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To be cited as: *ChemCatChem* 10.1002/cctc.202000914

Link to VoR: https://doi.org/10.1002/cctc.202000914

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COMMUNICATION

Phosphine-oxide-catalyzed Enantioselective Cross-aldol Reactions of Aldehydes with Trichlorosilane as Lewis Acid Promoter

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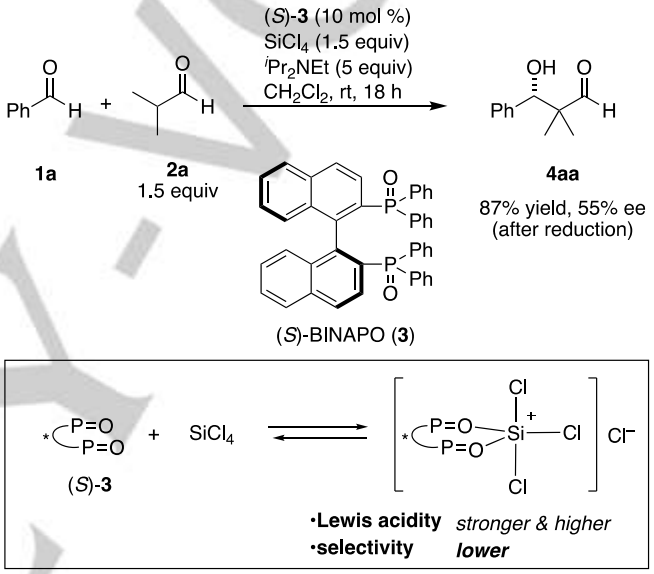
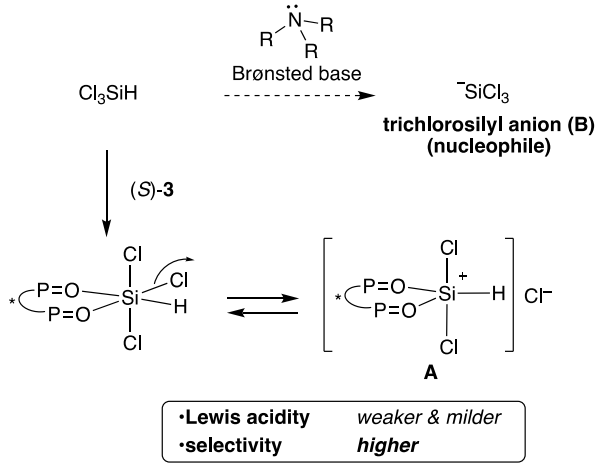
Abstract: A hypervalent silicon complex between trichlorosilane and a chiral phosphine oxide acts as an effective Lewis acid mediator that successfully promotes highly enantioselective cross-aldol reactions between two aldehydes. The high yielding transformation is realized with the assistance of triisobutylamine, which does not decompose trichlorosilane but rather converts the aldol donor into the silyl enol ether that undergoes the enantioselective cross-aldol reaction with a second aldehyde in combination with the chiral phosphine oxide catalyst.

Phosphine oxides were historically developed as precursors of phosphines that were used as metal ligands in organic chemistry; nowadays, their mature structural diversity has enabled the development of many Lewis-base-catalyzed asymmetric reactions.[1,2] Phosphine oxides are highly polar and behave as neutral coordinating Lewis bases; they readily form hypervalent silicon complexes *in situ* with chlorosilanes. These silicon complexes consist of Lewis acidic silicon sites with adjacent nucleophilic sites that facilitate aldol, allylation, and conjugate reduction reactions.[3] Our research group has developed a variety of phosphine-oxide-catalyzed asymmetric aldol reactions using these hypervalent silicon complexes.[4,5] Since, in most cases, aliphatic aldehydes are not tolerated as electrophiles due to the *in situ*-formation of silylated chlorohydrins with silicon tetrachloride in the presence of a Lewis base catalyst,[6] hypervalent silicon complexes discriminate between aromatic and aliphatic aldehydes to realize cross-aldol reactions. We reported the asymmetric cross-aldol reaction between an aromatic and an aliphatic aldehyde (**1a**, **2a**) by combining silicon tetrachloride with (*S*)-BINAPO (**3**), a chiral phosphine oxide catalyst; however, the enantioselectivity for product **4aa** was unsatisfactory (Scheme 1).[4b] Although numerous examples of asymmetric cross-aldol reactions via enamine intermediates have been described,[7-11] there are few alternative variations beyond the enamine-type activation mode. Given our interest in extending the potential of hypervalent silicon complexes formed from chiral phosphine oxide catalysts for asymmetric cross-aldol transformations, herein, we focused on a hypervalent silicon complex formed from trichlorosilane, which behaves as a weaker silyl reagent than silicon tetrachloride. Trichlorosilane is a commonly used reducing reagent for the metal-free asymmetric reductions of various substrates, including ketones, enones and imines.[12-15] The weaker and milder Lewis acidity of trichlorosilane compared to silicon tetrachloride was expected to promote the aldol reaction between two aldehydes in a more stereoselective fashion (Scheme 2).



