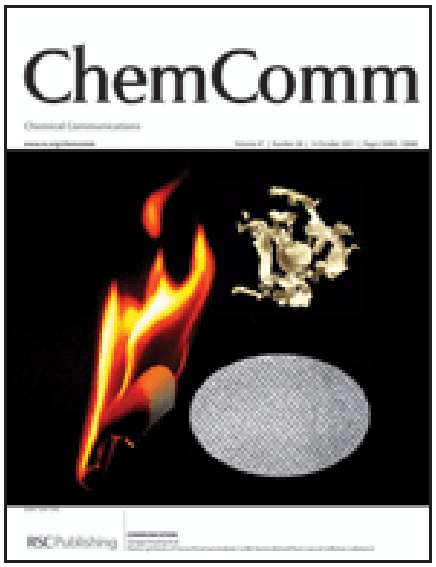

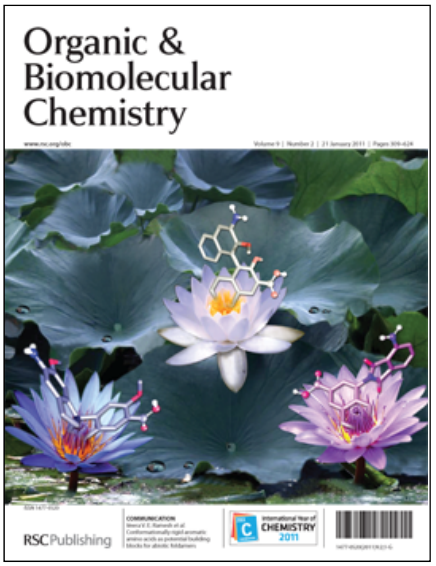

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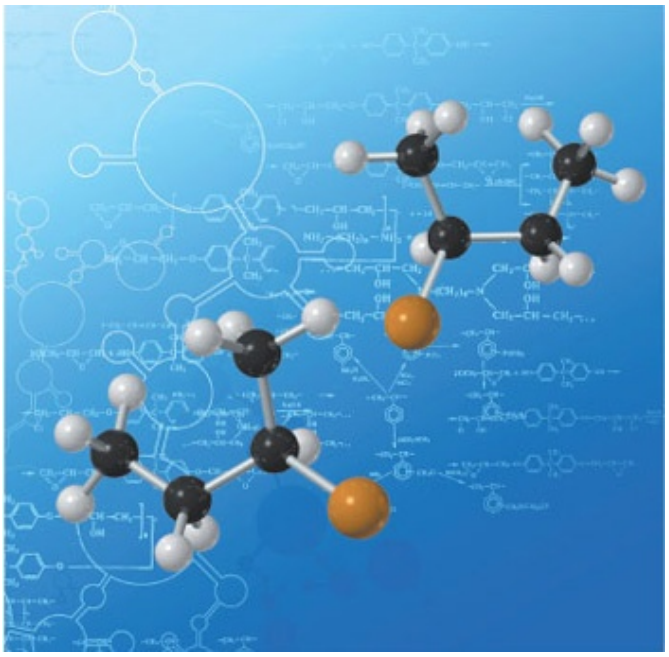

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COMMUNICATION

Trichlorosilyl triflate-mediated enantioselective directed cross-aldol reaction between ketones using a chiral phosphine oxide as an organocatalyst†‡

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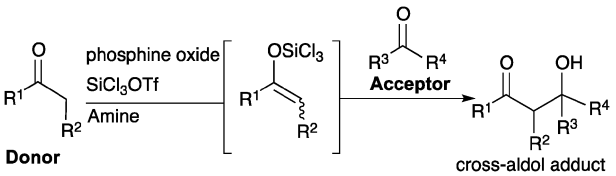
Trichlorosilyl triflate-promoted directed cross-aldol reaction between ketones in the presence of a chiral phosphine oxide as an organocatalyst is described. This is the first enantioselective cross-aldol reaction between simple ketones with good enantioselectivity.

