituents on $R^2$ (Me, $^i$Pr, $^t$Bu) resulted in low yields, see Ref. 4.
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