Scheme 1. Chiral phosphine-oxide-catalyzed, $SiCl_4$-mediated cross-aldol reaction.

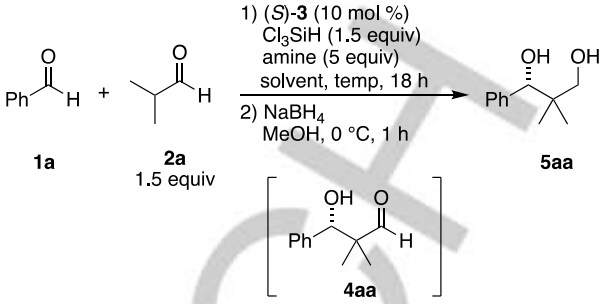
In this reaction, the phosphine oxide catalyst coordinates in a bidentate manner to trichlorosilane to form a hexacoordinated hypervalent silicon complex. The subsequent elimination of a chloride ion leads to pentacoordinated and highly Lewis-acidic hypervalent silicon complex **A**. We were concerned that complex **A** would mediate the reductions of aldehydes to alcohols without forming trichlorosilyl enol ethers. A second potential problem is related to the Brønsted acidity of the trichlorosilane proton under basic conditions, to form trichlorosilyl anion **B**.[16] To realize the desired trichlorosilane-mediated cross-aldol reactions between aldehydes, both of these issues required resolution. In this communication, we reveal the novel Lewis acid functionality of trichlorosilane in the phosphine-oxide-catalyzed cross-aldol reactions of aldehydes to realize highly enantioselective transformations.



Scheme 2. Reaction modes and properties of trichlorosilane.

We began our investigation by reacting aldehydes **1a** and **2a** in the presence of trichlorosilane and (*S*)-**3** in dichloromethane at room temperature (Table 1, entry 1, *cf.*, Scheme 1). The cross-aldol reaction proceeded moderately to afford the product in 25% yield, with a gratifying enantioselectivity (73% ee). Isolation and analysis were conducted after reduction of aldol adduct **4aa** to diol **5aa** with $NaBH_4$ in methanol. Since the tertiary amine used as the Brønsted base might affect the product yield through competitive deprotonation of trichlorosilane, we investigated several other amines (entries 2–5). Triethylamine, a less hindered and more nucleophilic amine, improved both the product yield and enantioselectivity (entry 2), whereas sterically congested *N*,*N*-dicyclohexylisobutylamine resulted in a lower product yield (41%, entry 3). These results indicate that the steric bulk of the amine notably affects reactivity in the trichlorosilane-mediated cross-aldol reaction. On the other hand, similar selectivities were observed, indicating that the amine is only involved in the deprotonation step and not in the enantio-determining step of the cross-aldol reaction. The use of triisobutylamine in the reaction gratifyingly afforded cross-aldol adduct **4aa** in 99% yield with 76% ee (entry 4). 2,6-Lutidine also gave a good result, similarly to that of triisobutylamine (entry 5). Solvent investigations revealed that acetonitrile and propionitrile gave **4aa** in good yields, albeit with lower selectivities (entries 6 and 7), whereas THF and toluene were detrimental to both chemical and optical yields (entries 8 and 9). While the enantioselectivity improved to 86% ee when the reaction was carried out at –20 °C in dichloromethane (entry 10), further temperature reductions led to dramatic decreases in yield without any significant increase in enantioselectivity (entries 11 and 12).[17]