Enantioselective construction of tetra-substituted stereogenic centers is a remarkable challenge for stereoselective syntheses.[1] One of the common methodologies for generating a tetra-substituted chiral center is applying the aldol addition to ketones, resulting in a formation of β-hydroxy carbonyl compounds with a tetra-substituted chiral carbon.[2] However, the enantioselective aldol reaction between ketones is still a challenging issue, because the aldol reaction of ketone acceptors has two main difficulties compared to that of aldehydes as follows: (1) ketones are less reactive than aldehydes; (2) enantio-facial selection of ketones is more difficult than that of aldehydes, due to both the smaller steric and electronic differences between the two substituents adjacent to carbonyl carbon. Recent progress in the enantioselective aldol reactions between two ketones addressed these problems, but the applicable substrates were still limited to pyruvates,[3] isatin derivatives,[4] and others.[5] The first enantioselective aldol addition to simple ketones was reported by Denmark in 2002, who used highly reactive trichlorosilyl ketene acetals as the aldol donors in the presence of a chiral Lewis base catalyst.[6,7] In 2003, Shibasaki and Kanai developed chiral copper-catalyzed enantioselective Mukaiyama-type aldol addition of silyl ketene acetals to ketones.[8] The direct-type aldol reaction between different simple ketones is extremely difficult because the precise recognition of aldol donors and acceptors is required. There is just one report by Tanabe in 1997, who achieved the direct-type aldol reaction of two simple ketones using a $TiCl_4$–Bu_3N system, quantitatively but not enantioselectively.[9]



Scheme 1 Cross-aldol reaction between two different ketones.

We have recently demonstrated that trichlorosilyl triflate mediated direct-type enantioselective aldol reaction occurs between aldehydes and ketones in the presence of chiral phosphine oxide, BINAP dioxide (BINAPO).[10,11] In our previous studies, quenching a reaction with deuterium oxide in the absence of an aldehyde was found to give the α-deuterized ketone. This observation implied the complete transformation of ketones into the silyl enol ether in the reaction media, leading us to believe that addition of different ketones may allow the cross-aldol reaction to proceed between two ketones (Scheme 1). Here, we report the first enantioselective aldol reaction of two different simple ketones **1** (Fig. 1) using trichlorosilyl triflate[12] and a chiral phosphine oxide **2** (Fig. 2).

Initially, using acetone (**1a**) and acetophenone (**1b**) as substrates, the cross-aldol reaction was examined (Scheme 2). After the treatment of **1a** with trichlorosilyl triflate (2.0 eq.) and diisopropylethylamine (10 eq.) in the presence of BINAPO (**2a**) in propionitrile, **1b** was added to the mixture.[13] The desired cross-aldol product **3ab** was obtained in 85% yield with good enantioselectivity (74% ee). When the addition order of ketones **1a** and **1b** was inverted, the aldol adduct **3ba** was obtained in 75% yield. This indicates that interconversion between the silyl enol ether and the ketone acceptor was suppressed under the

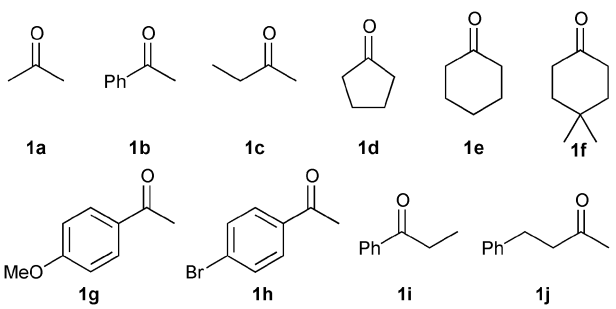


Fig. 1 Ketones used in this study.

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‡ Electronic supplementary information (ESI) available: Experimental details for the enantioselective aldol reaction, spectroscopic data for new compounds, HPLC data for the aldol products. See DOI: 10.1039/c2cc31543b

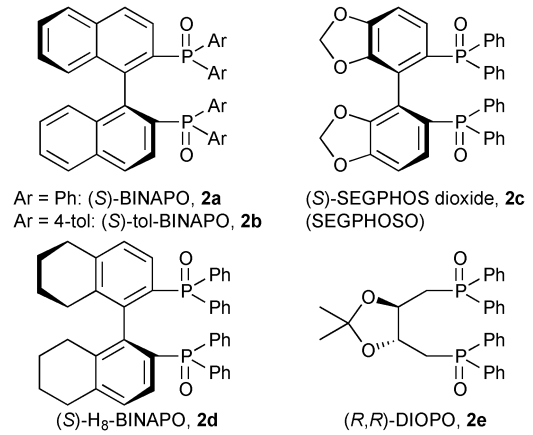
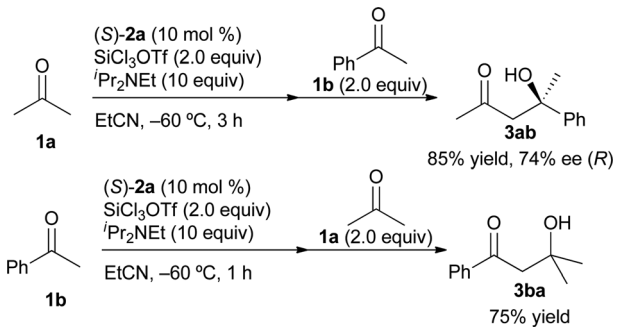