Table 1. Trichlorosilane-mediated enantioselective cross-aldol reactions between aldehydes **1a** and **2a**.[a]



entry	amine	solvent	temp, °C	yield, %	ee, %[b]
1	^{i}Pr$_2$NEt	CH_2Cl_2	25	25	73
2	Et_3N	CH_2Cl_2	25	69	75
3	Cy$_2$N^{i}Bu	CH_2Cl_2	25	41	75
4	^{i}Bu$_3$N	CH_2Cl_2	25	99	76
5	2,6-lutidine	CH_2Cl_2	25	93	74
6	^{i}Bu$_3$N	MeCN	25	93	61
7	^{i}Bu$_3$N	EtCN	25	93	58
8	^{i}Bu$_3$N	THF	25	18	30
9	^{i}Bu$_3$N	toluene	25	13	22
10	^{i}Bu$_3$N	CH_2Cl_2	–20	97	86
11	^{i}Bu$_3$N	CH_2Cl_2	–40	55	86
12	^{i}Bu$_3$N	CH_2Cl_2	–60	6	85

[a] Unless otherwise noted, the reactions were carried out by adding Cl_3SiH (1.5 equiv) to a solution of aldol acceptor **1a** (0.5 mmol), aldol donor **2a** (1.5 equiv), an amine (5.0 equiv), and (*S*)-**3** (10 mol %) in a solvent (5 mL). [b]Determined by HPLC.

Aldol reactions with silicon tetrachloride require sterically congested amines to avoid undesirable interactions with the silylating agent.[4] In contrast, less-hindered amines tended to give better results with trichlorosilane. Since the weaker electrophilicity of trichlorosilane prohibits coordination by the amine, a less-hindered amine can be used (Figure 1). Although the least sterically hindered amine (i.e., triethylamine) can react with trichlorosilane, thereby reducing the product yield, the greater steric hindrance of triisobutylamine and 2,6-lutidine successfully suppresses both the nucleophilic attack and deprotonation of trichlorosilane, ably mediating enolization of the aldol donor.

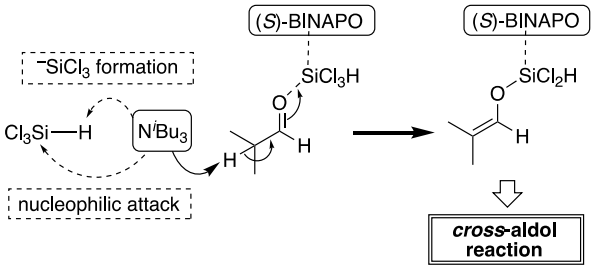
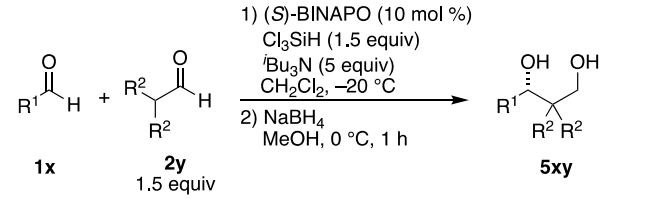
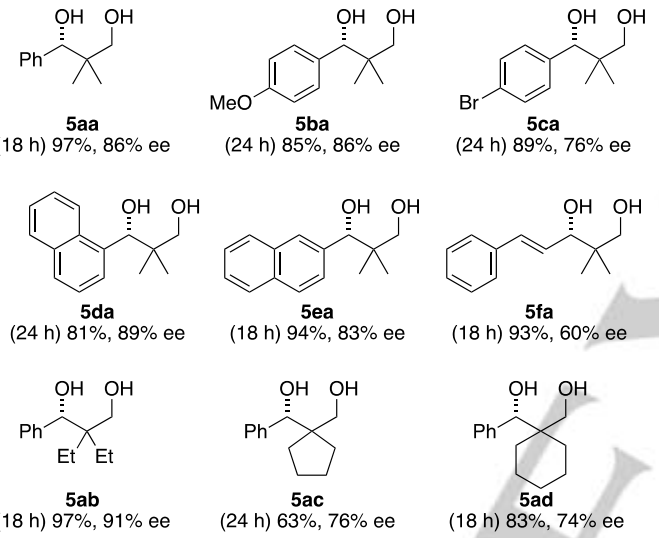


Figure 1. Impact of steric hindrance on reaction-path selection for triisobutylamine in the cross-aldol reaction.