Fig. 2 Chiral phosphine oxide catalysts used in this study.



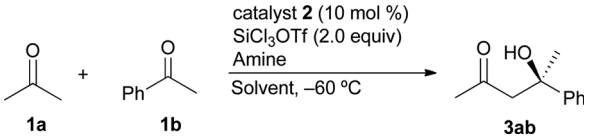
Scheme 2 Directed cross-aldol reaction between **1a** and **1b**.

conditions realizing a directed cross-aldol reaction between ketones.

To optimize the reaction conditions, we then screened the solvent for the cross-aldol reaction of ketone **1a** as an aldol donor and **1b** as an aldol acceptor (Table 1). Dichloromethane promoted self-aldol reaction of **1a**, decreasing the yield of the aldol adduct **3ab**, despite the improved enantioselectivity (entry 2). Isobutyronitrile slightly improved both the chemical and optical yields in comparison with propionitrile (entry 3).[14] Using isobutyronitrile as the solvent, the effect of amines was investigated (entries 3–7). Although nearly the same enantioselectivities were observed, triethylamine and 2,6-lutidine appear to suppress the aldol transformation (entries 4 and 5). On the other hand, sterically congested amines such as tributylamine and pempidine afforded the cross-aldol product **3ab** in good yield with high enantioselectivity (entries 6 and 7).[15] Among the amines tested, diisopropylethylamine was the best for this reaction (entry 3). Decreasing the amount of diisopropylethylamine and lowering the reaction temperature slightly improved the enantioselectivity (entries 8 and 9). Furthermore, use of five equivalents of diisopropylethylamine at −78 °C gave the best enantioselectivity (83% ee), though the reaction time was prolonged (entry 9).

The reactions of ketones **1a** and **1b** in the presence of various chiral phosphine oxides shown in Fig. 2 were performed (entries 10–13). Tol-BINAPO (**2b**) and SEGPHOS dioxide (SEGPHSO, **2c**) gave similar results to BINAPO (**2a**) (entries 10 and 11), whereas the decrease in the yield was observed when H_8-BINAPO (**2d**) was used (entry 12). DIOPO (**2e**), bearing a dioxolane skeleton as a chiral backbone, afforded low chemical and optical yields (entry 13). Triphenylphosphine

Table 1 Optimization for the cross-aldol reaction between **1a** and **1b**[a]