With the optimal reaction conditions in hand, we examined the cross-aldol reactions of various aldehydes (Scheme 3). *p*-Anisaldehyde (**1b**) bearing an electron-donating group was slightly less reactive with aldehyde **1a**, requiring 24 h for complete reaction, but product **5ba** was obtained with good enantioselectivity (86% ee). In contrast, slightly lower enantioselectivity was observed in the reaction of *p*-bromobenzaldehyde (**1c**) bearing an electron-withdrawing group.

Sterically hindered 1- and 2-naphthaldehydes (**1d** and **1e,** respectively) also reacted well to give good enantioselectivities (84% ee and 83% ee, respectively), whereas the enantioselectivity was lower in the reaction of cinnamaldehyde (**1f**), a conjugated aldol acceptor. Various aldol donors were next investigated in reactions with **1a**. α,α-Diethylated acetaldehyde **2b** gave product **5ab** with the highest enantioselectivity (91% ee). Cyclic aliphatic aldehydes **2c** and **2d** gave the corresponding products **5ac** and **5ad** in 76% ee and 74% ee, respectively.





[a]All reactions were carried out by adding Cl_3SiH (1.5 equiv) to a solution of aldol acceptor **1x** (0.5 mmol), aldol donor **2y** (1.5 equiv), $^iBu_3N$ (5.0 equiv), and (*S*)-**3** (10 mol %) in CH_2Cl_2 (5 mL) at –20 °C.

Scheme 3. Enantioselective cross-aldol reactions of various aldehydes.[a]

In summary, we demonstrated the utility of trichlorosilane as a Lewis acid mediator in phosphine-oxide-catalyzed aldol reactions, realizing highly enantioselective cross-aldol reactions between aldehydes. The key to this achievement is the use of triisobutylamine as an effective Brønsted base to afford the aldol products in good-to-high yields and enantioselectivities. In future work, we hope to develop an enantioselective tandem reaction that exploits the diverse functionalities of trichlorosilane.

Acknowledgements

This work was partially supported by the Naito Foundation, JSPS KAKENHI (No. 19K06997) from The Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Conflict of Interest

The authors declare no conflicts of interest.

Keywords: Aldol reaction • Enantioselectivity • Hypervalent silicon • Lewis base • Phosphine oxide

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[17] Although we screened various phosphine oxide catalysts to improve enantioselectivity, dramatic increases were not observed. Detailed catalyst-screening results are provided in the Supporting Information.

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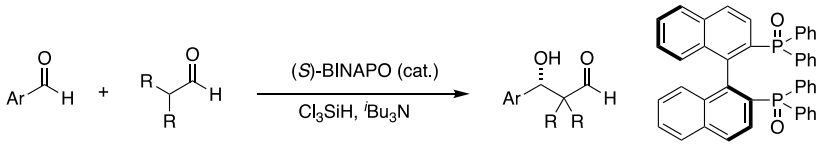

Phosphine-oxide-catalyzed Cross-aldol Reaction

(*S*)-BINAPO

Phosphine oxide catalysis with trichlorosilane. A hypervalent silicon complex formed between trichlorosilane and a chiral phosphine oxide acts as an effective Lewis acid mediator that successfully promotes the cross-aldol reaction between two aldehydes with good-to-high enantioselectivity. The high yielding transformation is realized by the assistance of triisobutylamine, which effectively promotes the silyl enolization of an aldol donor, resulting in the cross-aldol reaction with an aldol acceptor.

Keywords: Aldol reaction • Enantioselectivity • Hypervalent silicon • Lewis base • Phosphine oxide