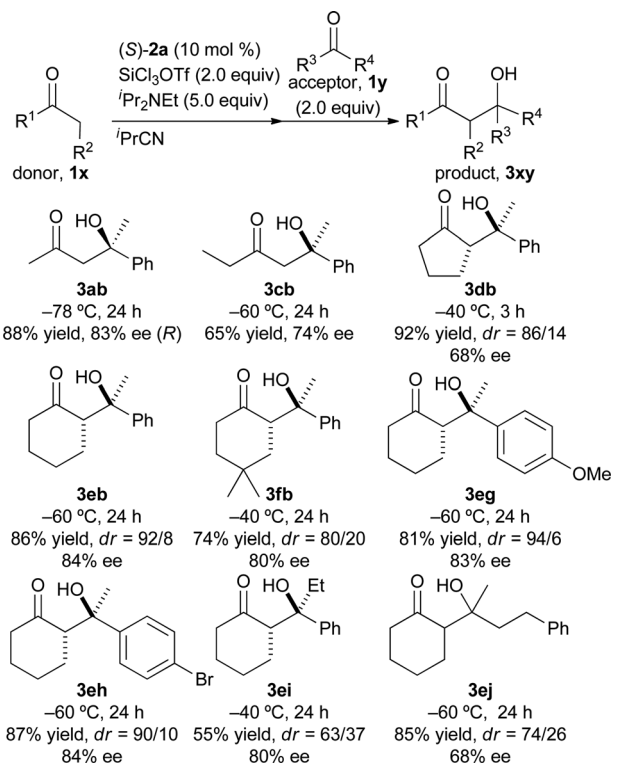


Entry	Solvent	Amine (eq.)	Catalyst	Time/h	Yield[b] (%)	ee[c] (%)
1	EtCN	^{i}Pr$_2$NEt (10)	**2a**	3	85	74
2	CH_2Cl_2	^{i}Pr$_2$NEt (10)	**2a**	24	44	78
3	^{i}PrCN	^{i}Pr$_2$NEt (10)	**2a**	3	87	76
4	^{i}PrCN	Et_3N (10)	**2a**	3	5	72
5	^{i}PrCN	2,6-Lutidine (10)	**2a**	3	2	71
6	^{i}PrCN	Bu_3N (10)	**2a**	3	58	74
7	^{i}PrCN	Pempidine (10)	**2a**	3	78	73
8	^{i}PrCN	^{i}Pr$_2$NEt (5)	**2a**	3	85	80
9[d]	^{i}PrCN	^{i}Pr$_2$NEt (5)	**2a**	24	88	83
10	^{i}PrCN	^{i}Pr$_2$NEt (5)	**2b**	6	80	77
11	^{i}PrCN	^{i}Pr$_2$NEt (5)	**2c**	6	72	74
12	^{i}PrCN	^{i}Pr$_2$NEt (5)	**2d**	3	43	74
13	^{i}PrCN	^{i}Pr$_2$NEt (5)	**2e**	24	36	38
14	^{i}PrCN	^{i}Pr$_2$NEt (5)	Ph_3PO[e]	24	10	—

[a] Unless otherwise noted, all reactions were carried out with ketone **1a** (0.5 mmol), ketone **1b** (1.0 mmol), trichlorosilyl triflate (1.0 mmol), ^{i}Pr$_2$NEt, and a catalyst **2** (0.05 mmol) in a solvent (5 mL) at −60 °C. [b] Yield of the isolated product after column chromatography. [c] Ee was determined by HPLC analysis. [d] The reaction was carried out at −78 °C. [e] Triphenylphosphine oxide (20 mol%) was used.

oxide, a monodentate catalyst was not effective indicating that bisphosphine oxide moieties on the catalyst were essential for the cross-aldol reaction between ketones (entry 14).

Using the phosphine oxide **2a** as an organocatalyst, the cross-aldol reactions between various types of ketones were conducted (Scheme 3). 2-Butanone (**1c**) required a higher temperature (−60 °C) to produce the product **3cb**. In the



Scheme 3 Enantioselective cross-aldol reaction.

reaction of cyclic ketones **1d–f** as an aldol donor, the diastereoselectivity was induced. Cyclopentanone (**1d**) bearing a 5-membered ring slightly decreased enantioselectivity (product **3db**), while cyclohexanones **1e** and **1f** with 6-membered rings provided good diastereo- and enantioselectivities.[16,17]

Using cyclohexanone (**1e**) as an aldol donor, the aldol acceptor was investigated. *p*-Methoxyacetophenone (**1g**) bearing an electron-donating group afforded the corresponding aldol product **3eg** with good stereoselectivity. In the reaction of *p*-bromoacetophenone (**1h**) bearing an electron-withdrawing group, a similar result was obtained. Propiophenone (**1i**) gave the decreased reactivity and diastereoselectivity but good enantioselectivity was observed (product **3ei**). Benzylacetone (**1j**), having small steric difference between both the methyl and methylene substituents on the carbonyl carbon, provided good diastereo- and enantioselectivities, though further improvement was required (product **3ej**).

In summary, we have developed the first phosphine oxide-catalyzed enantioselective directed cross-aldol reaction between simple ketones. The present method provided β-hydroxy carbonyl compounds bearing a tetra-substituted chiral carbon with good enantioselectivity. Detailed mechanistic studies, further improvement of the stereoselectivity, and application to other important carbon–carbon bond-forming reactions are currently under investigation.

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14 Isobutyronitrile possesses lower nucleophilicity and/or Lewis basicity than propionitrile, due to its steric hindrance and may not deactivate trichlorosilyl triflate.

15 Amines also have the nucleophilicities and Lewis basicities. Therefore, a sterically congested amine gave good results without deactivating trichlorosilyl triflate.

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